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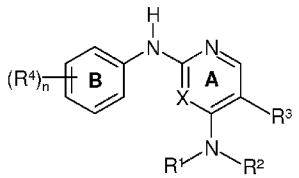
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(54) Title: HETEROCYCLIC DERIVATIVES AND METHODS OF USE THEREOF



(I)

(57) Abstract: Compounds of formula (I) and their pharmaceutically acceptable salts are described. Processes for their preparation, pharmaceutical compositions containing them, their use as medicaments and their use in the treatment of bacterial infections are also described.

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HETEROCYCLIC DERIVATIVES AND METHODS OF USE THEREOF

Field of the Invention

The present invention relates to pyrimidine and pyridine derivatives which demonstrate antibacterial activity, processes for their preparation, pharmaceutical compositions containing them as the active ingredient, to their use as medicaments and to their use in the manufacture of medicaments for use in the treatment of bacterial infections in warm-blooded animals such as humans. In particular, this invention relates to compounds useful for the treatment of bacterial infections in warm-blooded animals such as humans, more particularly to the use of these compounds in the manufacture of medicaments for use in the treatment of bacterial infections in warm-blooded animals such as humans.

Background of the Invention

The international microbiological community continues to express serious concern that the evolution of antibiotic resistance could result in strains against which currently available antibacterial agents will be ineffective. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compounds of the present invention are regarded as effective against both Gram-positive and certain Gram-negative pathogens.

Gram-positive pathogens, for example Staphylococci, Enterococci, Streptococci and mycobacteria, are particularly important because of the development of resistant strains which are both difficult to treat and difficult to eradicate from the hospital environment once established. Examples of such strains are methicillin resistant *staphylococcus aureus* (MRSA), methicillin resistant coagulase negative staphylococci (MRCNS), penicillin resistant *Streptococcus pneumoniae* and multiple resistant *Enterococcus faecium*.

The preferred clinically effective antibiotic for treatment of last resort of such resistant Gram-positive pathogens is vancomycin. Vancomycin is a glycopeptide and is associated with various toxicities, including nephrotoxicity. Furthermore, and most importantly, antibacterial resistance to vancomycin and other glycopeptides is also appearing. This resistance is increasing at a steady rate rendering these agents less and less effective in the treatment of Gram-positive pathogens. There is also now increasing resistance appearing towards agents such as β-lactams, quinolones and macrolides used for the treatment of upper respiratory tract

infections, also caused by certain Gram negative strains including *H.influenzae* and *M.catarrhalis*.

Consequently, in order to overcome the threat of widespread multi-drug resistant organisms, there is an on-going need to develop new antibiotics, particularly those with either a novel mechanism of action and/or containing new pharmacophoric groups.

Deoxyribonucleic acid (DNA) gyrase is a member of the type II family of topoisomerases that control the topological state of DNA in cells (Champoux, J. J.; 2001. Ann. Rev. Biochem. 70: 369-413). Type II topoisomerases use the free energy from adenosine triphosphate (ATP) hydrolysis to alter the topology of DNA by introducing transient double-stranded breaks in the DNA, catalyzing strand passage through the break and resealing the DNA. DNA gyrase is an essential and conserved enzyme in bacteria and is unique among topoisomerases in its ability to introduce negative supercoils into DNA. The enzyme consists of two subunits, encoded by *gyrA* and *gyrB*, forming an A_2B_2 tetrameric complex. The A subunit of gyrase (GyrA) is involved in DNA breakage and resealing and contains a conserved tyrosine residue that forms the transient covalent link to DNA during strand passage. The B subunit (GyrB) catalyzes the hydrolysis of ATP and interacts with the A subunit to translate the free energy from hydrolysis to the conformational change in the enzyme that enables strand-passage and DNA resealing.

Another conserved and essential type II topoisomerase in bacteria, called topoisomerase IV, is primarily responsible for separating the linked closed circular bacterial chromosomes produced in replication. This enzyme is closely related to DNA gyrase and has a similar tetrameric structure formed from subunits homologous to Gyr A and to Gyr B. The overall sequence identity between gyrase and topoisomerase IV in different bacterial species is high. Therefore, compounds that target bacterial type II topoisomerases have the potential to inhibit two targets in cells, DNA gyrase and topoisomerase IV; as is the case for existing quinolone antibacterials (Maxwell, A. 1997, Trends Microbiol. 5: 102-109).

DNA gyrase is a well-validated target of antibacterials, including the quinolones and the coumarins. The quinolones (*e.g.* ciprofloxacin) are broad-spectrum antibacterials that inhibit the DNA breakage and reunion activity of the enzyme and trap the GyrA subunit covalently complexed with DNA (Drlica, K., and X. Zhao, 1997, Microbiol. Molec. Biol. Rev. 61: 377-392). Members of this class of antibacterials also inhibit topoisomerase IV and as a result, the primary target of these compounds varies among species. Although the quinolones are successful antibacterials, resistance generated primarily by mutations in the

target (DNA gyrase and topoisomerase IV) is becoming an increasing problem in several organisms, including *S. aureus* and *Streptococcus pneumoniae* (Hooper, D. C., 2002, The Lancet Infectious Diseases 2: 530-538). In addition, quinolones, as a chemical class, suffer from toxic side effects, including arthropathy that prevents their use in children (Lipsky, B. A. and Baker, C. A., 1999, Clin. Infect. Dis. 28: 352-364). Furthermore, the potential for cardiotoxicity, as predicted by prolongation of the QT_c interval, has been cited as a toxicity concern for quinolones.

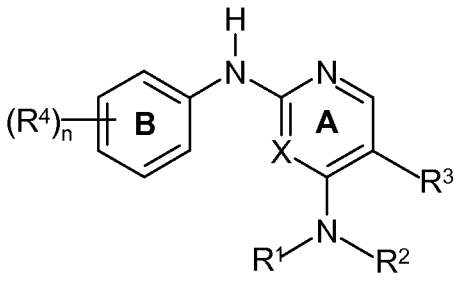
There are several known natural product inhibitors of DNA gyrase that compete with ATP for binding the GyrB subunit (Maxwell, A. and Lawson, D.M. 2003, Curr. Topics in Med. Chem. 3: 283-303). The coumarins are natural products isolated from *Streptomyces spp*., examples of which are novobiocin, chlorobiocin and coumermycin A1. Although these compounds are potent inhibitors of DNA gyrase, their therapeutic utility is limited due to toxicity in eukaryotes and poor penetration in Gram-negative bacteria (Maxwell, A. 1997, Trends Microbiol. 5: 102-109). Another natural product class of compounds that targets the GyrB subunit is the cyclothialidines, which are isolated from *Streptomyces filipensis* (Watanabe, J. et al 1994, J. *Antibiot*. 47: 32-36). Despite potent activity against DNA gyrase, cyclothialidine is a poor antibacterial agent showing activity only against some eubacterial species (Nakada, N, 1993, *Antimicrob. Agents Chemother*. 37: 2656-2661).

Synthetic inhibitors that target the B subunit of DNA gyrase and topoisomeraseIV are known in the art. For example, coumarin-containing compounds are described in patent application number WO 99/35155, 5,6-bicyclic heteroaromatic compounds are described in patent application WO 02/060879, and pyrazole compounds are described in patent application WO 01/52845 (US patent US6,608,087). AstraZeneca has also published certain applications describing anti-bacterial compounds: WO2005/026149, WO2006/087544, WO2006/087548, WO2006/087543, WO2006/092599, WO2006/092608, and WO2007/071965.

Summary of the Invention

We have discovered a new class of compounds which are useful for inhibiting DNA gyrase and / or topoisomerase IV.

In one embodiment, according to the present invention there is provided a compound of formula **(I)**:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X is CH or N;

R^1 is hydrogen, a C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-14}carbocyclyl, or a heterocyclyl, wherein R^1 may be optionally substituted on carbon by one or more R^6; and wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7; provided that R^1 is not a substituted or unsubstituted phenyl;

R^2 is hydrogen or a C_{1-6}alkyl; or

R^1 and R^2, together with the nitrogen to which they are attached, form a heterocyclyl, wherein said heterocyclyl may be optionally substituted on carbon by one or more R^8; wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^3 is a C_{6-14}aryl or a heteroaryl; wherein R^3 may be optionally substituted on carbon by one or more R^{14}; and wherein if said heteraryl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heteroaryl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{15}; provided that R^3 is not an unsubstituted phenyl or an unsubstituted thiophenyl;

R^4, for each occurrence, is independently selected from the group consisting of halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, carbamoyl, N-C_{1-6}alkylcarbamoyl, N-C_{1-6}alkoxycarbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl, N-(SO_2R')carbamoyl, N-C_{1-6}alkyl, C_{1-}

$_{6}$alkyl-S(O)$_a$-, $R^{17}R^{18}$N-S(O)$_a$-, C_{3-14}carbocyclyl, and heterocyclyl; or two R^4 taken together with the carbon atoms to which they are attached form a C_{3-14}carbocyclyl or a heterocyclyl, wherein each R^4 may be optionally substituted on carbon by one or more R^{16}, wherein if either of said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{26}; provided that ring B together with $-(R^4)_n$ is not 3,4,5-trimethoxyphenyl;

n is an integer from 1 to 5;

a is 0, 1, or 2;

R^6, R^8, and R^{14}, for each occurrence, are each independently selected from the group consisting of hydroxy, halo, cyano, nitro, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, mercapto, C_{1-6}alkoxy, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, -C(=N-OH)NH$_2$, -C(O)NHNH$_2$, phenoxy, carboxy, oxo, amino, N-C_{1-6}alkylamino, N,N-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonyl, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkanoylamino, C_{1-6}alkoxycarbonylamino, carbamoyl, N-C_{1-6}alkylcarbamoyl, N-C_{1-6}alkoxycarbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl, N-C_{1-6}alkyl-N-alkoxycarbamoyl, N-(SO$_2$R')carbamoyl, N-C_{1-6}alkyl-N-(SO$_2$R')carbamoyl, C_{1-6}alkylsulphonylamino, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, sulphamoylamino, *N*-(C_{1-6}alkyl)sulphamoylamino, *N,N*-(C_{1-6}alkyl)$_2$sulphamoylamino, C_{3-14}carbocyclyl-L- and heterocyclyl-L-; or two R^{14} taken together with the carbon atoms to which they are attached form a C_{3-14}carbocyclyl or a heterocyclyl; wherein R^6, R^8, and R^{14} may be each independently optionally substituted on carbon by one or more R^{10}; and wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if either of said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{11};

R' and R", for each occurrence, are independently selected from the group consisting of C_{1-6}alkyl, C_{6-14}aryl and heterocyclyl, wherein R' and R"may be optionally substituted on carbon by one or more R^{22} and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{23};

R^7, R^9, R^{15} and R^{23}, for each occurrence, are each independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkanoyl, carbamoyl, N-C_{1-6}alkylcarbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl, C_{3-14}carbocyclyl-C(O)-, heterocyclyl-C(O)-, (C_{1-6}alkyl)$_3$silyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, wherein R^7, R^9, and R^{15} may be each independently optionally substituted on carbon by one or more R^{12}; and wherein if said

hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

L, for each occurrence, is independent selected from a direct bond, -O-, -N(R^{25})-, -C(O)-, -N(R^{25})C(O)-, -C(O)N(R^{25})-, -S(O)$_s$-, -SO_2N(R^{25})- or -N(R^{25})SO_2-; wherein R^{25}, for each occurrence, is independently selected from hydrogen or C_{1-6}alkyl and s is 0, 1 or 2;

R^{10} and R^{12}, for each occurrence, are independently selected from the group consisting of C_{1-6}alkyl, phenyl, halo, cyano, nitro, oxo, carboxy, hydroxy, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, amino, N-C_{1-6}alkylamino, N,N-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, C_{1-6}alkylSO_2NH-, carbamoyl, N-C_{1-6}alkylcarbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl, N-C_{1-6}alkyloxycarbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, and heterocyclyl, wherein said R^{10} and R^{12} are independently optionally substituted on carbon by one or more C_{1-6}alkyl and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from $R^{13'}$;

R^{11}, R^{13}, $R^{13'}$, and R^{26}, for each occurrence, are each independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkanoyl, C_{3-6}cycloalkanoyl, carbamoyl, C_{1-6}alkanoyloxy, C_{1-6}alkylS(O)$_a$, arylS(O)$_a$ wherein a is 0 to 2, carboxy, sulphamoyl and urea wherein said R^{11}, R^{13}, $R^{13'}$, and R^{26} are independently optionally substituted on carbon by one or more amino, C_{1-6}alkyl, C_{1-6}alkoxy or heterocyclyl;

R^{16}, for each occurrence, is independently, a halo, hydroxy, a C_{1-6}alkyl, or a C_{1-6}alkoxy;

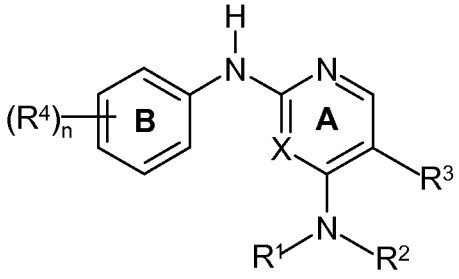
R^{17} and R^{18}, for each occurrence, are independently hydrogen or a C_{1-6}alkyl; or R^{17} and R^{18}, together with the nitrogen to which they are attached form a heterocyclyl;

R^{22}, for each occurrence, is independently selected from the group consisting of halo, C_{1-6}alkyl, S(O)$_a$R" wherein a is 0 to 2, C_{1-6}alkanoyl, C_{1-6}alkanoylamino and heterocyclyl wherein R^{22} may be optionally substituted on carbon by one or more R^{24};

R^{24} is selected from halo, C_{1-6}alkanoylamino, and heterocyclyl;

provided that –NR^1R^2 is not –$NHCH_3$ or -N(CH_3)$_2$.

In another embodiment, according to the present invention there is provided a compound of formula **(I)**:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X is CH or N;

R^1 is hydrogen, a C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-14}carbocyclyl, or a heterocyclyl, wherein R^1 may be optionally substituted on carbon by one or more R^6; and wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7; provided that R^1 is not a substituted or unsubstituted phenyl;

R^2 is hydrogen or a C_{1-6}alkyl;

R^1 and R^2, together with the nitrogen to which they are attached, form a heterocyclyl, wherein said heterocyclyl may be optionally substituted on carbon by one or more R^8; wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^3 is a C_{6-14}aryl or a heteroaryl; wherein R^3 may be optionally substituted on carbon by one or more R^{14}; and wherein if said heteraryl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heteroaryl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{15}; provided that R^3 is not an unsubstituted phenyl or an unsubstituted thiophenyl;

R^4, for each occurrence, is independently selected from the group consisting of halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_a$, $R^{17}R^{18}N$-$S(O)_a$, C_{3-14}carbocyclyl, and heterocyclyl; or two R^4 taken together with the carbon atoms to which they

are attached form a C_{3-14}carbocyclyl or a heterocyclyl, wherein each R^4 may be optionally substituted on carbon by one or more R^{16}; provided that ring B together with $-(R^4)_n$ is not 3,4,5-trimethoxyphenyl;

n is an integer from 1 to 5;

a is 0, 1, or 2;

R^6, R^8, and R^{14}, for each occurrence, are each independently selected from the group consisting of hydroxy, halo, cyano, nitro, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, mercapto, C_{1-6}alkoxy, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, -C(=N-OH)NH_2, phenoxy, carboxy, amino, N-C_{1-6}alkylamino, N,N-(C_{1-6}alkyl)$_2$amino, a heterocyclyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkanoylamino, C_{1-6}alkoxycarbonylamino, carbamoyl, N-C_{1-6}alkylcarbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylsulphonylamino, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, sulphamoylamino, *N*-(C_{1-6}alkyl)sulphamoylamino, *N,N*-(C_{1-6}alkyl)$_2$sulphamoylamino, C_{3-14}carbocyclyl-L- and heterocyclyl-L-; wherein R^6, R^8, and R^{14} may be each independently optionally substituted on carbon by one or more R^{10}; and wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{11};

R^7, R^9, and R^{15}, for each occurrence, are each independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkanoyl, carbamoyl, N-C_{1-6}alkylcarbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl, C_{3-14}carbocyclyl-C(O)-, heterocyclyl-C(O)-, (C_{1-6}alkyl)$_3$silyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, wherein R^7, R^9, and R^{15} may be each independently optionally substituted on carbon by one or more R^{12}; and wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

L, for each occurrence, is independent selected from a direct bond, -O-, -N(R^{25})-, -C(O)-, -N(R^{25})C(O)-, -C(O)N(R^{25})-, -S(O)$_s$-, -SO_2N(R^{25})- or -N(R^{25})SO_2-; wherein R^{25}, for each occurrence, is independently selected from hydrogen or C_{1-6}alkyl and s is 0, 1 or 2;

R^{10} and R^{12}, for each occurrence, are independently selected from the group consisting of C_{1-6}alkyl, phenyl, halo, cyano, nitro, carboxy, hydroxy, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl,

amino, N-C_{1-6}alkylamino, N,N-(C_{1-6}alkyl)$_2$amino, carbamoyl, N-C_{1-6}alkylcarbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl and N-C_{1-6}alkyloxycarbamoyl; and

R^{11} and R^{13}, for each occurrence, are each independently a C_{1-6}alkyl;

R^{16}, for each occurrence, is independently, a halo, hydroxy, a C_{1-6}alkyl, or a C_{1-6}alkoxy;

R^{17} and R^{18}, for each occurrence, are independently hydrogen or a C_{1-6}alkyl; or R^{17} and R^{18}, together with the nitrogen to which they are attached form a heterocyclyl;

provided that $-NR^1R^2$ is not $-NHCH_3$, $-N(CH_3)_2$.

In another embodiment, the invention provides pharmaceutical compositions comprising a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient or carrier.

In another embodiment, the invention provides a method of inhibiting bacterial DNA gyrase and/or bacterial topoisomerase IV in a warm-blooded animal in need of such treatment, comprising administering to the animal an effective amount of a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof. In a particular embodiment, the warm-blooded animal is a human.

In another embodiment, the invention provides a method of producing an antibacterial effect in a warm-blooded animal in need of such treatment, comprising administering to the animal an effective amount of a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof. In a particular embodiment, the warm-blooded animal is a human.

In another embodiment, the invention provides a method of treating a bacterial infection in a warm-blooded animal in need thereof, comprising administering to the animal an effective amount of a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof. In a particular embodiment, the warm-blooded animal is a human. In one embodiment, the bacterial infection is selected from the group consisting of community-acquired pneumoniae, hospital-acquired pneumoniae, skin and skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci. In a particular embodiment, the warm-blooded animal is a human.

In another embodiment, the invention provides compounds of formula **(I)** or a pharmaceutically acceptable salt thereof, for use as a medicament.

In another embodiment, the invention provides the use of a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in the production of an antibacterial effect in a warm-blooded animal. In a particular embodiment, the warm-blooded animal is a human.

In another embodiment, the invention provides the use of a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in inhibition of bacterial DNA gyrase and/or topoisomerase IV in a warm-blooded animal. In a particular embodiment, the warm-blooded animal is a human.

In another embodiment, the invention provides the use of a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use the treatment of a bacterial infection in a warm-blooded animal. In one embodiment, the bacterial infection is selected from the group consisting of community-acquired pneumoniae, hospital-acquired pneumoniae, skin and skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections, Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci. In a particular embodiment, the warm-blooded animal is a human.

In another embodiment, the invention provides a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in production of an anti-bacterial effect in a warm-blooded animal.

In another embodiment, the invention provides a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in inhibition of bacterial DNA gyrase and/or topoisomerase IV in a warm-blooded animal.

In another embodiment, the invention provides a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of a bacterial infection in a warm-blooded animal.

In another embodiment, the invention provides a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of community-acquired pneumoniae, hospital-acquired pneumoniae, skin and skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis,

febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections, Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis or Vancomycin-Resistant Enterococci.

Detailed Description of the Invention

In this specification the term alkyl includes both straight chained and branched saturated hydrocarbon groups. For example, "C_{1-6}alkyl" refers to an alkyl that has from 1 to 6 carbon atom and includes, for example, methyl, ethyl, propyl, isopropyl and *t*-butyl. However references to individual alkyl groups such as propyl are specific for the straight chain version only unless otherwise indicated (e.g., isopropyl). An analogous convention applies to other generic terms. Unless otherwise specified, when two or more alkyl groups are indicated by, for example, the term $(C_{1-6}alkyl)_2$ (such as in the term *N,N*-$(C_{1-6}alkyl)_2$amino), the alkyl groups can be the same or different.

The term "C_{2-6}alkenyl," as used herein refers to a straight chain or branched hydrocarbon having at least one double bond.

The term "C_{2-6}alkynyl," as used herein refers to a straight chain or branched hydrocarbon having at least one triple bond.

As used herein, the term "halo" refers to fluoro, chloro, bromo, and iodo.

A "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 4-14 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH_2- group can optionally be replaced by a -C(O)- and a ring nitrogen may be optionally substituted with one oxo to form an N-oxide and a ring sulfur may be optionally substituted with one or two oxo groups to form S-oxide(s). In one embodiment of the invention a "heterocyclyl" is a saturated, partially saturated or unsaturated, monocyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, it may, unless otherwise specified, be carbon or nitrogen linked. In a further aspect of the invention a "heterocyclyl" is an unsaturated, carbon-linked, monocyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen. Examples and suitable values of the term "heterocyclyl" are azepanyl, azetidinyl, morpholinyl, piperidinyl, piperazinyl, pyridinyl, pyranyl, pyrrolyl, pyrazolyl, isothiazolyl, indolinyl, quinolinyl, thienyl, 1,3-benzodioxolyl, benzothiazolyl, thiadiazolyl, oxadiazolyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl,

tetrahydropyranyl, imidazolyl, 4,5-dihydro-oxazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, isoxazolyl, thiazolyl, 1*H*-tetrazolyl, 1*H*-triazolyl, *N*-methylpyrrolyl, 4-pyridone, quinolin-4(1*H*)-one, pyridin-2(1*H*)-one, imidazo[1,2-a]pyridinyl, 1-isoquinolone, 2-pyrrolidone, 4-thiazolidone, quinoxalinyl, 5,6-dihydro[1,3]thiazolo[4,5-*d*]pyridazinyl, pyridine-*N*-oxide and quinoline-*N*-oxide. Suitable examples of "a nitrogen linked heterocyclyl" are morpholino, piperazin-1-yl, piperidin-1-yl and imidazol-1-yl. In a further aspect of the invention a "heterocyclyl" is a heteroaryl. The term "heteroaryl" refers to an unsaturated and aromatic heterocyclyl which has 5-14 ring atoms wherein at least one atom is chosen from nitrogen, sulphur or oxygen. Examples and suitable values for heteroaryl groups include pyridinyl, 1*H*-pyrrolyl, 1*H*-pyrazolyl, isothiazolyl, quinolinyl, thienyl, benzofuranyl, benzothiophenyl, benzothiazolyl, benzimidazolyl, thiadiazolyl, oxadiazolyl, 1*H*-imidazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, isoxazolyl, thiazolyl, thiophenyl, 1*H*-pyrazolyl, 1*H*-tetrazolyl, 1*H*-triazolyl, *N*-methylpyrrolyl, 4-oxo-1,4-dihydroquinolinyl, pyridin-2(1*H*)-one, imidazo[1,2-a]pyridinyl, 1*H*-indazol-1-yl, 1-isoquinolone, quinoxalinyl, pyridine-*N*-oxide and quinoline-*N*-oxide. In a particular embodiment, the heteroaryl is a 5- or 6-membered heteroaryl, for example, pyridinyl, 1*H*-pyrrolyl, 1*H*-pyrazolyl, isothiazolyl, thienyl, thiadiazolyl, oxadiazolyl, 1*H*-imidazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, isoxazolyl, thiazolyl, 1*H*-tetrazolyl, 1*H*-triazolyl, *N*-methylpyrrolyl, and pyridine-*N*-oxide. In another embodiment heteroaryl also includes pyridinyl-2(1*H*)-one and indolyl.

A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono-, bi- or tricyclic carbon ring that contains 3-14 atoms; wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-. In one embodiment, "carbocyclyl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Examples of carbocyclyls include cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl, naphthyl, tetralinyl, indanyl or 1-oxoindanyl. The term carbocyclyl encompasses both cycloalkyl and aryl groups. The term cycloalkyl refers to a C_{3-14}carbocyclyl which is completely saturated, for example cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The term "aryl" refers to a carbocyclyl which is completely unsaturated and is aromatic. A C_{6-14}aryl is an aromatic, mono-, bi- or tricyclic carbon ring that contains 6-14 atoms, for example phenyl or naphthenyl.

An example of "C_{1-6}alkanoyloxy" is acetoxy. Examples of "C_{1-6}alkoxycarbonyl" are methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C_{1-6}alkoxycarbonylamino" are methoxycarbonylamino, ethoxycarbonylamino, *n*- and

t-butoxycarbonylamino. Examples of "C_{1-6}alkoxy" are methoxy, ethoxy, isopropoxy, and *tert*-butoxy. Examples of "C_{1-6}alkanoylamino" are formamido, acetamido and propionylamino. Examples of "C_{1-6}alkylS(O)$_a$ wherein a is 0, 1, or 2" are methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulfonyl and ethylsulphonyl. Examples of "C_{1-6}alkanoyl" are propionyl and acetyl. Examples of "*N*-(C_{1-6}alkyl)amino" are methylamino and ethylamino. Examples of "*N,N*-(C_{1-6}alkyl)$_2$amino" are *N,N*-dimethylamino, *N,N*-diethylamino and *N*-ethyl-*N*-methylamino. Examples of "C_{2-6}alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C_{2-6}alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "*N*-(C_{1-6}alkyl)sulphamoyl" are *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. An example of "*N,N*-(C_{1-6}alkyl)$_2$sulphamoylamino" are *N,N*-dimethylsulphamoylamino. Examples of "*N*-(C_{1-6}alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$carbamoyl" are dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "*N*-(C_{1-6}alkoxy)carbamoyl" are methoxyaminocarbonyl and isopropoxyaminocarbonyl. Examples of "*N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl" are *N*-methyl-*N*-methoxyaminocarbonyl and *N*-methyl-*N*-ethoxyaminocarbonyl. Examples of "C_{3-6}cycloalkyl" are cyclopropyl, cyclobutyl, cyclopropyl and cyclohexyl. Examples of "C_{1-6}alkylsulphonylamino" are methylsulphonylamino, isopropylsulphonylamino and *t*-butylsulphonylamino. Examples of "C_{1-6}alkylsulphonylaminocarbonyl" are methylsulphonylaminocarbonyl, isopropylsulphonylaminocarbonyl and *t*-butylsulphonylaminocarbonyl. Examples of "C_{1-6}alkylsulphonyl" are methylsulphonyl, isopropylsulphonyl and *t*-butylsulphonyl.

Examples of "C_{1-3}alkylsulphonylcarbamoyl" are methylsulphonylcarbamoyl, i.e. $CH_3SO_2NHC(O)$-, and ethylsulphonylcarbamoyl, i.e. $CH_3CH_2SO_2NHC(O)$-.

When a carbon atom is substituted by "oxo" a -C(O)- is formed. Thus, for example, if a pyridyl group is substituted on carbon by oxo, a pyridinyl-one is formed, e.g. if the carbon in the two position of pyridine is substituted by oxo, pyridinyl-2(1*H*)-one is formed.

The term "formula **(I)**", unless otherwise specified, refers to all embodiments of formula **(I)**.

A compound of formula **(I)** may form stable acid or basic salts, and in such cases administration of a compound as a salt may be appropriate, and pharmaceutically acceptable salts may be made by conventional methods such as those described below.

Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulfonate, tosylate, α-glycerophosphate, fumarate, hydrochloride, citrate, maleate, tartrate and (less preferably) hydrobromide. Also suitable are salts formed with phosphoric and sulfuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N,N*-dibenzylethylamine, tris-(2-hydroxyethyl)amine, *N*-methyl d-glucamine and amino acids such as lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions..

However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically-acceptable or not.

Within the present invention it is to be understood that a compound of the formula **(I)**, or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which inhibits DNA gyrase and / or topoisomerase IV and is not to be limited merely to any one tautomeric form utilized within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein. The same applies to compound names.

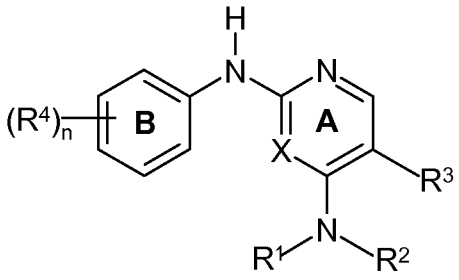
It will be appreciated by those skilled in the art that certain compounds of formula **(I)** contain an asymmetrically substituted carbon and/or sulfur atom, and accordingly may exist in, and be isolated in, optically-active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic or stereoisomeric form, or mixtures thereof, which form possesses properties useful in the inhibition of DNA gyrase and / or topoisomerase IV, it being well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, by enzymatic resolution, by biotransformation, or by chromatographic separation using a chiral stationary phase) and how to determine efficacy for the inhibition of DNA gyrase and / or topoisomerase IV by the standard tests described hereinafter.

By way of clarity, compounds of the invention included all isotopes of the atoms present in formula **(I)** and any of the examples or embodiments disclosed herein. For example, H (or hydrogen) represents any isotopic form of hydrogen including ^{1}H, ^{2}H (D), and ^{3}H (T); C represents any isotopic form of carbon including ^{12}C, ^{13}C, and ^{14}C; O represents any isotopic form of oxygen including ^{16}O, ^{17}O and ^{18}O; N represents any isotopic form of nitrogen including ^{13}N, ^{14}N and ^{15}N; P represents any isotopic form of phosphorous including ^{31}P and ^{32}P; S represents any isotopic form of sulfur including ^{32}S and ^{35}S; F represents any isotopic form of fluorine including ^{19}F and ^{18}F; Cl represents any isotopic form of chlorine including ^{35}Cl, ^{37}Cl and ^{36}Cl; and the like. In a preferred embodiment, compounds represented by formula **(I)** comprises isomers of the atoms therein in about their naturally occurring abundance. However, in certain instances, it is desirable to enrich one or more atom in a particular isotope which would normally be present in less abundance. For example, ^{1}H would normally be present in greater than 99.98% abundance; however, a compound of the invention can be enriched in ^{2}H or ^{3}H at one or more positions where H is present. In particular embodiments of the compounds of formula **(I)**, when, for example, hydrogen is enriched in the deuterium isotope, the symbol "D" is used to represent the enrichment in deuterium. In one embodiment, when a compound of the invention is enriched in a radioactive isotope, for example ^{3}H and ^{14}C, they may be useful in drug and/or substrate tissue distribution assays. It is to be understood that the invention encompasses all such isotopic forms which inhibit DNA gyrase and / or topoisomerase IV.

It is also to be understood that certain compounds of the formula **(I)**, and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which inhibit DNA gyrase and / or topoisomerase IV.

There follow particular and suitable values for certain substituents and groups referred to in this specification. These values may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore, or hereinafter. For the avoidance of doubt each stated species represents a particular and independent aspect of this invention.

In one embodiment the invention provides compounds represented by formula **(I)**:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X is CH or N;

R^1 is hydrogen, a C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-14}carbocyclyl, or a heterocyclyl, wherein R^1 may be optionally substituted on carbon by one or more R^6; and wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7; provided that R^1 is not a substituted or unsubstituted phenyl;

R^2 is hydrogen or a C_{1-6}alkyl;

R^1 and R^2, together with the nitrogen to which they are attached, form a heterocyclyl, wherein said heterocyclyl may be optionally substituted on carbon by one or more R^8; wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^3 is a C_{6-14}aryl or a heteroaryl; wherein R^3 may be optionally substituted on carbon by one or more R^{14}; and wherein if said heteraryl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heteroaryl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{15}; provided that R^3 is not an unsubstituted phenyl or an unsubstituted thiophenyl;

R^4, for each occurrence, is independently selected from the group consisting of halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_a$-, $R^{17}R^{18}N$-$S(O)_a$-, C_{3-14}carbocyclyl, and heterocyclyl; or two R^4 taken together with the carbon atoms to which they are attached form a C_{3-14}carbocyclyl or a heterocyclyl, wherein each R^4 may be optionally

substituted on carbon by one or more R^{16}; provided that ring B together with $-(R^4)_n$ is not 3,4,5-trimethoxyphenyl;

n is an integer from 1 to 5;

a is 0, 1, or 2;

R^6, R^8, and R^{14}, for each occurrence, are each independently selected from the group consisting of hydroxy, halo, cyano, nitro, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, mercapto, C_{1-6}alkoxy, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, -C(=N-OH)NH_2, phenoxy, carboxy, amino, N-C_{1-6}alkylamino, N,N-(C_{1-6}alkyl)$_2$amino, a heterocyclyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkanoylamino, C_{1-6}alkoxycarbonylamino, carbamoyl, N-C_{1-6}alkylcarbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylsulphonylamino, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, sulphamoylamino, *N*-(C_{1-6}alkyl)sulphamoylamino, *N,N*-(C_{1-6}alkyl)$_2$sulphamoylamino, C_{3-14}carbocyclyl-L- and heterocyclyl-L-; wherein R^6, R^8, and R^{14} may be each independently optionally substituted on carbon by one or more R^{10}; and wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{11};

R^7, R^9, and R^{15}, for each occurrence, are each independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkanoyl, carbamoyl, N-C_{1-6}alkylcarbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl, C_{3-14}carbocyclyl-C(O)-, heterocyclyl-C(O)-, (C_{1-6}alkyl)$_3$silyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, wherein R^7, R^9, and R^{15} may be each independently optionally substituted on carbon by one or more R^{12}; and wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

L, for each occurrence, is independent selected from a direct bond, -O-, -N(R^{25})-, -C(O)-, -N(R^{25})C(O)-, -C(O)N(R^{25})-, -S(O)$_s$-, -SO_2N(R^{25})- or -N(R^{25})SO_2-; wherein R^{25}, for each occurrence, is independently selected from hydrogen or C_{1-6}alkyl and s is 0, 1 or 2;

R^{10} and R^{12}, for each occurrence, are independently selected from the group consisting of C_{1-6}alkyl, phenyl, halo, cyano, nitro, carboxy, hydroxy, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, amino, N-C_{1-6}alkylamino, N,N-(C_{1-6}alkyl)$_2$amino, carbamoyl, N-C_{1-6}alkylcarbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl and N-C_{1-6}alkyloxycarbamoyl; and

R^{11} and R^{13}, for each occurrence, are each independently a C_{1-6}alkyl;

R^{16}, for each occurrence, is independently, a halo, hydroxy, a C_{1-6}alkyl, or a C_{1-6}alkoxy;

R^{17} and R^{18}, for each occurrence, are independently hydrogen or a C_{1-6}alkyl; or R^{17} and R^{18}, together with the nitrogen to which they are attached form a heterocyclyl;

provided that $-NR^1R^2$ is not $-NHCH_3$, $-N(CH_3)_2$.

In one embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein X is N.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein X is CH.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{1-6}alkyl that is optionally substituted on carbon by one or more R^6; and R^2 is hydrogen.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^1 is n-propyl, 3-(N,N-dimethylamino)-propyl, 3-(2-oxo-pyrrolidino)-propyl, 1-acetyl-piperidine-4-yl, 2-morpholino-ethyl, 2-acetamido-ethyl, 3-acetamido-propyl, pyridin-2-ylmethyl, pyridin-3-ylmethyl, pyridin-4-ylmethyl, 2-[(*tert*-butoxycarbonyl)amino]-ethyl, 2-carbamoyl-ethyl, 2-(pyridin-2-yl)-ethyl, 2-(pyridin-3-yl)-ethyl, 2-(pyridin-4-yl)ethyl, 2-(1,1-dioxo-thiomorpholino)-ethyl, 3-(1,1-dioxo-thiomorpholino)-propyl, 3-morpholino-propyl, 2-methoxyethyl, tetrahydrofuran-2-ylmethyl, 2-(isopropoxy)ethyl, furan-2-ylmethyl, ethoxycarbonylmethyl, phenoxyethyl, 1-(methoxycarbonyl)ethyl, 6-methyl-pyrazin-3-ylmethyl, isopropyl, 3-[(*tert*-butoxycarbonyl)amino]-propyl, 3-methoxypropyl, 2-(*N*,*N*-dimethylamino)-ethyl, 3-(1*H*-benzimidazol-2-yl)-propyl, 3-[(6-methyl-pyrazin-3-ylcarbonyl)amino]-propyl, 1-methyl-1*H*-imidazol-5-ylmethyl, 1-methyl-1*H*-imidazol-4-ylmethyl, tetrahydrofuran-3-yl, 1-methyl-1*H*-pyrazol-4-ylmethyl, 2-methoxy-1-methoxymethyl-ethyl, 3-amino-propyl, carboxymethyl, 1-carboxy-ethyl, 1*H*-benzimidazol-2-ylmethyl, 2-(1*H*-imidazol-4-yl)-ethyl, 2-(1*H*-benzimidazol-2-yl)-ethyl, 2-(1*H*-imidazol-1-yl)-ethyl, 2-(1*H*-pyrazol-1-yl)-ethyl, 2-(1*H*-pyrazol-4-yl)-ethyl, 2-(4-methyl-thiazole-5-yl)-ethyl, 2-(4-methyl-piperazino)-ethyl, 3-(1*H*-benzimidazol-2-yl)-propyl, 2-(5-methyl-1*H*-pyrazol-4-yl)-ethyl, 3-[(methylsulfonyl)amino]-propyl, or [1-(*tert*-butoxycarbonyl)-1*H*-benzimidazol-2-yl]methyl.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{1-6}alkyl which is optionally substituted with amino, carboxy, N,N-dimethylamino, 2-oxo-pyrrolidino, acetamido, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, (tert-butoxycarbonyl)amino, carbamoyl, methylsulfonylamino, morpholino, 1,1-dioxo-thiomorpholino, methoxy, tetrahydrofuran-2-yl, isopropoxy, furan-2-yl, ethoxycarbonyl, phenoxy, methoxycarbonyl, 6-methyl-pyrazin-3-yl, benzoimidazol-2-yl, [(6-methyl-pyrazin-3-yl)carbonyl]amino, 1*H*-imidazol-2-yl, 1*H*-imidazol-1-yl, 1-methyl-1*H*-imidazol-2-yl, 1-methyl-1*H*-pyrazol-4-yl, 5-methyl-1*H*-pyrazol-4-yl, 1*H*-pyrazol-1-yl, 1*H*-pyrazol-4-yl, 4-methyl-thiazole-5-yl, or 4-methyl-piperazino.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2, together with the nitrogen to which they are attached, form a heterocyclyl, wherein said heterocyclyl may be optionally substituted on carbon by one or more R^8; wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2, together with the nitrogen to which they are attached, form a 1*H*-pyrazol-1-yl, wherein said 1*H*-pyrazol-1-yl may be optionally substituted on carbon by one or more R^8.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^8 is independently a C_{1-6}alkyl or a C_{3-6}cycloalkyl wherein said R^8 is optionally substituted on carbon by one or more halo.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^8 is independently a C_{1-3}alkyl or a C_{3-6}cycloalkyl wherein said R^8 is optionally substituted on carbon by one or more fluoro.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2, together with the nitrogen to which they are attached, form a 1*H*-pyrazol-1-yl, wherein 1*H*-pyrazol-1-yl may be optionally substituted on carbon by one or more methyl, cyclopropyl or trifluoromethyl.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2, together with the nitrogen to

which they are attached, form piperidino, 4-hydroxy-piperidino, 3-hydroxymethyl-piperidino, 4-morpholino-piperidino, 4-(*N*-methyl-carbamoyl)-piperidino, 4-fluoro-piperidino, 4-methoxy-piperidino, 4-acetamido-piperidino, pyrrolidino, 3-hydroxy-pyrrolidino, 2-methyl-pyrrolidino, 2,5-dimethyl-pyrrolidino, azetidine-1-yl, 4-acetamidopiperidino, 3-trifluoromethyl-1*H*-pyrazol-1-yl, 3-trifluoromethyl-5-methyl-1*H*-pyrazol-1-yl, 1*H*-imidazol-1-yl, 4,5-dichloro-1*H*-imidazol-1-yl, 2-methyl-1*H*-imidazol-1-yl, 1*H*-pyrrol-1-yl, morpholino, 2,6-dimethylmorpholino, 3,5-dimethyl-pyrazol-1-yl, 4-(pyridin-4-yl)-1*H*-pyrazol-1-yl, 4-chloro-1*H*-pyrazol-1-yl, 4-trifluoromethyl-1*H*-imidazol-1-yl, 2-methyl-1*H*-imidazol-1-yl, 1,2,3-2*H*-triazol-2-yl, 1,2,3-1*H*-triazol-1-yl, 1,2,3-1*H*-benzotriazol-1-yl, 1,2,3-2*H*-benzotriazol-2-yl, 1*H*-[1,2,3]triazolo[4,5-b]pyridin-1-yl, 2*H*-[1,2,3]triazolo[4,5-b]pyridin-2-yl, azepan-1-yl, 4-aceto-piperazino, 4-(2-methoxy-ethyl)-piperazino, 4-methyl-piperazino, 4-[(*N*,*N*-dimethylamino)carbonyl]-piperazino, 4-(methylsulfonyl)-piperazino, or 4-cyclopropylcarbonyl-piperazino.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2, together with the nitrogen to which they are attached, form a heterocyclyl selected from1*H*-pyrazol-1-yl, 1*H*-benzotriazol-1-yl, 2*H*-benzotriazol-2-yl, and 1*H*-1,2,3-triazol-1-yl, wherein said heterocyclyl may be optionally substituted on carbon by one or more R^8; wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9. In one embodiment, R^8, for each occurrence, is independently selected from hydroxy, hydroxymethyl, morpholino, N-methylcarbamoyl, fluoro, methoxy, methyl, acetamido, trifluoromethyl, chloro, and pyridin-4-yl. In another embodiment, R^9, for each occurrence, is independently selected from a $C_{1\text{-}6}$alkyl, 2-methoxyethyl, acetyl, *N*,*N*-dimethylcarbamoyl, cyclopropylcarbonyl, methylsulfonyl and *tert*-butoxycarbonyl.

In another embodiment, R^1 is a $C_{3\text{-}14}$carbocyclyl; wherein R^1 may be optionally substituted on carbon by one or more R^6; provided that R^1 is not a substituted or unsubstituted phenyl. In one embodiment, R^1 is cyclohexyl. In another embodiment, R^6 is hydroxy.

In another embodiment, R^1 is a heterocycyl; wherein R^1 may be optionally substituted on carbon by one or more R^6; and wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an

-NH- moiety that nitrogen may be optionally substituted by a group selected from R^7; provided that R^1 is not a substituted or unsubstituted phenyl. In one embodiment, R^1 is piperidinyl or tetrahydrofuranyl which may be optionally substituted on carbon by one or more R^6; and wherein the -NH- moiety of piperidinyl may be optionally t substituted by a group selected from R^7.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^3 is a C_{6-14}aryl; wherein R^3 may be optionally substituted on carbon by one or more R^{14}; provided that R^3 is not an unsubstituted phenyl.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^3 is phenyl substituted on carbon by two R^{14} which taken together with the carbon atoms to which they are attached form a C_{3-14}carbocyclyl or a heterocyclyl; wherein R^{14} may be independently optionally substituted on carbon by one or more R^{10}; and wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{11}.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^3 is a heteroaryl; wherein R^3 may be optionally substituted on carbon by one or more R^{14}; and wherein if said heteraryl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heteroaryl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{15}; provided that R^3 is not an unsubstituted thiophenyl.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^{14}, for each occurrence, is independently selected from methoxycarbonyl, (methylsulfonyl)amino, ethoxycarbonyl, acetyl, amino, 5-oxo-4,5-dihydro-1,2,4-oxadiazolyl, trifluoromethyl, methoxy, (dimethylsulfamoyl)amino, cyano, fluoro, nitro, (E)-2-carboxyethenyl, 2-carboxy-ethyl, carboxy, (E)-2-ethoxycarbonylethenyl, (E)-2-carbamoyl-ethenyl, (E)-2-(N-methylcarbamoyl)-ethenyl, (E)-2-(N-methoxycarbamoyl)-ethenyl, N-methoxycarbamoyl, N-ethyl-carbamoyl, N-benzyl-carbamoyl, N,N-dimethylcarbamoyl, piperidinocarbonyl, 3,3-difluoro-piperidinocarbonyl, or N'-hydroxycarbamimidoyl.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^3 is phenyl; wherein R^3 is substituted on carbon by one or more R^{14}. For example, R^{14}, for each occurrence, is independently selected from methoxycarbonyl, (methylsulfonyl)amino, ethoxycarbonyl, trifluoromethyl, methoxy, (dimethylsulfamoyl)amino, cyano, fluoro, nitro, (E)-2-carboxyethenyl, 2-carboxy-ethyl, carboxy, (E)-2-ethoxycarbonylethenyl, (E)-2-carbamoyl-ethenyl, (E)-2-(N-methylcarbamoyl)-ethenyl, (E)-2-(N-methoxycarbamoyl)-ethenyl, N-methoxycarbamoyl, N-ethyl-carbamoyl, N-benzyl-carbamoyl, or N,N-dimethylcarbamoyl.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^3 is pyrimidinyl, indolinyl, pyridinyl, benzofuranyl, benzothiophenyl, thiophenyl, 1*H*-pyrazolyl, 4-oxo-1,4-dihydroquinolinyl, thiazolyl, quinolinyl, and benzimidazolyl; wherein R^3 may be optionally substituted on carbon by one or more R^{14}; and wherein if R^3 contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if R^3 contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{15}; provided that R^3 is not an unsubstituted thiophenyl. In one embodiment, R^{14}, for each occurrence, is independently selected from methoxycarbonyl, ethoxycarbonyl, acetyl, amino, 5-oxo-4,5-dihydro-1,2,4-oxadiazolyl, methoxy, carboxy, N-ethyl-carbamoyl, N-benzyl-carbamoyl, N,N-dimethylcarbamoyl, piperidinocarbonyl, 3,3-difluoro-piperidinocarbonyl, or N'-hydroxycarbamimidoyl. In another embodiment, R^{15}, for each occurrence, is independently selected from *tert*-butyl-dimethyl-silyl, 2-methoxyethyl, or tert-butoxycarbonyl.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^3 is 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-(methoxycarbonyl)-phenyl, 4-(ethoxycarbonyl)-phenyl, 3-[(methylsulfony)amino]-phenyl, 4-methoxy-3-trifluoromethyl, 3,4,5-trimethoxy-phenyl, 3-[(dimethylsulfamoyl)amino]-phenyl, 3-cyano-4-fluoro-phenyl, 3-nitrophenyl, 4-carboxyphenyl, 3-carboxyphenyl, 4-(2-carboxyethyl)-phenyl, 4-[(E)-2-carboxyethenyl]-phenyl, 3-[(E)-2-carboxyethenyl]-phenyl, 3-[(E)-2-ethoxycarbonylethenyl]-phenyl, 3-[(E)-2-(*N*-methylcarbamoyl)ethenyl]-phenyl, 3-[(E)-2-carbamoylethenyl]-phenyl, 3-[(E)-2-(N-methyloxycarbamoyl)ethenyl]-phenyl, 3-(*N*-ethylcarbamoyl)-phenyl, 3-(*N*-benzylcarbamoyl)-phenyl, 4-(*N*-ethylcarbamoyl)-phenyl, 4-(*N*,*N*-dimethylcarbamoyl)-phenyl, or 4-(*N*-benzylcarbamoyl)-phenyl.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^3 is 2-methoxypyrimidin-5-yl, indolin-6-yl, 5-ethoxycarbonyl-pyridin-3-yl, 2,6-dimethoxypyridin-4-yl, benzofuran-2-yl, 5-acetyl-thiophen-2-yl, 5-cyano-pyridin-3-yl, 1-(*tert*-butoxy-dimethyl-silyl)-1*H*-indolin-3-yl, 5-carboxy-thiophen-2-yl, 6-methoxy-pyridin-3-yl, 2-amino-pyrimidin-5-yl, 1*H*-pyrazol-4-yl, 6-amino-pyridin-3-yl, 2-methoxycarbonyl-benzothiophen-5-yl, 2-carboxy-benzothiophen-5-yl, pyridin-3-yl, pyrimidin-5-yl, 5-carboxy-pyridin-3-yl, 5-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-pyridin-3-yl, 4-oxo-3-ethoxycarbonyl-1-(2-methoxyethyl)-1,4-dihydroquinolin-6-yl, 4-oxo-3-carboxy-1-(2-methoxyethyl)-1,4-dihydroquinolin-6-yl, 4-methoxy-thiazol-2-yl, 3-carboxy-quinolin-6-yl, 5-(*N*,*N*-dimethylcarbamoyl)-thiophen-2-yl, 5-(*N*-methylcarbamoyl)-thiophen-2-yl, 5-(*N*-benzylcarbamoyl)-thiophen-2-yl, 5-(piperdinocarbonyl)-thiophen-2-yl, 5-(3,3-difluoropiperdinocarbonyl)-thiophen-2-yl, 5-(*N*-benzylcarbamoyl)-pyridin-3-yl, 5-(*N'*-hydroxycarbamimidoyl)-pyridin-3-yl, or 5-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-pyridin-3-yl.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^3 is 1-ethyl -(2-methoxyethyl)-4-oxo-1,4-dihydroquinolin-6-yl-carboxylate or 1*H*-indol-6-yl.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^3 is a pyridin-3-yl or 2-oxo-pyridin-5-yl group wherein said pyridin-3-yl or 2-oxo-pyridin-5-yl group may be optionally substituted on carbon by one or more R^{14} and wherein the N of said 2-oxo-pyridin-5-yl is substituted by a group selected from R^{15}.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^{14}, for each occurrence, is independently a carboxy, C_{1-6}alkoxy, C_{1-6}alkylsulphonylcarbamoyl, C_{1-6}alkoxycarbamoyl, or C_{1-6}alkyl$S(O)_a$ wherein a is 0, 1 or 2.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^{15}, for each occurrence, is independently a C_{1-6}alkyl wherein said C_{1-6}alkyl is optionally substituted by C_{1-6}alkoxy or saturated heterocyclyl.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^{14}, for each occurrence, is

independently a carboxy, C_{1-3}alkoxy, C_{1-3}alkylsulphonylcarbamoyl, C_{1-3}alkoxycarbamoyl, or C_{1-3}alkylS(O)$_a$ wherein a is 0, 1 or 2.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^{15}, for each occurrence, is independently a C_{1-3}alkyl wherein said C_{1-3}alkyl is optionally substituted by C_{1-3}alkoxy or saturated heterocyclyl.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^{15}, for each occurrence, is independently a C_{1-3}alkyl wherein said C_{1-3}alkyl is optionally substituted by C_{1-3}alkoxy or morpholino.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^3 is a 6-membered heteroaryl containing at least one nitrogen atom wherein one of the carbon atoms of said 6-membered heteroaryl ring may be optionally substituted with O to form a –(CO)-, and further wherein said 6-membered heteroaryl may be optionally substituted on carbon by one or more R^{14} and when one of the carbon atoms of said 6-membered heteroaryl ring is substituted with O to form a –(CO)-, the nitrogen of that 6-membered heteroaryl is substituted by a group selected from R^{15}.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^3 is 2-oxo-3-carboxy-1-ethyl-pyridin-5-yl, 2-oxo-3-carboxy-1-(2-methoxyethyl)-pyridin-5-yl, 3-carboxy-6-(2-dimethylaminoethoxy)-pyridin-5-yl, 3-(*N*-2-hydroxyethylcarbamoyl)-pyridin-5-yl, 3-*N*-(2-methylsulfonylethyl)carbamoyl-pyridin-5-yl, 2-methoxy-3-carboxy-pyridin-5-yl, 3-*N*-methylcarbamoyl-pyridin-5-yl, 2-oxo-3-carboxy-1-methyl-pyridin-5-yl, 2-oxo-3-*N*-(methylsulfonyl)-carbamoyl-1-methyl-pyridin-5-yl, 3-*N*-methoxycarbamoyl-pyridin-5-yl, 3-carboxy-pyridin-5-yl, 2-oxo-3-carboxy-1-(2-morpholinoethyl)-pyridin-5-yl, 3-carboxy-2-methylsulphanyl-pyridin-5-yl, 3-carboxy-pyridin-5-yl, 2-methoxy-3-(*N*-methylsulfonylcarbamoyl)-pyridin-5-yl, and 2-methoxy-3-(*N*-ethylsulfonylcarbamoyl)-pyridin-5-yl.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein n is 1.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein n is 2.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein n is 3.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein n is 4.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein n is 4.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^4, for each occurrence, is independently a halo, C_{1-6}alkyl or C_{1-6}alkoxy.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein n is 2 and R^4, for each occurrence, is independently a halo, C_{1-6}alkyl or C_{1-6}alkoxy.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein n is 2 and R^4, for each occurrence, is independently a F, Cl, methyl or methoxy.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein R^4, for each occurrence, is independently selected from methyl, hydroxymethyl, fluoro, chloro, bromo, 1*H*-tetrazole-1-yl, methoxy, cyano, 5-methyl-1*H*-tetrazole-1-yl, 2-methoxyethoxy, nitro, morpholinosulfonyl, or trifluoromethyl.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein n is 2 and one R^4 is fluoro and the other is chloro.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein two adjacent R^4 together with ring B form 1*H*-indolinyl.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein:

X is N;

R^1 is a C_{1-6}alkyl which is optionally substituted with on carbon with one or more R^6;

R^2 is hydrogen;

R^3 is 5-carboxy-pyridin-3-yl, 5-ethoxycarbonyl-pyridin-3-yl, 3-[(E)-2-carboxyethenyl]-phenyl, 3-[(E)-2-ethoxycarbonylethenyl]-phenyl, 3-[(E)-2-(N-methylcarbamoyl)ethenyl]-phenyl, or 3-[(E)-2-carbamoylethenyl]-phenyl;

n is 2; and

R^4, for each occurrence is independently selected from a halo.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein:

X is N;

R^1 is n-propyl, 3-(*N*,*N*-dimethylamino)-propyl, 2-(pyridin-2-yl)-ethyl, 2-(pyridin-3-yl)-ethyl, or 2-(pyridin-4-yl)ethyl;

R^2 is hydrogen;

R^3 is 5-carboxy-pyridin-3-yl, 5-ethoxycarbonyl-pyridin-3-yl, 3-[(E)-2-carboxyethenyl]-phenyl, 3-[(E)-2-ethoxycarbonylethenyl]-phenyl, 3-[(E)-2-(*N*-methylcarbamoyl)ethenyl]-phenyl, or 3-[(E)-2-carbamoylethenyl]-phenyl;

n is 2; and

one of R^4 is fluoro and the other is chloro.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein:

X is N;

R^1 and R^2, together with the nitrogen to which they are attached, form pyrazol-1-yl wherein said pyrazol-1-yl may be optionally substituted on carbon by one or more R^8;

R^3 is a 6-membered heteroaryl containing at least one nitrogen atom wherein one of the carbon atoms of said 6-membered heteroaryl ring may be optionally substituted with O to form a –(CO)-, and further wherein said 6-membered heteroaryl may be optionally substituted on carbon by one or more R^{14} and when one of the carbon atoms of said 6-membered heteroaryl ring is substituted with O to form a –(CO)-, the nitrogen of that 6-membered heteroaryl is substituted by a group selected from R^{15};

n is 2;

R^4, for each occurrence, is independently a halo, C_{1-6}alkyl or C_{1-6}alkoxy;

R^8, for each occurrence, is independently a C_{1-6}alkyl or a C_{3-6}cycloalkyl wherein said R^8 is optionally substituted on carbon by one or more fluoro;

R^{14}, for each occurrence, is independently a carboxy, C_{1-6}alkoxy, C_{1-3}alkylsulphonylcarbamoyl, N-C_{1-3}alkylcarbamoyl, N-C_{1-3}alkoxycarbamoyl, or C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2 wherein said R^{14} may be optionally substituted on carbon by one or more hydroxy, $(C_{1-3}alkyl)_2N$, or C_{1-3}alkylsulfonyl; and

R^{15}, for each occurrence, is independently a C_{1-6}alkyl wherein said C_{1-6}alkyl is optionally substituted by C_{1-6}alkoxy or saturated heterocyclyl.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein:

X is N;

R^1 and R^2, together with the nitrogen to which they are attached, form pyrazol-1-yl wherein said pyrazol-1-yl may be optionally substituted on carbon by one or more R^8;

R^3 is a 6-membered heteroaryl containing at least one nitrogen atom wherein one of the carbon atoms of said 6-membered heteroaryl ring may be optionally substituted with O to form a –(CO)-, and further wherein said 6-membered heteroaryl may be optionally substituted on carbon by one or more R^{14} and when one of the carbon atoms of said 6-membered heteroaryl ring is substituted with O to form a –(CO)-, the nitrogen of that 6-membered heteroaryl is substituted by a group selected from R^{15};

n is 2;

R^4, for each occurrence, is independently a halo, C_{1-6}alkyl or C_{1-6}alkoxy;

R^8, for each occurrence, is independently a methyl, trifluoromethyl or a cyclopropyl;

R^{14}, for each occurrence, is independently a carboxy, C_{1-6}alkoxy, C_{1-3}alkylsulphonylcarbamoyl, N-C_{1-3}alkylcarbamoyl, N-C_{1-3}alkoxycarbamoyl, or C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2 wherein said R^{14} may be optionally substituted on carbon by one or more hydroxy, $(C_{1-3}alkyl)_2N$, or C_{1-3}alkylsulfonyl; and

R^{15}, for each occurrence, is independently a C_{1-6}alkyl wherein said C_{1-6}alkyl is optionally substituted by C_{1-6}alkoxy or saturated heterocyclyl.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein:

X is N;

R^1 and R^2, together with the nitrogen to which they are attached, form pyrazol-1-yl wherein said pyrazol-1-yl may be optionally substituted on carbon by one or more R^8;

R^3 is a pyridin-3-yl or 2-oxo-pyridin-5-yl group wherein said pyridin-3-yl or 2-oxo-pyridin-5-yl group may be optionally substituted on carbon by one or more R^{14} and wherein the N of said 2-oxo-pyridin-5-yl is substituted by a group selected from R^{15};

n is 2;

R^4, for each occurrence, is independently a halo, C_{1-3}alkyl or C_{1-3}alkoxy;

R^8, for each occurrence, is independently a C_{1-3}alkyl optionally substituted on carbon by one or more fluoro;

R^{14}, for each occurrence, is independently a carboxy, C_{1-3}alkoxy, C_{1-3}alkylsulphonylcarbamoyl, N-C_{1-3}alkylcarbamoyl, N-C_{1-3}alkoxycarbamoyl, or C_{1-3}alkylS(O)$_a$ wherein a is 0, 1 or 2, wherein said R^{14} may be optionally substituted on carbon by one or more hydroxy, $(C_{1-3}alkyl)_2N$-, or C_{1-3}alkylsulfonyl;

R^{15}, for each occurrence, is independently a C_{1-3}alkyl wherein said C_{1-3}alkyl is optionally substituted by C_{1-3}alkoxy or saturated heterocyclyl.

In another embodiment the invention provides compounds represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, wherein:

X is N;

R^1 and R^2, together with the nitrogen to which they are attached, form a heterocyclyl selected from1*H*-pyrazol-1-yl, 1*H*-benzotriazol-1-yl, 2*H*-benzotriazol-2-yl, and 1*H*-1,2,3-triazol-1-yl, wherein said heterocyclyl may be optionally substituted on carbon by one or more R^8; wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^3 is 5-carboxy-pyridin-3-yl, 5-ethoxycarbonyl-pyridin-3-yl, 3-[(E)-2-carboxyethenyl]-phenyl, 3-[(E)-2-ethoxycarbonylethenyl]-phenyl, 3-[(E)-2-(*N*-methylcarbamoyl)ethenyl]-phenyl, or 3-[(E)-2-carbamoylethenyl]-phenyl;

n is 2;

R^4, for each occurrence is independently a halo;

R^8, for each occurrence, is independently hydroxy, hydroxymethyl, morpholino, N-methylcarbamoyl, fluoro, methoxy, methyl, acetamido, trifluoromethyl, chloro, or pyridin-4-yl;

R^9, for each occurrence, is independently a C_{1-6}alkyl, 2-methoxyethyl, acetyl, *N*,*N*-dimethylcarbamoyl, cyclopropylcarbonyl, methylsulfonyl or *tert*-butoxycarbonyl.

Particular compounds of the invention are the compounds of the Examples, and pharmaceutically acceptable salts thereof, each of which provides a further independent aspect of the invention. For those examples which are themselves in the form of a salt, a further independent aspect of the invention is those specific salts as well as other pharmaceutically acceptable salts thereof and the free bases therof. In further aspects, the present invention also comprises any two or more compounds of the Examples.

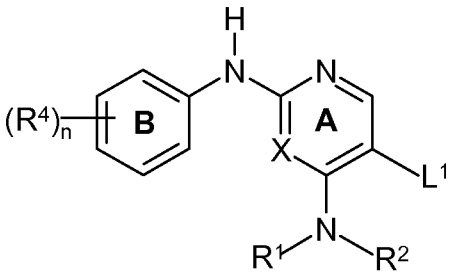
In another embodiment the invention provides compounds of Examples 319, 675, 677, 679, 681, 683, 684, 761, 815, 854, 861, 863, 909, 918, 919, 1019, 1026, 1075, 1076, 1086, 1087, 1088, 1143, 1145, 1152, 1159 and 1160, and or a pharmaceutically acceptable salt thereof.

In another embodiment the invention provides compounds of Examples 319, 638, 675, 677, 679, 681, 683, 684, 761, 815, 854, 861, 863, 909, 918, 919, 1019, 1026, 1075, 1076, 1086, 1087, 1088, 1143, 1145, 1152, 1159 and 1160, and or a pharmaceutically acceptable salt thereof.

In another embodiment, the invention provides pharmaceutical compositions comprising a pharmaceutically acceptable excipient or carrier and a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof.

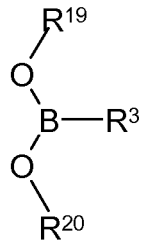
In a further aspect the present invention provides a process for preparing a compound of formula **(I)**, or a pharmaceutically-acceptable salt thereof, wherein variable groups in the schemes below are as defined in formula **(I)** unless otherwise specified. In general, the compounds of the invention can be prepared by adding Ring B, $-NR^1R^2$ and R^3 to a pyrimidine or pyridine core in any order. For example, formula *(I)* can be prepared by the following methods:

Process a: Reacting a compound of formula **(i)**:



(i)

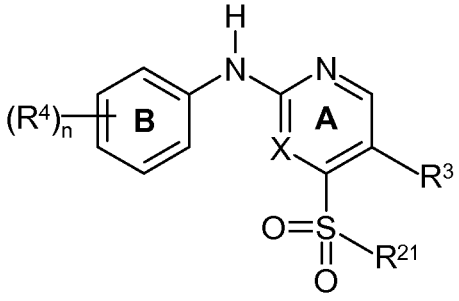
with a compound of formula **(ii)**:



(ii)

in the presence of a palladium(0) catalyst and a base, such as sodium carbonate, wherein L^1 is a displaceable group such as a halo; and R^{19} and R^{20} are each independently hydrogen or a C_{1-6}alkyl; or R^{19} and R^{20} together form a C_{2-4}alkylene bridge which may be optionally substituted with one or more independently selected C_{1-4}alkyl groups.

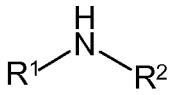
Process B: Reacting a compound of formula **(iii)**:



(iii)

wherein R^{21} is a C_{1-6}alkyl or a C_{6-14}aryl;

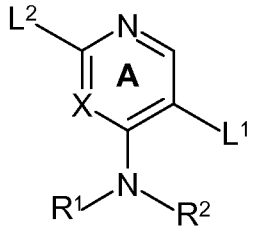
with a compound represented by formula **(iv)**:



(iv)

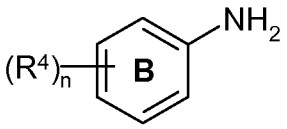
in the presence of a base, such as NaH, diisopropylethylamine, or NaOH. In some instances, it may be necessary to heat the reaction.

Compounds represented by formula **(i)** can be prepared by reacting a compound represented by formula **(v)**:



(v)

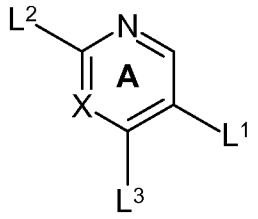
with a compound represented by formula **(vi)**:



(vi)

in the presence of an acid, such as HCl and heat, wherein L^1 and L^2 are each, independently, displaceable groups, such as a halo.

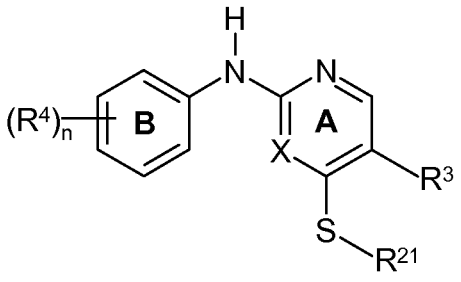
A compound represented by formula **(v)** can be prepared from a pyrimidine or pyridine derivative by reacting a compound represented by formula **(vii)**:



(vii)

with a compound represented by formula **(iv)** in the presence of a base and optionally heat, wherein L^1, L^2 and L^3 are each, independently, displaceable groups, such as a halo.

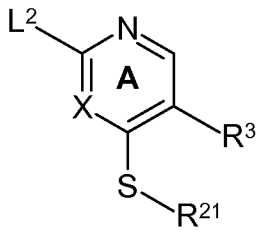
Compounds represented by formula **(iii)** can be prepared by treating a compound represented by formula **(viii)**:



(viii)

with a peroxide, such as 3-chloroperoxybenzoic acid.

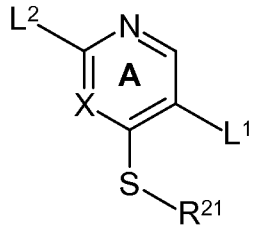
Compounds represented by formula **(viii)** can be prepared by reacting a compound represented by formula **(ix)**:



(ix)

with a compound represented by formula **(vi)** in the presence of an acid, such as HCl and heat.

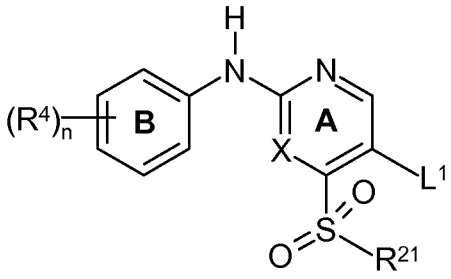
Compounds represented by formula **(ix)** can be prepared by reacting a compound represented by formula **(x)**:



(x)

with a compound represented by formula **(ii)** in the presence of a palladium(0) catalyst and a base, such as sodium carbonate.

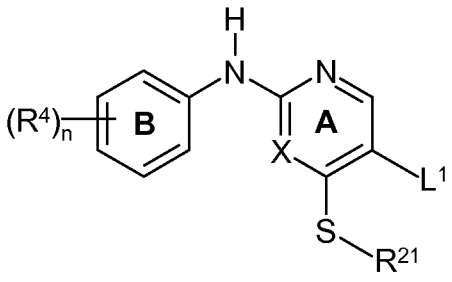
Alternatively, compounds represented by formula **(iii)** can be prepared by reacting a compound represented by formula **(xi)**:



(xi)

with a compound of formula **(ii)** in the presence of a palladium(0) catalyst and a base, such as sodium carbonate.

Compounds represented by formula **(xi)** can be prepared by treating a compound represented by formula **(xii)**:



(xii)

with a peroxide, such as 3-chloroperoxybenzoic acid.

Compounds represented by formula **(xii)** can be prepared by reacting a compound represented by formula **(x)** with an aniline derivative represented by formula **(vi)** in the presence of an acid, such as HCl and heat.

Compounds represented by formulas **(ii)**, **(iv)**, **(vi)**, **(vii)** and **(x)** can be purchased or prepared by standard methods known in the art.

The formation of a pharmaceutically-acceptable salt is within the skill of an ordinary organic chemist using standard techniques.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. The reagents used to introduce such ring substituents are either commercially available or are made by processes known in the art.

Introduction of substituents into a ring may convert one compound of the formula **(I)** into another compound of the formula **(I)**. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents, oxidation of substituents, esterification of substituents, amidation of substituents, formation of heteroaryl rings. Particular examples of aromatic substitution reactions include the introduction of alkoxides, diazotization reactions followed by introduction of thiol group, alcohol group, halogen group. Examples of modifications include; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl. (See Advanced Organic Chemistry, 4th Edition, by Jerry March, published by John Wiley & Sons 1992). In one embodiment, an ester substituent on a compound of formula **(I)** may be converted to a carboxylic acid by treating the ester with a base, such as sodium hydroxide, barium hydroxide, or trimethyltin hydroxide. In another embodiment, a carboxylic acid

substituent on a compound of formula **(I)** may be converted to an amide by reacting the carboxylic acid group with a primary or secondary amine in the presence of a peptide coupling reagent, such as O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), dicyclohexylcarbodiimide (DCC), or 1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide (EDC). The reagents and reaction conditions for such procedures are well known in the chemical art.

The skilled organic chemist will be able to use and adapt the information contained and referenced within the above references, and accompanying Examples therein and also the Examples herein, to obtain necessary starting materials, and products. If not commercially available, the necessary starting materials for the procedures such as those described above may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, or techniques which are analogous to the above described procedure or the procedures described in the examples. It is noted that many of the starting materials for synthetic methods as described above are commercially available and/or widely reported in the scientific literature, or could be made from commercially available compounds using adaptations of processes reported in the scientific literature. The reader is further referred to Advanced Organic Chemistry, 4th Edition, by Jerry March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in compounds. The instances where protection is necessary or desirable are known to those skilled in the art, as are suitable methods for such protection. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Greene, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991).

Examples of a suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, a silyl group such as trimethylsilyl or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively a silyl group such as trimethylsilyl may be removed, for example, by fluoride or by aqueous acid; or an arylmethyl

group such as a benzyl group may be removed, for example, by hydrogenation in the presence of a catalyst such as palladium-on-carbon.

A suitable protecting group for an amino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine or 2-hydroxyethylamine, or with hydrazine.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or for example, an allyl group which may be removed, for example, by use of a palladium catalyst such as palladium acetate.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art, or they may be removed during a later reaction step or work-up.

When an optically active form of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using an optically active starting material (formed, for example, by asymmetric induction of a suitable reaction step), or by resolution of a racemic form of the compound or intermediate using a standard procedure, or

by chromatographic separation of diastereoisomers (when produced). Enzymatic techniques may also be useful for the preparation of optically active compounds and/or intermediates.

Similarly, when a pure regioisomer of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using a pure regioisomer as a starting material, or by resolution of a mixture of the regioisomers or intermediates using a standard procedure.

Enzyme Potency Testing Methods

E.coli GyrB ATPase Inhibition Activity: Compounds may be tested for inhibition of *E. coli* GyrB ATPase activity using an ammonium molybdate/malachite green-based phosphate detection assay (Lanzetta, P. A., L. J. Alvarez, P. S. Reinach, and O. A. Candia, 1979, 100: 95-97). Assays are performed in multiwell plates in 30µl reactions containing: 50 mM Hepes buffer pH 7.5, 75 mM ammonium acetate, 8.0 mM magnesium chloride, 0.5 mM ethylenediaminetetraacetic acid, 5% glycerol, 1 mM 1,4-Dithio-DL-threitol, 200 nM bovine serum albumin, 1.6 µg/ml sheared salmon sperm DNA, 400 pM *E. coli* GyrA, 400 pM *E. coli* GyrB, 250 µM ATP, and the test compound in dimethylsulfoxide. Reactions are quenched with 30 µl of ammonium molybdate/malachite green detection reagent containing 1.2 mM malachite green hydrochloride, 8.5 mM ammonium molybdate tetrahydrate, and 1 M hydrochloric acid. Plates can be read in an absorbance plate reader at 650 nm and percent inhibition values are calculated using dimethylsulfoxide (2%)-containing reactions as 0% inhibition and EDTA-containing (2.4 µM) reactions as 100% inhibition controls. An IC_{50} measurement of compound potency for each compound can be determined from reactions performed in the presence of 10 different compound concentrations.

E. coli Topoisomerase IV ATPase Inhibition Activity: Compounds may be tested for inhibition of *E. coli* topoisomerase IV ATPase activity as described above for *E. coli* GyrB except the 30µl reactions contained the following: 20 mM TRIS buffer pH 8, 50 mM ammonium acetate, 8 mM magnesium chloride, 5% glycerol, 5 mM 1,4-Dithio-DL-threitol, 0.005% Brij-35, 5 µg/ml sheared salmon sperm DNA, 500 pM *E. coli* ParC, 500 pM *E. coli* ParE, 160 µM ATP, and test compound in dimethylsulfoxide. An IC_{50} measurement of compound potency for each compound can be determined from reactions performed in the presence of 10 different compound concentrations.

S. aureus GyrB ATPase Inhibition Activity: Compounds may be tested for inhibition of *S. aureus* GyrB ATPase activity using an ammonium molybdate/malachite green-based phosphate detection assay (Lanzetta, P. A., L. J. Alvarez, P. S. Reinach, and O. A. Candia, 1979, 100: 95-97). Assays are performed in multiwell plates in 30µl reactions containing: 50 mM Hepes buffer pH 7.5, 75 mM ammonium acetate, 8.0 mM magnesium chloride, 0.5 mM ethylenediaminetetraacetic acid, 5% glycerol, 1.0 mM 1,4-Dithio-DL-threitol, 200 nM bovine serum albumin, 1.0 µg/ml sheared salmon sperm DNA, 250 pM *E. coli* GyrA, 250 pM *S. aureus* GyrB, 250 µM ATP, and test compound in dimethylsulfoxide. Reactions are quenched with 30 µl of ammonium molybdate/malachite green detection reagent containing 1.2 mM malachite green hydrochloride, 8.5 mM ammonium molybdate tetrahydrate, and 1 M hydrochloric acid. Plates are read in an absorbance plate reader at 650 nm and percent inhibition values can be calculated using dimethylsulfoxide (2%)-containing reactions as 0% inhibition and EDTA-containing (2.4 µM) reactions as 100% inhibition controls. An IC_{50} measurement of compound potency for each compound can be determined from reactions performed in the presence of 10 different compound concentrations.

S. pneumoniae Topoisomerase IV ATPase Inhibition Activity: Compounds may be tested for inhibition of *S. pneumoniae* ParE ATPase activity using an ammonium molybdate/malachite green-based phosphate detection assay (Lanzetta, P. A., L. J. Alvarez, P. S. Reinach, and O. A. Candia, 1979, 100: 95-97). Assays are performed in multiwell plates in 30µl reactions containing: 20 mM Tris buffer pH 8.0, 50 mM ammonium acetate, 8.0 mM magnesium chloride, 0.5 mM ethylenediaminetetraacetic acid, 5% glycerol, 5 mM 1,4-Dithio-DL-threitol, 0.005 % Brij-35, 5 µg/ml sheared salmon sperm DNA, 1.25 nM *S. pneumoniae* ParE, 160 µM ATP, and test compound in dimethylsulfoxide. Reactions are quenched with 30 µl of ammonium molybdate/malachite green detection reagent containing 1.2 mM malachite green hydrochloride, 8.5 mM ammonium molybdate tetrahydrate, and 1 M hydrochloric acid. Plates are read in an absorbance plate reader at 650 nm and percent inhibition values are calculated using dimethylsulfoxide (2%)-containing reactions as 0% inhibition and EDTA-containing (20 µM) reactions as 100% inhibition controls. An IC_{50} measurement of compound potency for each compound can be determined from reactions performed in the presence of 10 different compound concentrations.

Many of the compounds of the invention were tested in an assay substantially similar to the assays described above for measuring the inhibition of *E.coli* GyrB ATPase, *E. coli*

Topoisomerase IV ATPase, *S. aureus* GyrB ATPase, and *S. pneumoniae* Topoisomerase IV ATPase, and had IC_{50} values of <200μM in one or more assays.

The compounds of the examples (**Ex**) were tested in an assay substantially similar to the assay described above for measuring the inhibition of *S. pneumoniae* Topoisomerase IV ATPase and were found to have a percent inhibition (**% Inh**) of *S. pneumoniae* Topoisomerase IV ATPase as shown in the table below.

Ex	% Inh (13 μM)	Ex	% Inh (13 μM)	Ex	% Inh (13 μM)
1	5.14	393	82	785	100
2	77.79	394	94	786	No data
3	56.76	395	No data	787	97
4	93.06	396	No data	788	No data
5	103.92	397	No data	789	99
6	101.54	398	No data	790	No data
7	98.67	399	No data	791	97
8	87.61	400	No data	792	No data
9	59.99	401	No data	793	100
10	99.35	402	No data	794	No data
11	18.19	403	30	795	100
12	107.54	404	81	796	No data
13	101.67	405	85	797	100
14	100.45	406	99	798	No data
15	100.40	407	86	799	100
16	55.30	408	100	800	99
17	54.79	409	77	801	No data
18	96.62	410	100	802	100
19	95.81	411	No data	803	100
20	74.62	412	No data	804	No data
21	71.67	413	No data	805	100
22	85.33	414	No data	806	No data
23	95.77*	415	No data	807	100
24	98.10*	416	No data	808	100

Ex	% Inh (13 μM)	Ex	% Inh (13 μM)	Ex	% Inh (13 μM)
25	90.49*	417	No data	809	100
26	91.67*	418	No data	810	100
27	89.22*	419	No data	811	100
28	62.56	420	No data	812	100
29	99.74*	421	No data	813	100
30	No data	422	No data	814	100
31	86.00*	423	No data	815	100
32	91.12*	424	No data	816	100
33	80.97	425	No data	817	100
34	84.28	426	No data	818	100
35	58.29	427	No data	819	100
36	No data	428	No data	820	100
37	76.29	429	No data	821	100
38	62.33	430	No data	822	100
39	63.01	431	No data	823	100
40	72.38	432	No data	824	100
41	72.67	433	No data	825	100
42	77.52	434	No data	826	96
43	74.34	435	51	827	100
44	78.37	436	69	828	100
45	81.93	437	75	829	100
46	93.48*	438	81	830	100
47	74.75	439	62	831	89
48	79.84*	440	85	832	100
49	85.56	441	74	833	100
50	77.81	442	No data	834	98
51	88.84	443	85	835	95
52	69.48	444	7	836	94
53	70.48	445	34	837	94
54	77.50	446	No data	838	99
55	44.37	447	50	839	100

Ex	% Inh (13 μM)	Ex	% Inh (13 μM)	Ex	% Inh (13 μM)
56	46.29	448	82	840	99
57	No data	449	No data	841	No data
58	58.02	450	86	842	97
59	51.83	451	70	843	No data
60	72.29	452	76	844	100
61	74.81	453	92	845	92
62	70.98	454	92	846	97
63	69.89	455	No data	847	97
64	65.39	456	26	848	100
65	75.92	457	28	849	No data
66	62.11	458	No data	850	No data
67	53.39	459	100	851	98
68	72.92	460	100	852	100
69	76.96	461	100	853	No data
70	86.60	462	85	854	100
71	66.66	463	67	855	94
72	52.62	464	36	856	100
73	89.64	465	59	857	100
74	102.75	466	78	858	No data
75	97.60	467	76	859	100
76	79.28	468	80	860	No data
77	83.04	469	64	861	100
78	80.87	470	49	862	No data
79	No data	471	84	863	100
80	No data	472	100	864	No data
81	72.58	473	62	865	No data
82	80.14	474	100	866	No data
83	No data	475	93	867	No data
84	79.57	476	100	868	6
85	66.79	477	100	869	93
86	91.06*	478	100	870	100

Ex	% Inh (13 μM)	Ex	% Inh (13 μM)	Ex	% Inh (13 μM)
87	96.55	470	3	871	100
88	101.86	480	No data	872	100
89	85.32*	481	No data	873	100
90	24.59	482	99	874	100
91	83.09	483	66	875	98
92	3.56	484	No data	876	0
93	79.62	485	85	877	100
94	77.52	486	No data	878	88
95	-0.48	487	84	879	91
96	62.18	488	92	880	91
97	75.87	489	97	881	97
98	59.40	490	100	882	100
99	81.99	491	87	883	99
100	74.23	492	No data	884	100
101	8.69	493	9	885	100
102	73.52	494	No data	886	0.008*
103	79.47	495	No data	887	100
104	76.25	496	100	888	No data
105	79.20*	497	61	889	No data
106	40.76	498	41	890	91
107	No data	499	34	891	41
108	-18.05	500	83	892	100
109	52.40	501	No data	893	99
110	27.63	502	10	894	No data
111	-13.87	503	147*	895	No data
112	0.15	504	83	896	No data
113	34.30	505	19	897	100
114	No data	506	33	898	100
115	28.78	507	74	899	97
116	82.02	508	0	900	100
117	73.36	509	100	901	97

Ex	% Inh (13 μM)	Ex	% Inh (13 μM)	Ex	% Inh (13 μM)
118	80.57	510	97	902	97
119	32.04	511	100	903	No data
120	73.88	512	100	904	No data
121	49.63	513	No data	905	No data
122	57.89	514	No data	906	No data
123	66.40	515	No data	907	No data
124	31.26	516	98*	908	No data
125	17.53	517	100	909	100
126	35.73	518	33	910	3.4*
127	26.47	519	No data	911	58
128	-16.23	520	No data	912	99
129	74.86	521	No data	913	100
130	No data	522	No data	914	100
131	No data	523	No data	915	100
132	No data	524	No data	916	99
133	No data	525	No data	917	100
134	No data	526	No data	918	100
135	No data	527	No data	919	99
136	No data	528	100	920	100
137	No data	529	100	921	99
138	No data	530	100	922	100
139	80.08	531	100	923	100
140	83.48	532	100	924	97
141	63.33	533	100	925	88
142	86.20	534	49	926	100
143	88.58	535	100	927	98
144	76.37	536	100	928	85
145	77.41	537	100	929	82
146	79.71	538	100	930	72
147	65.42	539	100	931	100
148	120.46	540	100	932	100

Ex	% Inh (13 μM)	Ex	% Inh (13 μM)	Ex	% Inh (13 μM)
149	82.21	541	97	933	100
150	53.34	542	85	934	100
151	50.07	543	68	935	100
152	0.54	544	100	936	100
153	No data	545	100	937	17
154	No data	546	100	938	91
155	No data	547	71	939	No data
156	No data	548	95	940	76
157	No data	549	94	941	54
158	No data	550	100	942	100
159	No data	551	100	943	No data
160	No data	552	100	944	No data
161	74.79	553	No data	945	No data
162	No data	554	No data	946	No data
163	54.95	555	No data	947	No data
164	46.95	556	No data	948	No data
165	56.92	557	No data	949	No data
166	37.43	558	No data	950	No data
167	31.15	559	No data	951	No data
168	66.36	560	No data	952	No data
169	34.23	561	99	953	No data
170	45.98	562	100	954	No data
171	3.62	563	100	955	No data
172	-32.84	564	92	956	100
173	34.72	565	100	957	100
174	52.08	566	52	958	93
175	80.01	567	100	959	93
176	88.95	568	100	960	100
177	68.87	569	No data	961	100
178	83.02	570	91	962	98
179	93.94	571	17	963	100

Ex	% Inh (13 μM)	Ex	% Inh (13 μM)	Ex	% Inh (13 μM)
180	-56.89	572	100	964	40
181	No data	573	100	965	100
182	No data	574	96	966	100
183	No data	575	100	967	100
184	No data	576	100	968	94
185	No data	577	No data	969	100
186	No data	578	No data	970	100
187	No data	579	No data	971	100
188	No data	580	No data	972	100
189	No data	581	No data	973	No data
190	No data	582	No data	974	89
191	No data	583	No data	975	100
192	No data	584	No data	976	No data
193	No data	585	100	977	74
194	No data	586	100	978	82
195	No data	587	100	979	No data
196	No data	588	100	980	No data
197	No data	589	100	981	No data
198	No data	590	100	982	100
199	No data	591	100	983	No data
200	No data	592	100	984	No data
201	No data	593	No data	985	No data
202	No data	594	No data	986	No data
203	No data	595	No data	987	30
204	No data	596	No data	988	69
205	No data	597	No data	989	100
206	No data	598	82	990	100
207	No data	599	94	991	No data
208	No data	600	100	992	No data
209	No data	601	100	993	100
210	No data	602	100	994	No data

Ex	% Inh (13 μM)	Ex	% Inh (13 μM)	Ex	% Inh (13 μM)
211	76.62	603	No data	995	89
212	14.52	604	100	996	No data
213	55.80	605	No data	997	100
214	101.05*	606	No data	998	100
215	No data	607	No data	999	No data
216	96.35*	608	No data	1000	64
217	82.44	609	No data	1001	No data
218	80.91	610	No data	1002	100
219	78.99	611	No data	1003	No data
220	78.95	612	No data	1004	No data
221	81.00	613	No data	1005	No data
222	76.18	614	No data	1006	No data
223	77.38	615	100	1007	No data
224	78.53	616	99	1008	83
225	81.13	617	100	1009	92
226	79.47	618	98	1010	81
227	78.99	619	100	1011	No data
228	78.47	620	96	1012	No data
229	85.03*	621	100	1013	No data
230	79.57	622	98	1014	No data
231	81.45	623	100	1015	No data
232	80.98*	624	89	1016	94
233	75.42	625	No data	1017	90
234	73.21	626	No data	1018	No data
235	81.24	627	No data	1019	100
236	73.58	628	No data	1020	No data
237	85.41	629	No data	1021	No data
238	72.64	630	No data	1022	No data
239	85.07	631	No data	1023	No data
240	45.83	632	No data	1024	100
241	71.51	633	No data	1025	98

Ex	% Inh (13 μM)	Ex	% Inh (13 μM)	Ex	% Inh (13 μM)
242	61.27	634	No data	1026	98
243	83.49	635	100	1027	94
244	76.30	636	100	1028	No data
245	83.10	637	100	1029	No data
246	74.86	638	100	1030	100
247	42.22	639	100	1031	No data
248	66.09	640	100	1032	No data
249	70.79	641	100	1033	20
250	74.44	642	100	1034	96
251	79.92	643	100	1035	51
252	81.77	644	84	1036	100
253	75.11	645	No data	1037	No data
254	16.75	646	100	1038	No data
255	72.85	647	No data	1039	90
256	78.79	648	100	1040	86
257	83.81	649	No data	1041	100
258	87.99	650	No data	1042	49
259	104.12	651	No data	1043	No data
260	102.75*	652	No data	1044	No data
261	106.27	653	86	1045	No data
262	80.45	654	No data	1046	No data
263	86.20	655	89	1047	No data
264	87.75	656	78	1048	100
265	84.87	657	100	1049	99
266	109.42	658	96	1050	No data
267	87.34	659	100	1051	0
268	83.00	660	No data	1052	0
269	77.98	661	No data	1053	0
270	87.69	662	No data	1054	0
271	86.60	663	No data	1055	No data
272	81.11	664	No data	1056	85

Ex	% Inh (13 μM)	Ex	% Inh (13 μM)	Ex	% Inh (13 μM)
273	94.36*	665	No data	1057	83
274	87.96	666	No data	1058	87
275	134.39	667	56	1059	85
276	80.31*	668	85	1060	87
277	85.88	669	68	1061	92
278	77.03	670	100	1062	91
279	80.39	671	92	1063	94
280	83.38	672	100	1064	100
281	95.81	673	100	1065	68
282	117.09	674	No data	1066	100
283	89.92	675	100	1067	98
284	69.38	676	No data	1068	100
285	61.89	677	100	1069	100
286	89.83	678	100	1070	93
287	97.17*	679	No data	1071	100
288	82.87*	680	100	1072	95
289	88.25	681	100	1073	99
290	80.47*	682	100	1074	100
291	90.12	683	100	1075	97
292	80.95	684	100	1076	99
293	85.27	685	100	1077	99
294	73.17	686	100	1078	100
295	82.65	687	100	1079	100
296	77.61	688	99	1080	100
297	127.50	689	99	1081	100
298	80.68	690	100	1082	100
299	98.73	691	No data	1083	99
300	82.35	692	97	1084	100
301	72.19	693	97	1085	100
302	82.95	694	100	1086	92
303	81.98	695	100	1087	100

Ex	% Inh (13 μM)	Ex	% Inh (13 μM)	Ex	% Inh (13 μM)
304	55.83	696	No data	1088	100
305	89.24	697	No data	1089	100
306	84.84*	698	No data	1090	100
307	80.62	699	No data	1091	100
308	101.10*	700	No data	1092	100
309	69.39	701	No data	1093	100
310	80.03	702	No data	1094	99
311	81.76	703	No data	1095	100
312	101.14*	704	No data	1096	100
313	80.35	705	No data	1097	100
314	83.37	706	No data	1098	100
315	62.78	707	No data	1099	100
316	80.03	708	No data	1100	75
317	84.88*	709	No data	1101	82
318	92.27	710	No data	1102	96
319	90.59*	711	100	1103	76
320	100.54*	712	No data	1104	0.014*
321	83.69	713	No data	1105	82
322	74.95	714	No data	1106	21*
323	99.55*	715	No data	1107	<0.5*
324	76.90	716	No data	1108	18
325	102.26	717	No data	1109	28
326	101.43	718	No data	1110	99
327	98.99	719	No data	1111	88
328	70.79	720	100	1112	71
329	115.51	721	100	1113	72
330	106.22	722	93	1114	100
331	59.79	723	94	1115	93
332	62.06	724	No data	1116	97
333	69.81	725	No data	1117	No data
334	103.60	726	100	1118	No data

Ex	% Inh (13 μM)	Ex	% Inh (13 μM)	Ex	% Inh (13 μM)
335	76.47	727	No data	1119	No data
336	83.69	728	100	1120	79
337	64.44	729	89	1121	99
338	58.42	730	No data	1122	100
339	84.35	731	No data	1123	100
340	83.27	732	100	1124	42
341	87.22	733	100	1125	51
342	77.02	734	No data	1126	100
343	-22.31	735	No data	1127	100
344	82.01	736	100	1128	67
345	82.65	737	97	1129	83
346	79.54	738	No data	1130	99
347	42.22	739	No data	1131	100
348	85.73*	740	No data	1132	100
349	83.61	741	No data	1133	100
350	69.03	742	100	1134	100
351	82.81	743	94	1135	100
352	26.72	744	100	1136	99
353	83.90	745	100	1137	100
354	80.46	746	No data	1138	94
355	86.62*	747	No data	1139	96
356	86.45	748	No data	1140	100
357	85.27	749	No data	1141	100
358	63.03	750	No data	1142	100
359	86.13*	751	No data	1143	100
360	111.70	752	No data	1144	100
361	94.76	753	No data	1145	100
362	107.49	754	100	1146	100
363	57.94	755	100	1147	100
364	112.09	756	56	1148	24
365	110.14	757	19	1149	100

Ex	% Inh (13 μM)	Ex	% Inh (13 μM)	Ex	% Inh (13 μM)
366	80.48	758	98	1150	100
367	103.97	759	100	1151	100
368	104.93	760	100	1152	100
369	122.37	761	100	1153	100
370	128.96	762	No data	1154	No data
371	82.25	763	No data	1155	No data
372	80.94	764	No data	1156	88
373	82.85	765	No data	1157	No data
374	81.16	766	No data	1158	No data
375	75.94	767	No data	1159	100
376	87.16	768	No data	1160	100
377	78.89	769	No data	1161	81
378	75.17	770	100	1162	100
379	No data	771	100	1163	100
380	37	772	81	1164	100
381	No data	773	55	1165	No data
382	No data	774	100	1166	100
383	No data	775	100	1167	100
384	No data	776	100	1168	100
385	No data	777	100	1169	100
386	No data	778	No data	1170	100
387	No data	779	No data	1171	No data
388	72	780	100	1172	100
389	85	781	99	1173	100
390	No data	782	No data	1174	100
391	No data	783	No data	1175	99
392	74	784	70	1176	100

Note: Examples which are marked with "*" are an average of two or more data points.

Bacterial Susceptibility Testing Methods

Compounds may be tested for antimicrobial activity by susceptibility testing in liquid media. Compounds may be dissolved in dimethylsulfoxide and tested in 10 doubling dilutions in the susceptibility assays. The organisms used in the assay may be grown overnight on suitable agar media and then suspended in a liquid medium appropriate for the growth of the organism. The suspension can be a 0.5 McFarland and a further 1 in 10 dilution can be made into the same liquid medium to prepare the final organism suspension in 100 μL. Plates can be incubated under appropriate conditions at 37 °C for 24 hrs prior to reading. The Minimum Inhibitory Concentration (MIC) may be determined as the lowest drug concentration able to reduce growth by 80% or more.

In an assay comparable to the above, compounds of the invention had MICs as shown in the table below:

Example	Spn 548(gram +) (μM)	Spy 838 (gram +) (μM)	Mca 445 (gram -) (μM)
46	3.13	8.84	3.13
176	6.25	12.5	0.78
211	25.00	25.00	12.5

According to a further feature of the invention there is provided a compound of the formula **(I)**, or a pharmaceutically-acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

In one embodiment, the invention provides a method of treating a bacterial infection in an animal, such as a human, comprising administering to the animal or human an effective amount of a compound of any one of formulas **(I)**, or a pharmaceutically acceptable salt thereof.

We have found that compounds of the present invention inhibit bacterial DNA gyrase and / or topoisomerase IV and are therefore of interest for their antibacterial effects. In one aspect of the invention the compounds of the invention inhibit bacterial DNA gyrase and are therefore of interest for their antibacterial effects. In one aspect of the invention, the compounds of the invention inhibit topoisomerase IV and are therefore of interest for their antibacterial effects. In one aspect of the invention, the compounds of the invention inhibit both DNA gyrase and topoisomerase IV and are therefore of interest for their antibacterial

effects. Thus, the compounds of the invention are useful in treating or preventing bacterial infections.

In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Acinetobacter baumanii*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Acinetobacter haemolyticus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Acinetobacter junii*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Acinetobacter johnsonii*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Acinetobacter lwoffi*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Bacteroides bivius*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Bacteroides fragilis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Burkholderia cepacia*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Campylobacter jejuni*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Chlamydia pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Chlamydia urealyticus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Chlamydophila pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Clostridium difficile*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Enterobacter aerogenes*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Enterobacter cloacae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Enterococcus faecalis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Enterococcus faecium*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Escherichia coli*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Gardnerella vaginalis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Haemophilus parainfluenzae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Haemophilus influenzae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Helicobacter pylori*. In one aspect of the invention an "infection" or "bacterial infection" refers to an

infection caused by *Klebsiella pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Legionella pneumophila*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Methicillin-resistant *Staphylococcus aureus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Methicillin-susceptible *Staphylococcus aureus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Moraxella catarrhalis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Morganella morganii*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Mycoplasma pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Neisseria gonorrhoeae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Penicillin-resistant *Streptococcus pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Penicillin-susceptible *Streptococcus pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus magnus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus micros*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus anaerobius*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus asaccharolyticus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus prevotii*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus tetradius*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus vaginalis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Proteus mirabilis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Pseudomonas aeruginosa*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Quinolone-Resistant *Staphylococcus aureus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Quinolone-Resistant *Staphylococcus epidermis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Salmonella typhi*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Salmonella paratyphi*. In

one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Salmonella enteritidis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Salmonella typhimurium*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Serratia marcescens*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Staphylococcus aureus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Staphylococcus epidermidis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Staphylococcus saprophyticus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Streptoccocus agalactiae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Streptococcus pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Streptococcus pyogenes*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Stenotrophomonas maltophilia*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Ureaplasma urealyticum*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Vancomycin-Resistant *Enterococcus faecium*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Vancomycin-Resistant *Enterococcus faecalis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Vancomycin-Resistant *Staphylococcus aureus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Vancomycin-Resistant *Staphylococcus epidermis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Mycobacterium tuberculosis. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Clostridium perfringens. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Klebsiella oxytoca. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Neisseria miningitidis. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Fusobacterium spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Peptococcus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Proteus vulgaris. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Coagulase-negative Staphylococcus

(including Staphylococcus lugdunensis, Staphylococcus capitis, Staphylococcus hominis, and Staphylococcus saprophyticus).

In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Acinetobacter spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Bacteroides spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Burkholderia spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Campylobacter spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Chlamydia spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Chlamydophila spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Clostridium spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Enterobacter spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Enterococcus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Escherichia spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Gardnerella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Haemophilus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Helicobacter spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Klebsiella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Legionella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Moraxella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Morganella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Mycoplasma spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Neisseria spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Peptostreptococcus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Proteus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Pseudomonas spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Salmonella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Serratia spp.

In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Staphylococcus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Streptoccocus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Stenotrophomonas spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Ureaplasma spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by aerobes. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by obligate anaerobes. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by facultative anaerobes. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by gram-positive bacteria. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by gram-negative bacteria. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by gram-variable bacteria. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by atypical respiratory pathogens. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Enterics. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Shigella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Citrobacter.

In one aspect of the invention "infection" or "bacterial infection" refers to a gynecological infection. In one aspect of the invention "infection" or "bacterial infection" refers to a respiratory tract infection (RTI). In one aspect of the invention "infection" or "bacterial infection" refers to a sexually transmitted disease. In one aspect of the invention "infection" or "bacterial infection" refers to a urinary tract infection. In one aspect of the invention "infection" or "bacterial infection" refers to acute exacerbation of chronic bronchitis (ACEB). In one aspect of the invention "infection" or "bacterial infection" refers to acute otitis media. In one aspect of the invention "infection" or "bacterial infection" refers to acute sinusitis. In one aspect of the invention "infection" or "bacterial infection" refers to an infection caused by drug resistant bacteria. In one aspect of the invention "infection" or "bacterial infection" refers to catheter-related sepsis. In one aspect of the invention "infection" or "bacterial infection" refers to chancroid. In one aspect of the invention "infection" or "bacterial infection" refers to chlamydia. In one aspect of the invention "infection" or "bacterial infection" refers to community-acquired pneumonia (CAP). In one

aspect of the invention "infection" or "bacterial infection" refers to complicated skin and skin structure infection. In one aspect of the invention "infection" or "bacterial infection" refers to uncomplicated skin and skin structure infection. In one aspect of the invention "infection" or "bacterial infection" refers to endocarditis. In one aspect of the invention "infection" or "bacterial infection" refers to febrile neutropenia. In one aspect of the invention "infection" or "bacterial infection" refers to gonococcal cervicitis. In one aspect of the invention "infection" or "bacterial infection" refers to gonococcal urethritis. In one aspect of the invention "infection" or "bacterial infection" refers to hospital-acquired pneumonia (HAP). In one aspect of the invention "infection" or "bacterial infection" refers to osteomyelitis. In one aspect of the invention "infection" or "bacterial infection" refers to sepsis. In one aspect of the invention "infection" or "bacterial infection" refers to syphilis. In one aspect of the invention "infection" or "bacterial infection" refers to ventilator-associated pneumonia. In one aspect of the invention "infection" or "bacterial infection" refers to intraabdominal infections. In one aspect of the invention "infection" or "bacterial infection" refers to gonorrhoeae. In one aspect of the invention "infection" or "bacterial infection" refers to meningitis. In one aspect of the invention "infection" or "bacterial infection" refers to tetanus. In one aspect of the invention "infection" or "bacterial infection" refers to tuberculosis.

In one embodiment, it is expected that the compounds of the present invention will be useful in treating bacterial infections including, but not limited to community-acquired pneumoniae, hospital-acquired pneumoniae, skin & skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci.

According to a further feature of the present invention there is provided a method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically-acceptable salt thereof.

According to a further feature of the invention there is provided a method for inhibition of bacterial DNA gyrase and / or topoisomerase IV in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an

effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof as defined hereinbefore.

According to a further feature of the invention there is provided a method of treating a bacterial infection in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof as defined hereinbefore.

According to a further feature of the invention there is provided a method of treating a bacterial infection selected from community-acquired pneumoniae, hospital-acquired pneumoniae, skin & skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococciin a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof as defined hereinbefore.

A further feature of the present invention is a compound of formula **(I)**, and pharmaceutically acceptable salts thereof for use as a medicament. Suitably the medicament is an antibacterial agent.

According to a further aspect of the invention there is provided the use of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an anti-bacterial effect in a warm-blooded animal such as a human being.

According to a further aspect of the invention there is provided the use of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in inhibition of bacterial DNA gyrase and / or topoisomerase IV in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of a bacterial infection in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, in the manufacture of

a medicament for use in the treatment of a bacterial infection selected from community-acquired pneumoniae, hospital-acquired pneumoniae, skin & skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci in a warm-blooded animal such as a human being.

According to a further aspect of the invention there is provided a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the production of an anti-bacterial effect in a warm-blooded animal such as a human being.

According to a further aspect of the invention there is provided a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in inhibition of bacterial DNA gyrase and / or topoisomerase IV in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of a bacterial infection in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of a bacterial infection selected from community-acquired pneumoniae, hospital-acquired pneumoniae, skin & skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci in a warm-blooded animal such as a human being.

In order to use a compound of the formula **(I)**, or a pharmaceutically-acceptable salt thereof, (hereinafter in this section relating to pharmaceutical composition "a compound of this invention") for the therapeutic (including prophylactic) treatment of mammals including humans, in particular in treating infection, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula **(I)**, or a pharmaceutically-acceptable salt thereof, and a pharmaceutically-acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula **(I)**, as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier for use in producing an anti-bacterial effect in an warm-blooded animal, such as a human being.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula **(I)**, as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier for use in inhibition of bacterial DNA gyrase and / or topoisomerase IV in an warm-blooded animal, such as a human being.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula **(I)**, as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier for use in the treatment of a bacterial infection in an warm-blooded animal, such as a human being.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula **(I)**, as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier for use in the treatment of a bacterial infection selected from community-acquired pneumoniae, hospital-acquired pneumoniae, skin & skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci in an warm-blooded animal, such as a human being.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more coloring, sweetening, flavoring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavoring and/or coloring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurized aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile

fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The compounds of the invention described herein may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination. Suitable classes and substances may be selected from one or more of the following:

i) other antibacterial agents for example macrolides e.g. erythromycin, azithromycin or clarithromycin; quinolones e.g. ciprofloxacin or levofloxacin; ß-lactams e.g. penicillins e.g. amoxicillin or piperacillin; cephalosporins e.g. ceftriaxone or ceftazidime; carbapenems, e.g. meropenem or imipenem etc; aminoglycosides e.g. gentamicin or tobramycin; or oxazolidinones; and/or

ii) anti-infective agents for example, an antifungal triazole e.g. or amphotericin; and/or

iii) biological protein therapeutics for example antibodies, cytokines, bactericidal/permeability-increasing protein (BPI) products; and/or

iv) efflux pump inhibitors.

Therefore, in a further aspect of the invention there is provided a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, and a chemotherapeutic agent selected from:

i) one or more additional antibacterial agents; and/or

ii) one or more anti-infective agents; and/or

iii) biological protein therapeutics for example antibodies, cytokines, bactericidal/permeability-increasing protein (BPI) products; and/or

iv) one or more efflux pump inhibitors.

In another embodiment, the invention relates to a method of treating a bacterial infection in an animal, such as a human, comprising administering to the animal an effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, and a chemotherapeutic agent selected from:

i) one or more additional antibacterial agents; and/or

ii) one or more anti-infective agents; and/or

iii) biological protein therapeutics for example antibodies, cytokines, bactericidal/permeability-increasing protein (BPI) products; and/or

iv) one or more efflux pump inhibitors.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration, the severity of the illness being treated, and whether or not an additional chemotherapeutic agent is administered in combination with a compound of the invention. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, the severity of the illness being treated, and whether or not an additional chemotherapeutic agent is administered in combination with a compound of the invention. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

As noted above, one embodiment of the present invention is directed to treating or preventing diseases caused by bacterial infections, wherein the bacteria comprise a GyrB ATPase or topoisomerase IV ATPase enzyme. "Treating a subject with a disease caused by a

bacterial infection" includes achieving, partially or substantially, one or more of the following: the reducing or amelioration of the progression, severity and/or duration of the infection, arresting the spread of an infection, ameliorating or improving a clinical symptom or indicator associated with a the infection (such as tissue or serum components), and preventing the reoccurrence of the infection.

As used herein, the terms "preventing a bacterial infection" refer to the reduction in the risk of acquiring the infection, or the reduction or inhibition of the recurrence of the infection. In a preferred embodiment, a compound of the invention is administered as a preventative measure to a patient, preferably a human, before a surgical procedure is preformed on the patient to prevent infection.

As used herein, the term "effective amount" refers to an amount of a compound of this invention for treating or preventing a bacterial infection is an amount which is sufficient to prevent the onset of an infection, reduce or ameliorate the severity, duration, or progression, of an infection, prevent the advancement of an infection, cause the regression of an infection, prevent the recurrence, development, onset or progression of a symptom associated with an infection, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy.

In addition to its use in therapeutic medicine, compounds of formula **(I)**, and their pharmaceutically acceptable salts, are also useful as pharmacological tools in the development and standardization of *in-vitro* and *in-vivo* test systems for the evaluation of the effects of inhibitors of DNA gyrase and / or topoisomerase IV in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and particular embodiments of the compounds of the invention described herein also apply.

Experimental

The invention is now illustrated but not limited by the following Examples in which unless otherwise stated :-

(i) evaporations were carried out by rotary evaporation in-vacuo and work-up procedures were carried out after removal of residual solids by filtration;

(ii) operations were generally carried out at ambient temperature, that is typically in the range 18-26 °C and without exclusion of air unless otherwise stated, or unless the skilled person would otherwise work under an inert atmosphere;

(iii) column chromatography (by the flash procedure) was used to purify compounds and was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;

(iv) yields are given for illustration only and are not necessarily the maximum attainable; the structure of the end-products of the invention were generally confirmed by NMR and mass spectral techniques; proton magnetic resonance spectra is quoted and was generally determined in DMSO-d_6 unless otherwise stated using a Bruker DRX-300 spectrometer operating at a field strength of 300 MHz or a Bruker Avance-II spectrometer operating at a field strength of 400 MHz. Chemical shifts are reported in parts per million downfield from tetramethysilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; d, doublet; AB or dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; t, triplet, m, multiplet; br, broad; fast-atom bombardment (FAB) mass spectral data were generally obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected or using Agilent 1100series LC/MSD equipped with Sedex 75ELSD, run in atmospheric pressure chemical ionisation mode and, where appropriate, either positive ion data or negative ion data were collected; mass spectra were run with an electron energy of 70 electron volts in the chemical ionization (CI) mode using a direct exposure probe; where indicated ionization was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported;

(vi) each intermediate was purified to the standard required for the subsequent stage and was characterised in sufficient detail to confirm that the assigned structure was correct; purity was assessed by high pressure liquid chromatography, thin layer chromatography, or NMR and identity was determined by infra-red spectroscopy (IR), mass spectroscopy or NMR spectroscopy as appropriate;

(vii) Where unspecified, the total amount of solvent(s) used in a given transformation was such that the concentration of the limiting substrate in the reaction mixture was between 0.1 to 0.5 Molar.

(viii) the following abbreviations may be used:

ACN is acetonitrile;

$CDCl_3$ is deuterated chloroform;

DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene;

DCM is dichloromethane;

DIEA is diisopropyl ethylamine;

DMF is *N,N*-dimethylformamide;

DMSO is dimethylsulfoxide;

EDC is 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide;

EtOAc is ethyl acetate;

EtOH is ethanol;

HATU is N-[(dimethylamino)-1H,2,3-triazolo[4,5-b-]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide;

HOBT is 1-hydroxybenzotriazole;

MeOH is methanol;

MS is mass spectroscopy;

NMP is N-Methylpyrrolidone;

RT or rt is room temperature;

SM is starting material;

T_3P is *n*-propyl phosphonic acid cyclic anhydride

TBTU is *O*-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate;

TFA is trifluoroacetic acid;

TFAA is trifluoroacetic anhydride;

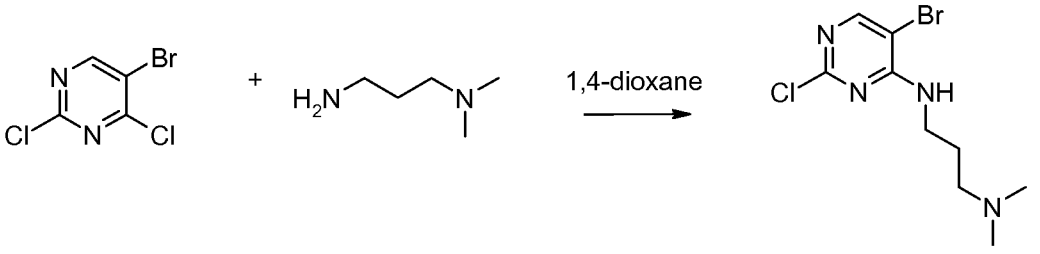
THF is tetrahydrofuran;

(ix) temperatures are quoted as °C; and

(x) vol designates 1 mL of solvent or reagent per g of material used as the limiting agent.

Intermediates

Intermediate 1: N'-(5-Bromo-2-chloro-pyrimidin-4-yl)-N,N-dimethyl-propane-1,3-diamine



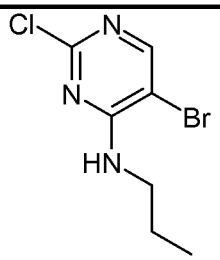
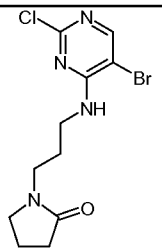
Intermediate 1

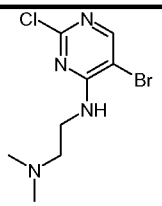
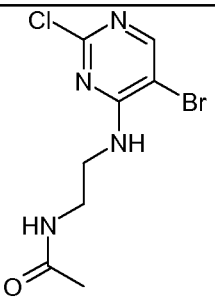
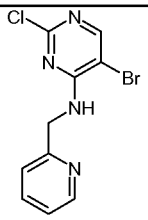
To a stirred solution of N,N-dimethyl-propane-1,3-diamine (40 mmol, 5 mL) in dioxane (40 mL) at room temperature under nitrogen atmosphere was added 5-bromo-2,4-dichloro-pyrimidine (6.6 g, 30 mmol) as a solid. Further dilution (ethyl acetate 30 mL) became necessary as the reaction progressed. The mixture was stirred overnight; the un-reacted hydrochloride salt of N,N-dimethyl-propane-1,3-diamine was removed by filtration. The filtrate was concentrated to give the title compound as a yellow solid in 86% yield (7.6 g).

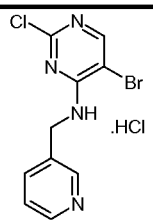
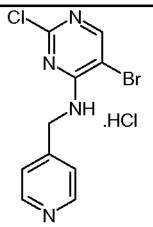
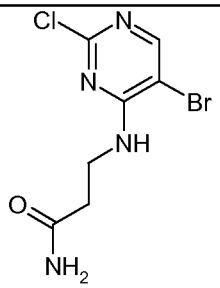
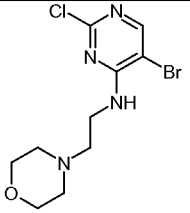
MS(ES): 293.1(M) and 295.1(M+2) for $C_9H_{14}BrClN_4$.

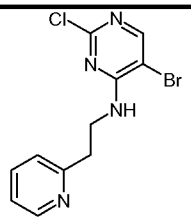
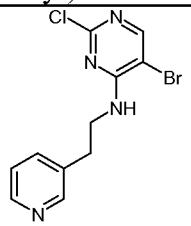
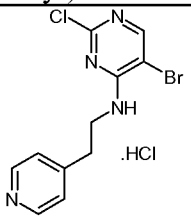
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.77-1.80 (m, 2H), 2.32 (s, 6H), 2.56 (t, J = 5.76 Hz, 2H), 3.60 (dt, J = 9.36, 4.68 Hz, 2H), 8.05 (s, 1H), 8.7 (br s, 1H).

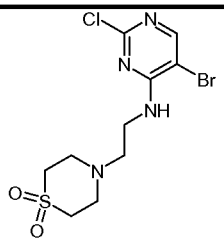
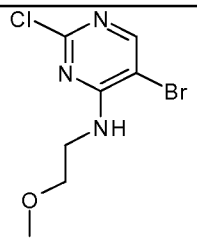
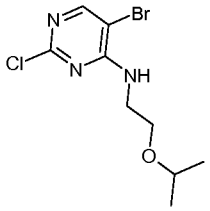
The following intermediates were prepared using the general method described above for **Intermediate 1** using 5-bromo-2,4-dichloro-pyrimidine and the starting material (SM) indicated.

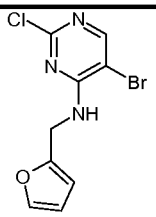
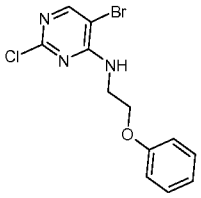
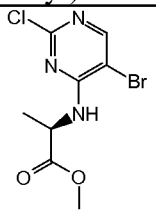
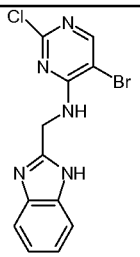
Int	Compound	Data	SM
2	 (5-Bromo-2-chloro-pyrimidin-4-yl)-propyl-amine	^{1}H NMR 400 MHz, DMSO-d_6 : δ 0.9 (m, 3H), 1.5–1.6 (m, 2H), 3.28–3.33 (m, 2H), 7.74 (br s, 1H), 8.2 (s, 1H).	n-propylamine
3	 1-[3-(5-Bromo-2-chloro-pyrimidin-4-ylamino)-propyl]-pyrrolidin-2-one	MS(ES):333 (M) and 334 (M+1) for $C_{11}H_{14}BrClN_4O$. 400 MHz, DMSO-d_6 : δ 1.7 (m, 2H), 1.95 (m, 2H), 2.21 (t, J = 4 Hz, 2H), 3.2 (m, 2H), 3.39 – 3.27 (m, 4H), 7.73 (br s, 1H), 8.22 (s, 1H).	1-(3-Amino-propyl)-pyrrolidin-2-one

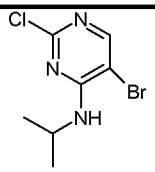
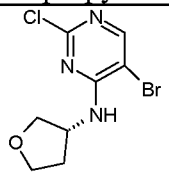
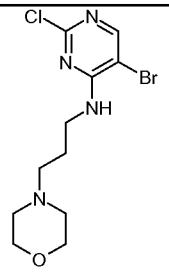
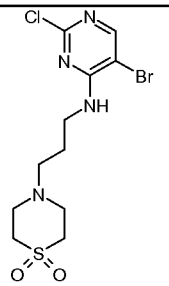
Int	Compound	Data	SM
4	 N'-(5-Bromo-2-chloro-pyrimidin-4-yl)-N,N-dimethyl-ethane-1,2-diamine	The compound was taken to the next step without any characterization.	N,N-dimethyl-ethane-1,2-diamine
5	 N-[2-(5-Bromo-2-chloro-pyrimidin-4-ylamino)-ethyl]-acetamide	The compound was taken to the next step without any characterization.	N-(2-Amino-ethyl)-acetamide
6	 (5-Bromo-2-chloro-pyrimidin-4-yl)-(pyridin-2-ylmethyl)-amine	MS(ES): 299(M) and 301(M+2) for $C_{10}H_8BrClN_4$.	C-Pyridin-3-yl-methylamine

Int	Compound	Data	SM
7	 (5-Bromo-2-chloro-pyrimidin-4-yl)-(pyridin-3-ylmethyl)-amine HCl salt	The compound was taken to the next step without any characterization.	C-Pyridin-3-yl-methylamine
8	 (5-Bromo-2-chloro-pyrimidin-4-yl)-(pyridin-4-ylmethyl)-amine HCl salt	The compound was taken to the next step without any characterization.	C-Pyridin-4-yl-methylamine
9	 3-(5-Bromo-2-chloro-pyrimidin-4-ylamino)-propionamide	^{1}H NMR 300 MHz, DMSO-d_6 : δ 2.37 (t, J = 7.2Hz, 2H), 3.50 – 3.56 (m, 2H), 6.91 (br s, 1H), 7.39 (br s, 1H), 7.70 (br s, 1H), 8.23 (s, 1H).	3-Amino-propionamide
10	 (5-Bromo-2-chloro-pyrimidin-4-yl)-(2-morpholin-4-yl-ethyl)-amine	The compound was taken to the next step without any characterization.	2-Morpholin-4-yl-ethylamine

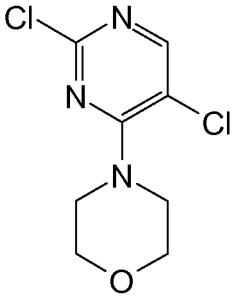
Int	Compound	Data	SM
11	 (5-Bromo-2-chloro-pyrimidin-4-yl)-(2-pyridin-2-yl-ethyl)-amine	The compound was taken to the next step without any characterization.	2-Pyridin-2-yl-ethylamine
12	 (5-Bromo-2-chloro-pyrimidin-4-yl)-(2-pyridin-3-yl-ethyl)-amine	The compound was taken to the next step without any characterization.	2-Pyridin-3-yl-ethylamine
13	 (5-Bromo-2-chloro-pyrimidin-4-yl)-(2-pyridin-4-yl-ethyl)-amine HCl salt	MS(ES): 313.59 (M) and 315 (M+2) for $C_{11}H_{10}BrClN_4$. 400 MHz, DMSO-d_6 : 3.18 (m, 2H), 3.74 (m, 2H), 7.8 (m, 1H), 7.95 (d, J = 6.64Hz, 2H), 8.24 (s, 1H), 8.82 (d, J = 6.64 Hz, 2H).	2-Pyridin-4-yl-ethylamine

Int	Compound	Data	SM
14	 (5-Bromo-2-chloro-pyrimidin-4-yl)-[2-(1,1-dioxo-1l6-thiomorpholin-4-yl)-ethyl]-amine	MS(ES): 369.7(M) and 371(M+2) for $C_{10}H_{14}BrClN_4O_2S$. 400 MHz, DMSO-d_6 : δ 2.68 (t, *J* = 6.52 Hz, 2H), 2.96 (m, 4H), 3.05 (m, 4H), 3.46 (q, *J* = 6.36 Hz, 2H), 7.61 (t, *J* = 5.60 Hz, 1H), 8.24 (s, 1H).	2-(1,1-Dioxo-1λ^6-thiomorpholin-4-yl)-ethylamine
15	 (5-Bromo-2-chloro-pyrimidin-4-yl)-(2-methoxy-ethyl)-amine	The compound was taken to the next step on the basis of ^{1}H NMR. 400 MHz DMSO-d_6 : δ 1.33 (t, *J* = 7.1 Hz, 3H), 3.25 (s, 3H), 3.52 (q, *J* = 5.4 Hz, 4H), 4.36 (q, *J* = 7.1 Hz, 2H), 6.9 (brs, 1H), 7.29 (t, *J* = 9.12 Hz, 1H), 7.6 (m, 1H), 7.86 (s, 1H), 8.2(m, *J* = 2.7 Hz, 2H), 8.77 (d, *J* = 2.2Hz, 1H), 9.04 (d, *J* = 2 Hz, 1H), 9.48 (br s, 1H).	2-Methoxy-ethylamine
16	 (5-Bromo-2-chloro-pyrimidin-4-yl)-(2-isopropoxy-ethyl)-amine	The compound was taken to the next step without any characterization	2-Isopropoxy-ethylamine

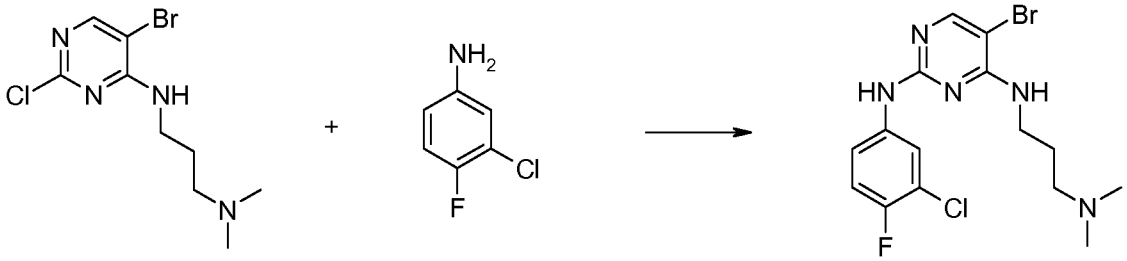
Int	Compound	Data	SM
17	 (5-Bromo-2-chloro-pyrimidin-4-yl)-(furan-2-ylmethyl)-amine	MS(ES): 288 (M) and 290(M+2) for $C_9H_7BrClN_3O$. 400 MHz DMSO-d_6 : δ 4.54 (d, *J* = 5.88 Hz, 1H), 6.25 (d, *J* = 3.16 Hz, 1H), 6.37-6.38 (m, 1H), 7.57 (t, *J* = 0.92 Hz, 1H), 8.23 (t, *J* = 5.88 Hz, 1H), 8.28 (s, 1H).	C-Furan-2-yl-methylamine
18	 (5-Bromo-2-chloro-pyrimidin-4-yl)-(2-phenoxy-ethyl)-amine	The compound was taken to the next step without any characterization.	2-Phenoxy-ethylamine
19	 Methyl (2*R*)-2-[(5-bromo-2-chloropyrimidin-4-yl)amino]propanoate	MS(ES): 294 (M) and 296(M+2) for $C_8H_9BrClN_3O_2$. 400 MHz $CDCl_3$ δ : 1.55 (d, *J* = 7.08 Hz, 3H), 3.81 (s, 3H), 4.81 (m, 1H), 6.14 (d, *J* = 6.16 Hz, 1H), 8.18 (s, 1H).	2R-Amino-propionic acid methyl ester
20	 (1H-Benzoimidazol-2-ylmethyl)-(5-bromo-2-chloro-pyrimidin-4-yl)-amine	MS(ES): 338 (M) and 340 (M+2) for $C_{12}H_9BrClN_5$. 300 MHz, DMSO-d_6: δ 4.79 (d, *J* = 5.79 Hz, 2H), 7.13 (m, 2H), 7.47 (d, *J* = 3.8 Hz, 2H), 8.3 (m, 1H), 12.24 (br s, 1H).	C-(1H-Benzoimidazol-2-yl)-methylamine

Int	Compound	Data	SM
21	 (5-Bromo-2-chloro-pyrimidin-4-yl)-isopropyl-amine	300 MHz, DMSO-d_6 : δ 1.18 (d, J = 6.6 Hz, 6H), 4.24 (m, 1H), 7.31 (d, J = 7.5 Hz, 1H), 8.21 (s, 1H).	Isopropyl-amine
22	 5-bromo-2-chloro-N-[(3R)-oxolan-3-yl]pyrimidin-4-amine	MS(ES): 279(M+H) for $C_8H_9BrClN_3O$. 300 MHz $CDCl_3$ δ : 1.11 (m, 1H), 2.33 (m, 1H), 3.69-4.00 (m, 4H), 4.68 (br. m, 1H), 5.56 (br. s, 1H), 8.08 (s, 1H).	(3R)-oxolan-3-amine
23	 (5-Bromo-2-chloro-pyrimidin-4-yl)-(3-morpholin-4-yl-propyl)-amine	The compound was taken to the next step without any characterization.	3-Morpholin-4-yl-propylamine
24	 (5-Bromo-2-chloro-pyrimidin-4-yl)-[3-(1,1-dioxo-1l6-thiomorpholin-4-yl)-propyl]-amine	MS(ES): 383(M) and 385(M+2) for $C_{11}H_{16}BrClN_4O_2S$. 400 MHz, CD_3OD : δ 1.79-1.86 (m, 2H), 2.62 (t, J = 6.56 Hz, 2H), 3.01-3.03 (m, 4H), 3.12-3.14 (m, 4H), 3.58 (t, J = 6.96 Hz, 1H), 8.12 (s, 1H).	3-(1,1-Dioxo-1λ^6-thiomorpholin-4-yl)-propylamine

The following intermediates were prepared using the general method described above for **Intermediate 1** using the starting materials (SM) indicated.

Int	Compound	Data	SM
25	 4-(2,5-dichloropyrimidin-4-yl)morpholine	MS: ES+ 234 for $C_8H_9Cl_2N_3O$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 3.60 - 3.81 (m, 8 H) 8.32 (s, 1 H)	2,4,5-trichloro pyrimidine and morpholine

Intermediate 26: 5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(3-dimethylamino-propyl)-pyrimidine-2,4-diamine



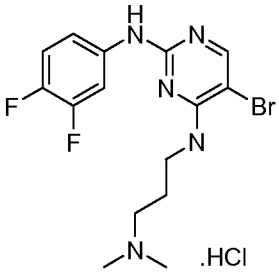
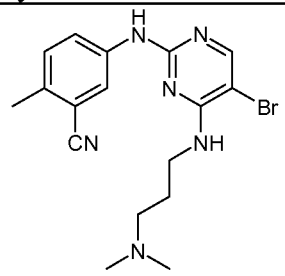
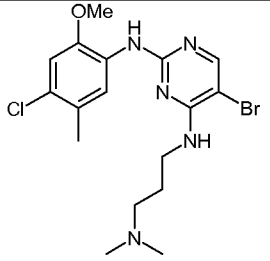
Intermediate 1 **Intermediate 26**

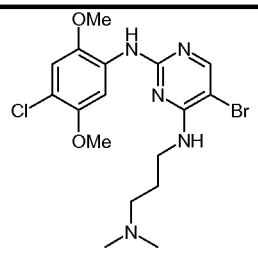
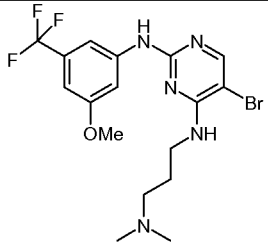
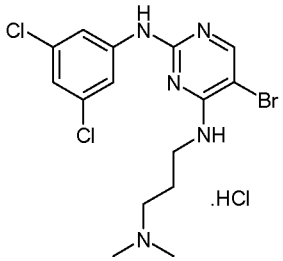
A solution of N'-(5-Bromo-2-chloro-pyrimidin-4-yl)-N,N-dimethyl-propane-1,3-diamine (**Intermediate 1**, 10 g, 34 mmol), 3-chloro-4-fluoroaniline (34 mmol, 4.95 g) and 2.6 M HCl in 1,4-dioxane (40 mL) was warmed to 100 °C with constant stirring. The reaction was monitored by TLC. Upon completion of reaction, the mixture was cooled to room temperature. The white solid was filtered off, washed with n-butanol and ether to afford the product as a fluffy white solid in 73 % yield (24 mmol; 10 g).

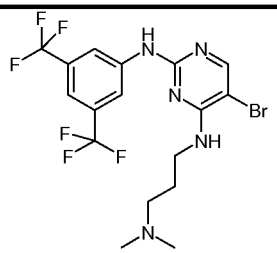
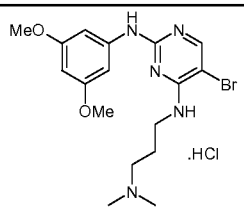
MS(ES): 402 (M) and 404 (M+2) for $C_{15}H_{18}BrClFN_5$

^{1}H-NMR (400 MHz, DMSO-d6): 1.95-1.98 (m, 2H), 2.72 (s, 3H), 2.73 (s, 3H), 3.03-3.07 (m, 2H), 3.43-3.48 (m, 2H), 7.37 (t, J = 9.20 Hz, 1H), 7.54 (m, 1H), 8.02 (dd, J = 6.80, 2.40 Hz, 1H), 8.13 (s, 1H), 9.80 (s, 1H), 10 (s, 1H).

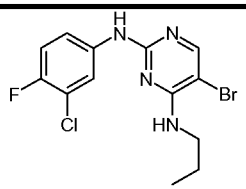
The following intermediates were prepared using the general method described above for **Intermediate 26** using N'-(5-Bromo-2-chloro-pyrimidin-4-yl)-N,N-dimethyl-propane-1,3-diamine **Intermediate 1** and the starting material (SM) indicated.

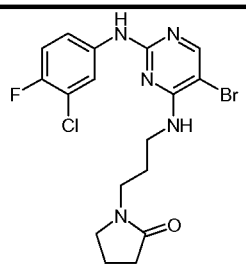
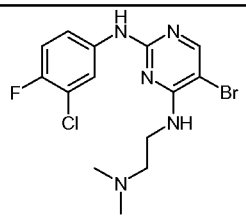
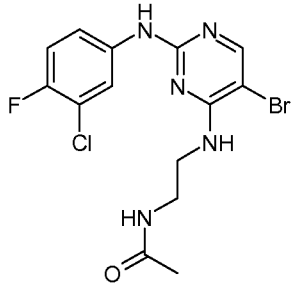
Int	Compound	Data	SM
27	 5-Bromo-N^2-(3,4-difluoro-phenyl)-N^4-(3-dimethylamino-propyl)-pyrimidine-2,4-diamine hydrochloride salt	MS(ES): 388(M+2) for $C_{15}H_{18}BrF_2N_5$. 400 MHz, DMSO- d_6: δ 1.99 (t, J = 7.4 Hz, 2H), 2.69 (s, 3H), 2.70 (s, 3H), 3.02 (m, 2H), 3.47-3.48 (m, 2H), 7.36-7.38 (m, 1H), 7.42-7.47(m, 1H), 7.80 (ddd, J = 14.86, 6.58, 3.40 Hz, 1H), 8.24 (br s, 2H), 10.5 (br s, 1H), 10.7 (br s, 1H).	3,4-Difluoro-phenylamine
28	 5-[5-Bromo-4-(3-dimethylamino-propylamino)-pyrimidin-2-ylamino]-2-methyl-benzonitrile	MS(ES): 389(M) for $C_{17}H_{21}BrN_6$. 400 MHz, CD_3OD: δ 1.91-1.95 (m, 2H), 2.41 (s, 6H), 2.47 (s, 3H), 2.64-2.67 (m, 2H), 3.56 (t, J = 8 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.6 (dd, J = 4.0, 8.0 Hz, 1H), 7.95 (s, 1H), 8.29 (d, 1H).	5-Amino-2-methyl-benzonitrile
29	 5-Bromo-N^2-(4-chloro-2-methoxy-5-methyl-phenyl)-N^4-(3-dimethylamino-propyl)-pyrimidine-2,4-diamine	MS(ES): 428(M) for $C_{17}H_{23}BrClN_5O$. 400 MHz, DMSO- d_6: δ 1.60-1.80(m, 2H), 2.14 (s, 6H), 2.25 (s, 3H), 2.30-2.40 (m, 2H), 3.40-3.50 (m, 2H), 3.83 (s, 3H), 7.04 (s, 1H), 7.5 (br s, 1H), 7.60 (s, 1H), 7.99 (s, 1H), 8.19 (s, 1H).	4-Chloro-2-methoxy-5-methyl-phenylamine

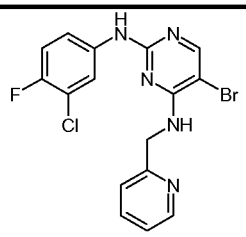
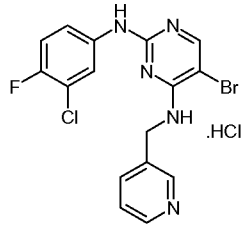
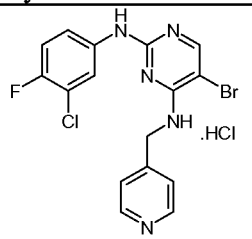
Int	Compound	Data	SM
30	 5-Bromo-N^2-(4-chloro-2,5-dimethoxy-phenyl)-N^4-(3-dimethylamino-propyl)-pyrimidine-2,4-diamine	MS(ES): 444.7(M) for $C_{17}H_{23}BrClN_5O_2$. 400 MHz, DMSO- d_6: δ 1.70-1.73(m, 2H), 2.20 (s, 6H), 2.25 (s, 3H), 2.30-2.40 (m, 2H), 3.46-3.47 (m, 2H), 3.80 (s, 3H), 3.82 (s, 3H), 7.08 (s, 1H), 7.61 (br s, 1H), 8.02 (s, 1H), 8.19 (s, 1H).	4-Chloro-2,5-dimethoxy-phenylamine
31	 5-Bromo-N^4-(3-dimethylamino-propyl)-N^2-(3-methoxy-5-trifluoromethyl-phenyl)-pyrimidine-2,4-diamine	MS(ES): 448(M) and 450(M+2) for $C_{17}H_{21}BrF_3N_5O$ 400 MHz, CD_3OD: δ 2.08-2.12 (m, 2H), 2.87 (s, 6H), 3.14-3.18 (m, 2H), 3.67 (t, J = 6.64 Hz, 2H), 3.92 (s, 3H), 7.13 (s, 1H), 7.38 (t, J = 1.84 Hz, 1H), 7.55 (s, 1H), 8.15 (s, 1H).	3-Methoxy-5-trifluoromethyl-phenylamine
32	 5-Bromo-N^2-(3,5-dichloro-phenyl)-N^4-(3-dimethylamino-propyl)-pyrimidine-2,4-diamine hydrodrochloride salt	MS(ES): 418 (M) and 420(M+2) for $C_{15}H_{18}BrCl_2N_5$. 400 MHz, DMSO-d6: δ 1.97-2.04 (m, 2H), 2.71 (s, 6H), 3.03-3.08 (br s, 2H), 3.46-3.51 (m, 2H), 7.13 (d, J = 1.2 Hz, 1H), 7.65 (br s, 1H), 7.82 (d, J = 1.6 Hz, 1H), 8.16 (d, J = 1.2 Hz, 1H), 10.0 (br s, 1H), 10.4 (br s, 1H).	3,5-Dichloro-phenylamine

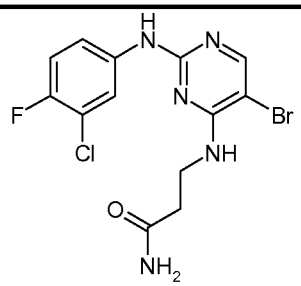
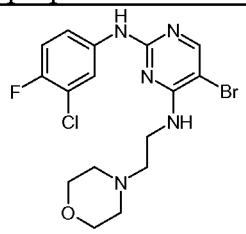
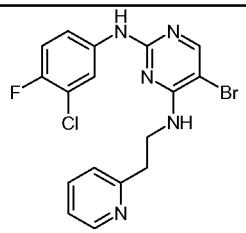
Int	Compound	Data	SM
33	 N^2-(3,5-Bis-trifluoromethyl-phenyl)-5-bromo-N^4-(3-dimethylamino-propyl)-pyrimidine-2,4-diamine	MS(ES): 486.4(M) for $C_{17}H_{18}BrF_6N_5$. 400 MHz, DMSO-d6: δ 1.69-1.76 (m, 2H), 2.15 (s, 6H), 2.34 (t, J = 6.4 Hz, 2H), 3.48 (t, J = 6.4 Hz, 2H), 7.52 (s, 1H), 7.73 (t, J = 4.8 Hz, 1H), 8.1 (s, 1H), 8.47 (s, 2H), 9.96 (s, 1H).	3,5-Bis-trifluoromethyl-phenylamine
34	 5-Bromo-N^2-(3,5-dimethoxy-phenyl)-N^4-(3-dimethylamino-propyl)-pyrimidine-2,4-diamine hydrodrochloride salt	MS(ES): 410(M) and 412 (M+2)for $C_{17}H_{24}BrN_5O_2$. 400 MHz, CD_3OD: δ 2.09-2.13 (m, 2H), 2.88 (s, 6H), 3.16-3.20 (m, 2H), 3.65 (t, J = 6.8 Hz, 2H), 3.83 (s, 6H), 6.49 (t, J = 2.2 Hz, 1H), 6.69 (d, J = 2.2 Hz, 2H), 8.05 (s, 1H).	3,5-Dimethoxy-phenylamine

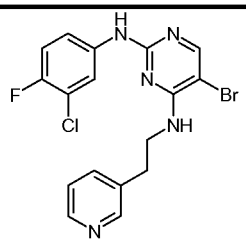
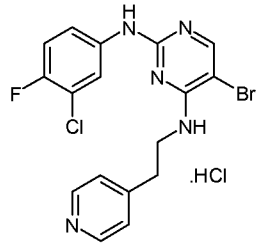
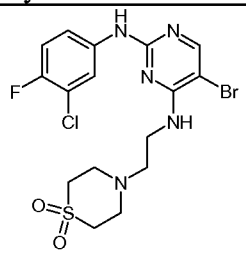
The following intermediates were prepared using the general method described above for **Intermediate 26** using 3-chloro-4-fluoroaniline and the starting material (SM) indicated.

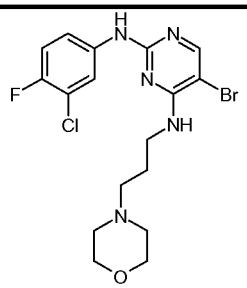
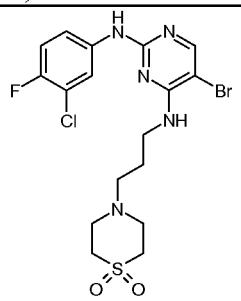
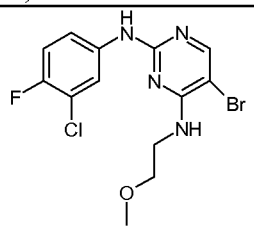
Int	Compound	Data	SM
35	 5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-propyl-pyrimidine-2,4-diamine	MS(ES): 359. (M) and 360(M+1) for. $C_{13}H_{13}BrClFN_4$ 400 MHz, DMSO-d_6 : δ 0.91 (t, J = 7.48 Hz, 3H), 1.55-1.64 (m, 2H), 3.34-3.38 (m, 2H), 7.13 (t, J = 5.72 Hz, 1H), 7.28 (t, J = 9.08 Hz, 1H), 7.52 (ddd, J = 9.06, 4.26, 2.68 Hz, 1H), 8.02 (s, 1H), 8.16 (dd, J = 6.92, 2.64 Hz, 1H), 9.43 (s, 1H).	(5-Bromo-2-chloro-pyrimidin-4-yl)-propyl-amine **(Intermediate 2)**

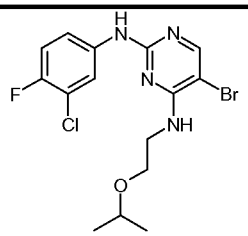
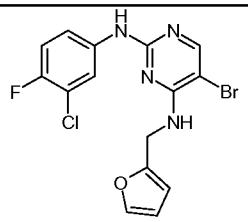
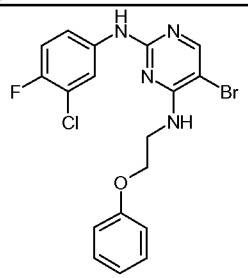
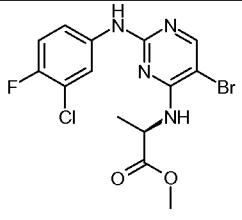
Int	Compound	Data	SM
36	 1-{3-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-propyl}-pyrrolidin-2-one	MS(ES): 442.8 (M) for $C_{17}H_{18}BrClFN_5O$. 400 MHz, DMSO-d_6 : δ 1.74-1.79 (m, 2H), 1.84-1.91 (m, 2H), 2.18 (t, J = 8.16 Hz, 2H), 3.21 (t, J = 6.80 Hz, 2H), 3.30 (t, J = 7.00 Hz, 2H), 3.36-3.57 (m, 2H), 7.43 (t, J = 9.00 Hz, 1H), 7.50 (ddd, J = 8.90, 4.22, 2.84 Hz, 1H), 7.95 (dd, J = 6.72, 2.48 Hz, 1H), 8.17-8.21 (m, 1H), 8.23 (s, 1H), 10.44 (br s, 1H).	1-[3-(5-Bromo-2-chloro-pyrimidin-4-ylamino)-propyl]-pyrrolidin-2-one **(Intermediate 3)**
37	 5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-dimethylamino-ethyl)-pyrimidine-2,4-diamine	MS(ES): 388 (M) and 390 (M+2) for $C_{14}H_{16}BrClFN_5$. 400 MHz, MeOD : δ 2.90 (s, 6H), 3.40 (t, *J* = 5.9 Hz, 2H), 3.89 (t, *J* = 5.96 Hz, 2H), 7.38 (t, *J* = 8.84 Hz, 1H), 7.42 – 7.45 (m, 1H), 7.72 (dd, *J* = 2.52, 6.52 Hz, 1H), 8.13 (s, 1H).	N'-(5-Bromo-2-chloro-pyrimidin-4-yl)-N,N-dimethyl-ethane-1,2-diamine **(Intermediate 4)**
38	 N-{2-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-ethyl}-acetamide	MS(ES): 402 (M) and 404 (M+2) for $C_{14}H_{14}BrClFN_5O$ 400 MHz, DMSO-d_6 : δ 1.79 (s, 3H), 3.29 (m, 2H), 3.46 (q, *J* = 5.8 Hz, 2H), 7.1 (t, *J* = 5.28 Hz, 1H), 7.29 (t, *J* = 9.16 Hz, 1H), 7.61-7.67 (m, 1H), 7.96 (t, *J* = 5.52 Hz, 1H), 8.02 (dd, J = 6.88, 2.64 Hz, 1H), 8.06 (s, 1H), 9.44 (s, 1H).	N-[2-(5-Bromo-2-chloro-pyrimidin-4-ylamino)-ethyl]-acetamide **(Intermediate 5)**

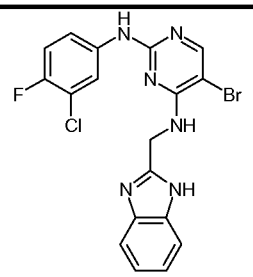
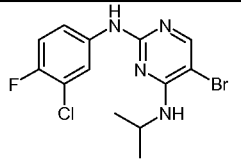
Int	Compound	Data	SM
39	 5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine	MS(ES): 408.9 (M+1) and 410(M+2)for $C_{16}H_{12}BrClFN_5$. 400 MHz, DMSO-d_6 : δ 4.71 (d, *J* = 5.84 Hz, 2H), 7.15 (t, *J* = 9.12 Hz, 1H), 7.23-7.27 (m, 2H), 7.43 (m, 1H), 7.69-7.76 (m, 2H), 7.86 (dd, *J* = 6.76, 2.56 Hz, 1H), 8.11 (s, 1H), 8.54 (ddd, *J* = 4.74, 1.64, 0.84 Hz, 1H), 9.41 (s, 1H).	(5-Bromo-2-chloro-pyrimidin-4-yl)-(pyridin-2-ylmethyl)-amine **(Intermediate 6)**
40	 5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(pyridin-3-ylmethyl)-pyrimidine-2,4-diamine hydrodrochloride salt	MS(ES): 410 (M+2) for $C_{16}H_{12}BrClFN_5$. 400 MHz, DMSO-d_6 : 4.79 (d, *J* = 4 Hz, 2H), 7.3-7.34 (m, 1H), 7.38-7.4 (m, 1H), 7.70-7.72 (br s, 1H), 8.02 (dd, *J* = 8, 4 Hz, 1H), 8.28 (s, 1H), 8.5 (d, *J* = 4 Hz, 1H), 8.62 (br s, 1H), 8.82 (d, *J* = 4 Hz, 1H), 8.93 (s, 1H), 10.36 (br s, 1H).	(5-Bromo-2-chloro-pyrimidin-4-yl)-(pyridin-3-ylmethyl)-amine HCl salt **(Intermediate 7)**
41	 5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-pyridin-4-ylmethyl-pyrimidine-2,4-diamine hydrodrochloride salt	MS(ES): 408.6 (M) and 409.8 (M+2) for$C_{16}H_{12}BrClFN_5$. 400 MHz, DMSO-d_6 : 4.84 (d, *J* = 5.84 Hz, 2H), 7.2 (t, *J* = 9.08 Hz, 1H), 7.3 (m, 1H), 7.70 (m, 1H), 7.91 (d, *J* = 6.56 Hz, 2H), 8.05 (s, 1H), 8.19 (s, 1H), 8.81 (d, *J* = 6.64 Hz, 2H), 9.58 (s, 1H).	(5-Bromo-2-chloro-pyrimidin-4-yl)-(pyridin-4-ylmethyl)-amine HCl salt **(Intermediate 8)**

Int	Compound	Data	SM
42	 3-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-propionamide	MS(ES): 388.8 (M) 389.8 (M+1) for $C_{13}H_{12}BrClFN_5O$. 400 MHz, DMSO-d_6 : δ 2.42 (t, *J* = 7 Hz, 2H), 3.59 (q, *J* = 6.84 Hz, 2H), 6.89 (br s, 1H), 7.01 (t, *J* = 5.64 Hz, 1H), 7.26 (t, *J* = 9.12 Hz, 1H), 7.35 (s, 1H), 7.68 (ddd, *J* = 9.06, 4.18, 2.72 Hz, 1H), 8.03 (m, 2H), 9.46 (s, 1H).	3-(5-Bromo-2-chloro-pyrimidin-4-ylamino)-propionamide **(Intermediate 9)**
43	 5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-morpholin-4-yl-ethyl)-pyrimidine-2,4-diamine	MS(ES): 430(M) and 432 (M+2) for $C_{16}H_{18}BrClFN_5O$. 400 MHz, DMSO-d_6 : δ 2.40 (br s, 4H), 2.48-2.53 (m, 2H), 3.48-3.56 (m, 6H), 6.92 (t, *J* = 5.44 Hz, 1H), 7.27 (t, *J* = 9.08 Hz, 1H), 7.57 (ddd, *J* = 9.06, 4.26, 2.68 Hz, 1H), 8.05 (m, 2H), 9.42 (s, 1H).	(5-Bromo-2-chloro-pyrimidin-4-yl)-(2-morpholin-4-yl-ethyl)-amine **(Intermediate 10)**
44	 5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine	MS(ES): 424(M+1) for $C_{17}H_{14}BrClFN_5$. 400 MHz, MeOD : δ 3.39 (t, *J* = 6.4 Hz, 2H), 3.95 (t, *J* = 6.44 Hz, 2H), 7.36 (t, *J* = 8.84 Hz, 1H), 7.38 (m, 1H), 7.6 (dd, *J* = 2.52, 6.56 Hz, 1H), 7.9 (d, *J* = 8 Hz, 1H), 7.95 (t, *J* = 7.24 Hz, 1H), 8.12 (s, 1H), 8.45 (dt, *J* = 10.97, 1.36 Hz, 1H), 8.74 (d, *J* = 5.8 Hz, 1H).	(5-Bromo-2-chloro-pyrimidin-4-yl)-(2-pyridin-2-yl-ethyl)-amine **(Intermediate 11)**

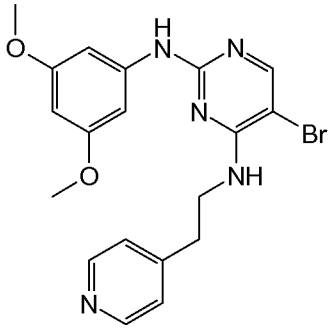
Int	Compound	Data	SM
45	 5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-pyridin-3-yl-ethyl)-pyrimidine-2,4-diamine	MS(ES):422(M) and 424(M+2) for $C_{17}H_{14}BrClFN_5$. 400 MHz, DMSO-d_6 : δ 3.13 (t, *J* = 4 Hz, 2H), 3.70-3.75 (m, 2H), 7.39 (m, 1H), 7.48-7.52 (m, 1H), 7.95-8.01 (m, 3H), 8.22 (s, 1H), 8.39 (d, *J* = 8 Hz, 2H), 8.79 (d, *J* = 8 Hz, 2H), 8.83 (d, 2H), 10.33 (br s, 1H).	(5-Bromo-2-chloro-pyrimidin-4-yl)-(2-pyridin-3-yl-ethyl)-amine **(Intermediate 12)**
46	 5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-pyridin-4-yl-ethyl)-pyrimidine-2,4-diamine hydrodrochloride salt	MS(ES):422.7(M) and 424 (M+1) for. $C_{17}H_{14}BrClFN_5$. 400 MHz, DMSO-d_6 : δ 3.21 (t, *J* = 6.80 Hz, 2H), 3.75-3.77 (m, 2H), 7.33 (m, 1H), 7.50 (m, 1H), 7.60 (br s, 1H), 7.89 (d, *J* = 6.12 Hz, 2H), 8.01 (dd, *J* = 6.82, 2.60 Hz, 1H), 8.13 (s, 1H), 8.81 (d, *J* = 6.44 Hz, 2H), 9.90 (br s, 1H).	(5-Bromo-2-chloro-pyrimidin-4-yl)-(2-pyridin-4-yl-ethyl)-amine HCl salt **(Intermediate 13)**
47	 5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-[2-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-ethyl]-pyrimidine-2,4-diamine	MS(ES): 478(M) and 480(M+2) for $C_{16}H_{18}BrClFN_5O_2S$. 400 MHz, DMSO-d_6 : δ 2.72 (t, *J* = 6.68 Hz, 2H), 2.96-2.97 (m, 4H), 3.03-3.04 (m, 4H), 3.48-3.52 (m, 2H), 6.95 (t, *J* = 5.32 Hz, 1H), 7.29 (t, *J* = 9.08 Hz, 1H), 7.57 (ddd, *J* = 9.10, 4.24, 2.72 Hz, 1H), 8.03-8.05 (m, 2H), 9.40 (s, 1H),	(5-Bromo-2-chloro-pyrimidin-4-yl)-[2-(1,1-dioxo-1l6-thiomorpholin-4-yl)-ethyl]-amine **(Intermediate 14)**

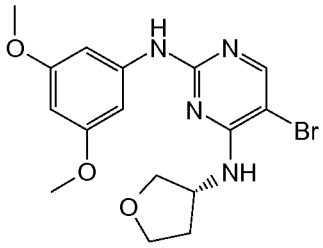
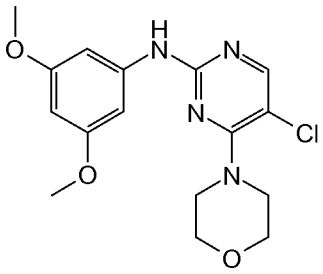
Int	Compound	Data	SM
48	 5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(3-morpholin-4-yl-propyl)-pyrimidine-2,4-diamine	MS (ES): 444(M) and 446(M+2) for $C_{17}H_{20}BrClFN_5O$. 400 MHz, DMSO-d_6 : δ 1.72-1.77 (m, 2H) 2.33-2.38 (m, 6H), 3.42-3.46 (m, 2H), 3.55-3.57 (t, *J* = 9.04 Hz, 4H), 7.22-7.30 (m, 2H), 7.53 (ddd, *J* = 8.98, 4.16, 2.76 Hz, 1H), 8.02 (s, 1H), 8.13 (dd, *J* = 6.88, 2.60 Hz, 1H), 9.43 (s, 1H).	(5-Bromo-2-chloro-pyrimidin-4-yl)-(3-morpholin-4-yl-propyl)-amine **(Intermediate 23)**
49	 5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-[3-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-propyl]-pyrimidine-2,4-diamine	MS(ES): 492(M) and 494(M+2) for $C_{17}H_{20}BrClFN_5O_2S$. 400 MHz, DMSO-d_6 : δ 1.71-1.76 (m, 2H), 2.82 (m, 4H), 2.87 (m, 4H), 3.45 (q, *J* = 6.28 Hz, 2H), 7.17 (t, *J* = 5.56 Hz, 1H), 7.3 (t, *J* = 9.08 Hz, 1H), 7.54 (ddd, *J* = 9.08, 4.22, 2.8 Hz, 1H), 8.04 (s, 1H), 8.13 (dd, *J* = 6.92, 2.56 Hz, 1H), 9.45 (s, 1H).	(5-Bromo-2-chloro-pyrimidin-4-yl)-[3-(1,1-dioxo-1l6-thiomorpholin-4-yl)-propyl]-amine **(Intermediate 24)**
50	 5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-methoxy-ethyl)-pyrimidine-2,4-diamine	The compound was taken to the next step on the basis of ^{1}H NMR. 300 MHz DMSO-d_6 : δ 3.3 (m, 3H), 3.5 (m, 4H), 7.34-7.46 (m, 2H), 7.9 (m, 2H), 8.2 (s, 1H), 10.3 (s, 1H).	(5-Bromo-2-chloro-pyrimidin-4-yl)-(2-methoxy-ethyl)-amine **(Intermediate 15)**

Int	Compound	Data	SM
51	 5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-isopropoxy-ethyl)-pyrimidine-2,4-diamine	MS(ES): 403 (M) and 405 (M+2) for $C_{15}H_{17}BrClFN_4O$. 300 MHz DMSO-d_6: δ 1.0 (dd, *J* = 6.18, 20.04 Hz, 6 H), 3.55 (br s, 5H), 6.93 (s, 1H), 7.27 (t, 9.12 Hz, 1H), 7.55 (ddd, *J* = 2.67, 4.17, 9.09 Hz, 1H), 8.04 (s, 1H), 8.07 (dd, *J* = 2.64, 6.87 Hz, 1H), 9.44 (s, 1H).	(5-Bromo-2-chloro-pyrimidin-4-yl)-(2-isopropoxy-ethyl)-amine **(Intermediate 16)**
52	 5-Bromo-N2-(3-chloro-4-fluoro-phenyl)-N4-(furan-2-ylmethyl)-pyrimidine-2,4-diamine	MS(ES): 396.9 (M) and 398.9 (M+2) for $C_{15}H_{11}BrClFN_4O$. 400 MHz DMSO-d_6: δ 4.59 (d, *J* = 5.88 Hz, 2H), 6.22 (d, *J* = 2.88 Hz, 1H), 6.37 (dd, *J* = 3.16, 1.84 Hz, 1H), 7.35 (t, *J* = 9.04 Hz, 1H), 7.48 (ddd, *J* = 8.96, 4.26, 2.72 Hz, 1H), 7.58 (dd, *J* = 1.78, 0.80 Hz, 1H), 7.95 (dd, *J* = 6.76, 2.56 Hz, 1H), 8.43 (br s, 1H).	(5-Bromo-2-chloro-pyrimidin-4-yl)-(furan-2-ylmethyl)-amine **(Intermediate 17)**
53	 5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-phenoxy-ethyl)-pyrimidine-2,4-diamine	MS(ES): 437 (M) and 439.1 (M+2) for $C_{18}H_{15}BrClFN_4O$. 400 MHz) DMSO-d_6: δ 3.77 (q, *J* = 6.08 Hz, 2H), 4.14 (t, *J* = 6.24 Hz, 2H), 6.9 (m, 3H), 7.22 (m, 4H), 7.53 (ddd, *J* = 9.08, 4.2, 2.72 Hz, 1H), 8.07 (dd, *J* = 7.2, 3.2 Hz, 2H), 9.46 (s, 1H).	(5-Bromo-2-chloro-pyrimidin-4-yl)-(2-phenoxy-ethyl)-amine **(Intermediate 18)**
54	 methyl (2R)-2-[[2-[(3-chloro-4-fluorophenyl)amino]-5-bromo-pyrimidin-4-yl]amino]propanoate	MS(ES): 403 (M) and 404.8 (M+2) for $C_{14}H_{13}BrClFN_4O_2$. 400 MHz DMSO-d_6 : δ 1.49 (d, *J* = 7.28 Hz, 3H), 3.60 (s, 3H), 4.69 (m, 1H), 7.11 (d, *J* = 7.36 Hz, 1H), 7.27 (t, *J* = 9.08 Hz, 1H), 7.52 (ddd, *J* = 9.06, 4.18, 2.72 Hz, 1H), 7.93 (dd, *J* = 6.80, 2.56 Hz, 1H), 8.12 (s, 1H), 9.47 (s, 1H)	Methyl (2*R*)-2-[(5-bromo-2-chloropyrimidin-4-yl)amino]-propanoate **(Intermediate 19)**

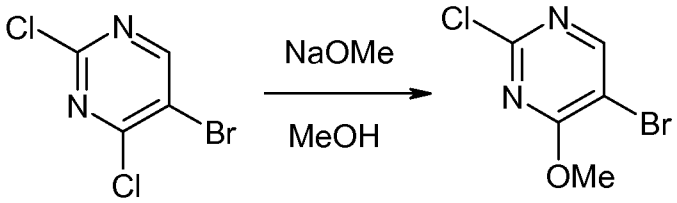
Int	Compound	Data	SM
55	 N^4-(1*H*-Benzoimidazol-2-ylmethyl)-5-bromo-N^2-(3-chloro-4-fluoro-phenyl)-pyrimidine-2,4-diamine	MS(ES): 447 (M) and 449(M+2) for $C_{18}H_{13}BrClFN_6$. 300 MHz, DMSO-d_6 : δ 5.06 (d, *J* = 5.19Hz, 2H), 7.17(t, *J* = 9.09 Hz, 1H), 7.42 (m, 1H), 7.51 (dd, *J* = 3.16, 6.15 Hz, 2H), 7.63 (br s, 1H), 7.76 (dd, *J* = 3.12, 6.12 Hz, 2H), 8.11 (br s, 1H), 8.24 (s, 1H), 9.84 (s, 1H).	(1H-Benzoimidazol-2-ylmethyl)-(5-bromo-2-chloro-pyrimidin-4-yl)-amine **(Intermediate 20)**
56	 5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-isopropyl-pyrimidine-2,4-diamine	MS(ES): 359 (M) and 360(M+1) for $C_{13}H_{13}BrClFN_4$. 300 MHz, DMSO-d_6 : δ 1.23 (d, *J* = 6.54 Hz, 6H), 4.28 (m, 1H), 6.56(d, *J* = 7.95 Hz, 1H), 7.28 (t, *J* = 9.12 Hz, 1H), 7.51 (td, *J* = 4.11, 7.65 Hz, 1H), 8.04 (s, 1H), 8.15 (dd, *J* = 2.61, 6.9 Hz, 1H), 9.44 (s, 1H).	(5-Bromo-2-chloro-pyrimidin-4-yl)-isopropyl-amine **(Intermediate 21)**

The following intermediates were prepared using the general method described above for **Intermediate 26** using the starting materials (SM) indicated

Int	Compound	Data	SM
57	 5-bromo-N^2-(3,5-dimethoxyphenyl)-N^4-(2-(pyridin-4-yl)ethyl) pyrimidine-2,4-diamine	MS: ES+ 431 for $C_{19}H_{20}BrN_5O_2$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 3.20 (t, *J*=6.78 Hz, 2 H) 3.70 (s, 6 H) 3.77 (q, *J*=6.47 Hz, 2 H) 6.28 (t, *J*=1.98 Hz, 1 H) 6.80 (d, *J*=2.07 Hz, 2 H) 7.88 (d, *J*=6.22 Hz, 2 H) 8.29 (s, 1 H) 8.36 (br. s., 1 H) 8.81 (d, *J*=6.22 Hz, 2 H) 10.51 (br. s., 1 H)	**Intermediate 12** and 3,5-dimethoxy aniline

Int	Compound	Data	SM
58	 (R)-5-bromo-N^2-(3,5-dimethoxyphenyl)-N^4-(tetrahydrofuran-3-yl) pyrimidine-2,4-diamine	MS: ES+ 396 for $C_{16}H_{19}BrN_4O_3$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 2.02 - 2.28 (m, 2 H) 3.63 - 3.78 (m, 7 H) 3.83 - 3.94 (m, 2 H) 4.55 - 4.69 (m, *J*=12.67, 6.26, 6.08, 6.08 Hz, 2 H) 6.28 (t, 1 H) 6.83 (d, *J*=2.26 Hz, 2 H) 8.02 (br. s., 1 H) 8.26 (s, 1 H) 10.34 (br. s., 1 H)	**Intermediate 22** and 3,5-dimethoxy aniline
59	 5-chloro-N-(3,5-dimethoxyphenyl)-4-morpholinopyrimidin-2-amine	MS: ES+ 351 for $C_{16}H_{19}ClN_4O_3$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 3.60 - 3.77 (m, *J*=3.96 Hz, 14 H) 6.16 (s, 1 H) 6.89 (d, *J*=2.07 Hz, 2 H) 8.19 (s, 1 H) 9.85 (s, 1 H)	**Intermediate 25** and 3,5-dimethoxy aniline

Intermediate 60: 5-Bromo-2-chloro-4-methoxypyrimidine



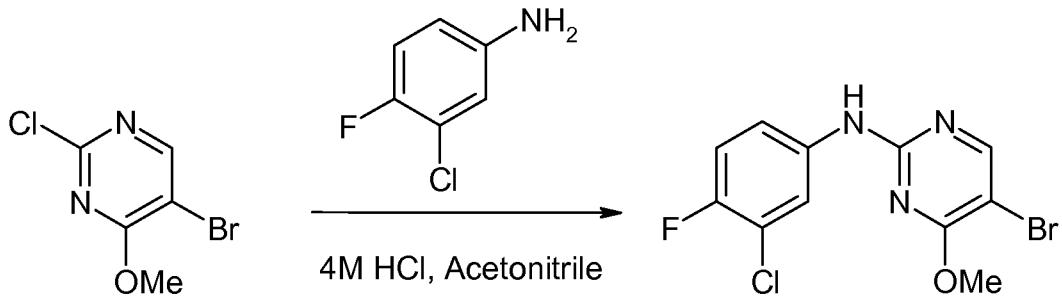
Intermediate 60

To a stirred solution of 5-bromo-2,4-dichloropyrimidine (65 mmol, 15 g) in methanol (150 mL) at room temperature under nitrogen atmosphere, sodium methoxide (72 mmol, 3.91 g) was added portionwise. The mixture was stirred at RT for 4h and the solvent was removed *in vacuo*. The resulting solid was dissolved in chloroform (2 x 250 mL), washed with water and brine. The organic layer was dried over sodium sulfate and concentrated under vacuum to yield 5-bromo-2-chloro-4-methoxypyrimidine as a white solid in 92 % yield (60.4 mmol, 13.5 g). The compound was taken to the next step without further purification.

MS(ES): 223.0(M) and 224.8(M+2) for $C_5H_4BrClN_2O$.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.11 (s, 3H), 8.44 (s, 1H)

Intermediate 61: (5-bromo-4-methoxy-pyrimidin-2-yl)-(3-chloro-4-fluoro-phenyl)-amine



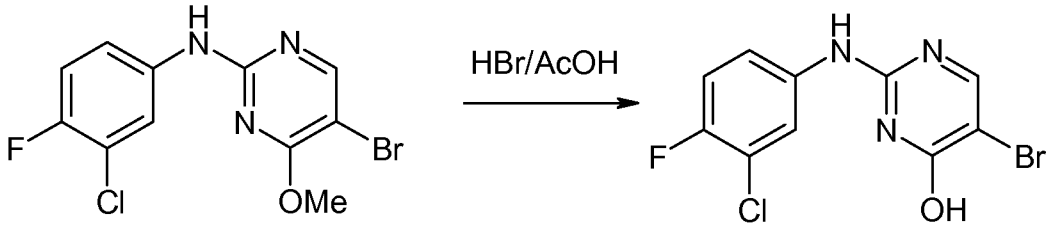
Intermediate 60 **Intermediate 61**

To a stirred solution of 5-bromo-2-chloro-4-methoxypyrimidine (**Intermediate 60,** 60 mmol, 13.5 g) and 3-chloro-4-fluoroaniline (60.3 mmol, 9.23 g) in acetonitrile (140 mL), 4 M HCl in 1,4-dioxane (14 mL) was added dropwise. The resulting solution was refluxed at 100 °C with constant stirring. The solvent was removed *in vacuo* and the residue was basified with 10% $NaHCO_3$ solution, then extracted with ethyl acetate (2 x 250 mL). The combined organic layers were washed with water and brine, dried over sodium sulfate and concentrated under vacuum. The residue was purified by column chromatography (silicagel, 60-120 mesh) using 5% EtOAc in hexane to yield (5-bromo-4-methoxy-pyrimidin-2-yl)-(3-chloro-4-fluoro-phenyl)-amine as a white solid in 70 % yield (42 mmol, 14 g).

MS(ES): 332 (M) for $C_{11}H_8BrClFN_3O$.

^{1}H-NMR (400 MHz, DMSO-d6): δ 4.0 (s, 3H), 7.37 (t, *J* = 9.20 Hz, 1H), 7.62 (ddd, J = 9.02, 4.12, 2.84 Hz, 1H), 8.04 (dd, *J* = 6.80, 2.60 Hz, 1H), 8.41 (s, 1H), 9.94 (s, 1H).

Intermediate 62: 5-Bromo-2-(3-chloro-4-fluoroanilino)-pyrimidin-4-one



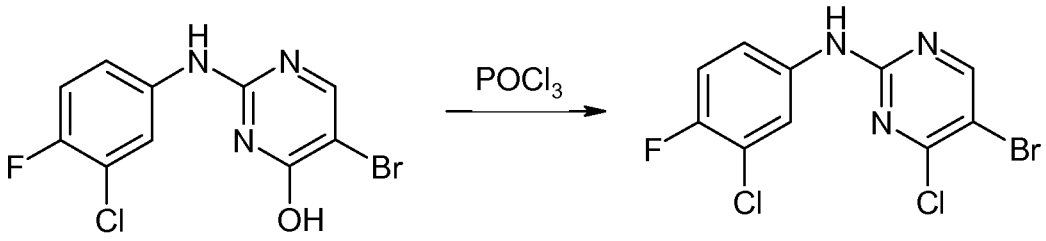
Intermediate 61 **Intermediate 62**

(5-Bromo-4-methoxy-pyrimidin-2-yl)-(3-chloro-4-fluoro-phenyl)-amine (**Intermediate 61,** 12 mmol, 4 g) was dissolved in 30-33% HBr in acetic acid (AcOH, 60 mmol, 13.5 g; 40 mL) and cooled to 0-5 °C. 47% aqueous HBr (20 mL) was added and refluxed for 4 h. The reaction mass was cooled to RT and poured over crushed ice. After all of the ice melted, the product was collected by filtration and dried under vacuum to provide 5-bromo-2-(3-chloro-4-fluoroanilino)-pyrimidin-4-one (11.67 mmol, 3.7 g, 97% yield).

MS(ES): 318 (M) and 320 (M+2) for $C_{10}H_6BrClFN_3O$.

^{1}H-NMR (400 MHz, DMSO-d6): δ 7.34-7.43 (m, 1H), 7.44-7.45 (m, 1H), 7.91 (dd, *J* = 6.74, 2.56 Hz, 1H), 8.08 (s, 1H), 9.11 (br s, 1H).

Intermediate 63: 5-Bromo-2-(3-chloro-4-fluoroanilino)-4-chloro-pyrimidine



Intermediate 62 **Intermediate 63**

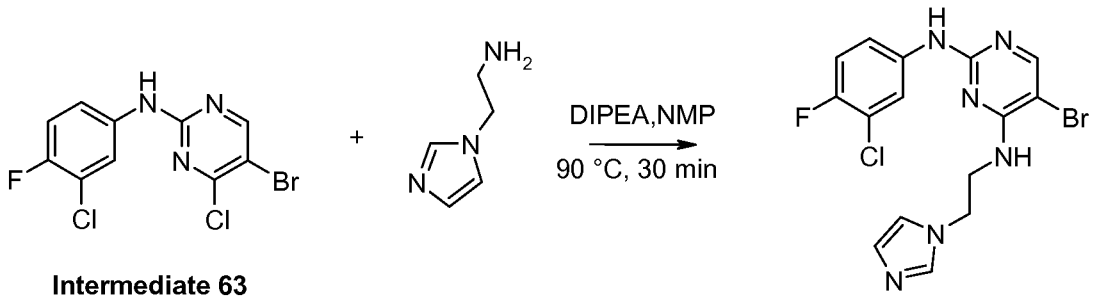
A solution of 5-bromo-2-(3-chloro-4-fluoroanilino)-pyrimidin-4-one (**Intermediate 62**, 18.3 mmol, 6.5 g) in phosphorus oxychloride (21 mL) was heated to reflux for 2 hours, cooled to RT, poured carefully onto a mixture of ice (200 mL) and saturated $NaHCO_3$ (20 mL) with stirring. The product was extracted with EtOAc (2 x 250 mL). The combined organic layers were washed with water, brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by column chromatography (silicagel, 60-120 mesh) using 3% EtOAc in hexane to yield 5-bromo-2-(3-chloro-4-fluoroanilino)-4-chloro-pyrimidine (15 mmol, 5.1 g).

MS(ES): 318 (M) and 320 (M+2) for $C_{10}H_5BrCl_2FN_3$

^{1}H NMR (400 MHz, DMSO-d6): δ 7.37 (t, *J* = 9.12 Hz, 1 H), 7.57 (ddd, *J* = 8.90, 4.19, 2.54 Hz, 1 H), 7.93 (dd, *J* = 6.69, 2.54 Hz, 1 H), 8.71 (s, 1 H), 10.38 (s, 1 H).

^{19}F NMR (376 MHz, DMSO-d6): δ -124.12 (s, 1 F).

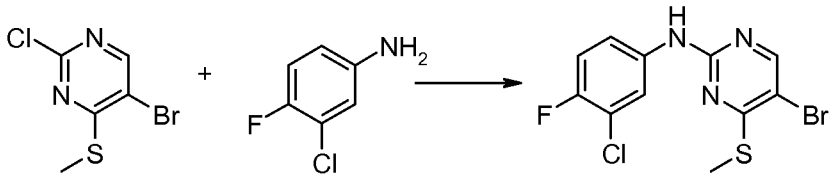
Intermediate 64: 5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-[2-(1*H*-imidazol-1-yl)ethyl]pyrimidine-2,4-diamine



Intermediate 63 **Intermediate 64**

To 500 mg of 5-bromo-4-chloro-*N*-(3-chloro-4-fluorophenyl)pyrimidin-2-amine (**Intermediate 63,** 1.48 mmol) in NMP (5 mL), was added *N*, *N*-diisopropylethylamine (3.04 mL, 1.78 mmol) and 2-imidazol-1-yl-ethylamine (1.63 mmol, 181 mg) under inert atmosphere. The reaction mixture was heated to 90 °C for 30 min. After completion of the reaction, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The crude mixture was purified by column chromatography using 2 % MeOH in $CHCl_3$ to obtain 5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-[2-(1*H*-imidazol-1-yl)ethyl]pyrimidine-2,4-diamine in 26 % yield (0.39 mmol, 160 mg). MS(ES): 411 (M) and 413 (M+2) for $C_{15}H_{13}BrClFN_6$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.71 (q, *J* = 6.00 Hz, 2H), 4.22 (t, *J* = 6.20 Hz, 2H), 6.86 (s, 1H), 7.11 (s, 1H), 7.17 (t, *J* = 5.64 Hz, 1H), 7.29 (t, *J* = 9.12 Hz, 1H), 7.53-7.56 (m, 1H), 7.56 (s, 1H), 8.02 (dd, *J* = 2.64, 6.84 Hz, 1H), 8.07 (s, 1H), 9.45 (s, 1H).

Intermediate 65: (5-Bromo-4-methylsulfanyl-pyrimidin-2-yl)-(3-chloro-4-fluoro-phenyl)-amine



Intermediate 65

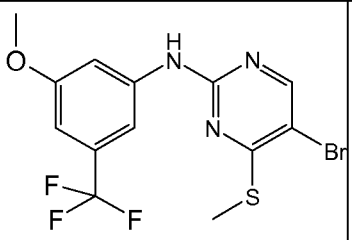
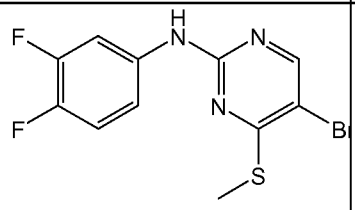
5-Bromo-2-chloro-4-(methylthio)pyrimidine (125 mmol, 30 g) was suspended in n-BuOH (300 mL) with 3-chloro-4-fluoroaniline (125 mmol, 18.22 g). The reaction was then treated

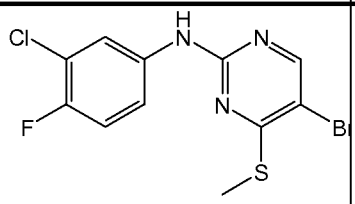
with 4 N HCl (100 mmol, 25 mL) in dioxane and refluxed at 100 °C for 1.5 h under nitrogen. The reaction was cooled to room temperature, diluted with diethyl ether and the solid was filtered and dried to afford 29 g of (5-bromo-4-methylsulfanyl-pyrimidin-2-yl)-(3-chloro-4-fluoro-phenyl)-amine as a pale yellow solid (83 mmol, 67 %).

MS(ES): 348(M) and 350(M+2) for $C_{11}H_8BrClFN_3S$.

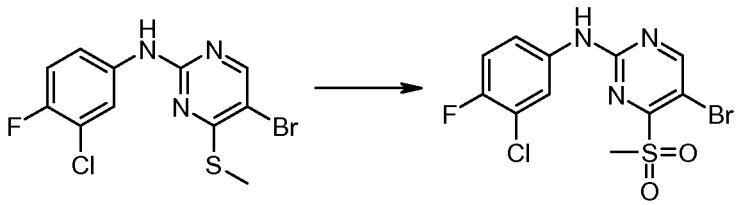
^{1}H-NMR 300MHz DMSO-d_6 : δ 2.55 (s, 3H), 7.34 (t, *J* = 9.0 Hz, 1H), 7.56-7.59 (m, 1H), 8.08 (t, *J* = 4.5 Hz, 1H), 8.33 (s, 1H), 9.98 (s, 1H).

The following intermediates were prepared using the general method described above for **Intermediate 65** using 5-bromo-2-chloro-4-(methylthio)pyrimidine and the starting material (SM) indicated.

Int	Compound	Data	SM
66	 5-bromo-*N*-[3-methoxy-5-(trifluoromethyl)phenyl]-4-(methylthio)pyrimidin-2-amine	MS: ES+ 395 for $C_{13}H_{11}BrF_3N_3OS$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 2.56 (s, 3 H) 3.79 (s, 3 H) 6.82 (s, 1 H) 7.53 (s, 1 H) 7.87 (s, 1 H) 8.36 (s, 1 H) 10.10 (s, 1 H)	3-methoxy-5-trifluoro methylaniline
67	 5-bromo-*N*-(3,4-difluorophenyl)-4-(methylthio)pyrimidin-2-amine	MS: ES+ 333 for $C_{11}H_8BrF_2N_3S$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 2.55 (s, 3 H) 7.23 - 7.49 (m, 2 H) 7.90 (ddd, *J*=13.85, 7.44, 2.45 Hz, 1 H) 8.33 (s, 1 H) 9.99 (s, 1 H)	3,4-difluoro aniline

Int	Compound	Data	SM
68	 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(methyl thio)pyrimidin-2-amine	MS: ES+ 349 for $C_{11}H_8BrClFN_3S$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 2.55 (s, 3 H) 7.34 (t, *J*=9.14 Hz, 1 H) 7.57 (ddd, *J*=9.09, 4.19, 2.73 Hz, 1 H) 8.07 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.33 (s, 1 H) 9.96 (s, 1 H)	3-chloro-4-fluoro aniline

Intermediate 69: (5-Bromo-4-methanesulfonyl-pyrimidin-2-yl)-(3-chloro-4-fluoro-phenyl)-amine

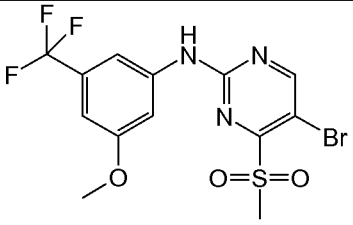
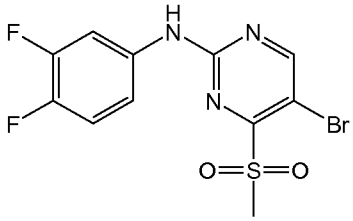


Intermediate 65 **Intermediate 69**

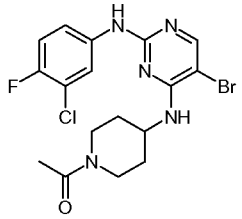
5-Bromo-2-[N-(3-chloro-4-fluorophenyl)]-4-(methylthio)pyrimidin-2-amine (**Intermediate 65**, 86 mmol, 30 g) was suspended in DCM (450 mL), cooled to 0 °C and 3-chloroperoxybenzoic acid (m-CPBA, 344 mmol, 59 g) was added. The suspension became a solution after stirring at 0 °C for 30 min. The reaction mixture was then allowed to warm up slowly to room temperature. 1N aqueous sodium hydroxide solution (344 mL) was added and the solution was stirred for 10 minutes. The solid which precipitated was filtered off and washed with water, dichloromethane, diethyl ether and dried. The first crop of the title compound, thus obtained, weighed 10 g. The mother liquor was dried over sodium sulfate and concentrated to yield a residue. Diethyl ether was added to the residue and the mixture was stirred for 15 minutes. The ether layer was filtered off. The residual solid was dissolved in $CHCl_3$-MeOH, then hexane was added to this mixture. The solid that precipitated was filtered off and dried. The second crop of the title compound, thus obtained, weighed 3.5 g. The total yield of (5-bromo-4-methanesulfonyl-pyrimidin-2-yl)-(3-chloro-4-fluoro-phenyl)-amine was 41 % (35.3 mmol, 13.5 g). MS(ES): 380 (M) for $C_{11}H_8BrClFN_3O_2S$.

^{1}H-NMR 400MHz DMSO-d_6 : δ 3.45 (s, 3H), 7.40 (t, J = 9.08 Hz, 1H), 7.55-7.58 (m, 1H), 7.96 (dd, J = 6.74, 2.60 Hz, 1H), 8.93 (s, 1H), 10.51 (s, 1H).

The following intermediates were prepared using the general method described above for **Intermediate 69** using m-CPBA and the starting material (SM) indicated.

Int	Compound	Data	SM
70	 5-Bromo-N-(3-methoxy-5-(trifluoromethyl)phenyl)-4-(methylsulfonyl)pyrimidin-2-amine	MS: ES+ 427 for $C_{13}H_{11}BrF_3N_3O_3S$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 3.46 (s, 3 H) 3.82 (s, 3 H) 6.91 (s, 1 H) 7.55 - 7.60 (m, 1 H) 7.70 (s, 1 H) 8.97 (s, 1 H) 10.63 (s, 1 H)	**Intermediate 66**
71	 5-Bromo-N-(3,4-difluorophenyl)-4-(methylsulfonyl) pyrimidin-2-amine	MS: ES+ 365 for $C_{11}H_8BrF_2N_3O_2S$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 3.45 (s, 3 H) 7.36 - 7.44 (m, 2 H) 7.75 - 7.89 (m, 1 H) 8.93 (s, 1 H) 10.53 (s, 1 H)	**Intermediate 67**

Intermediate 72: 1-{4-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-piperidin-1-yl}-ethanone

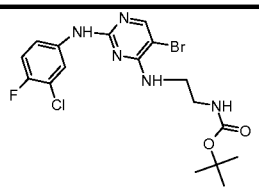
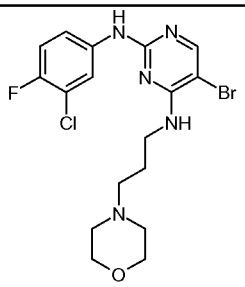


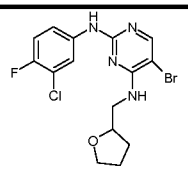
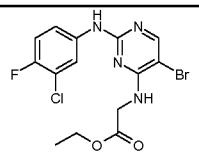
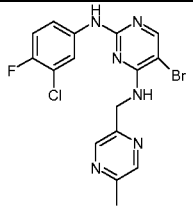
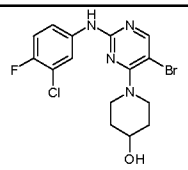
5- Bromo-2-[N-(3-chloro-4-fluorophenyl)]-4-(methyl sulfonyl)pyrimidin-2-amine (**Intermediate 69**, 1g, 2.63 mmol) was suspended in NMP (5 mL), treated with N,N-diisopropylethylamine (0.5 mL, 3.02 mmol), and 1-(4-amino-piperidin-1-yl)-ethanone (1 eq 2.63 mmol) in a sealed tube. The reaction was heated in the microwave reactor at 100 °C for 30 min. The reaction mixture was added to water and stirred for 15 min. The precipitated solid was filtered and dried to provide the 1-{4-[5-bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-piperidin-1-yl}-ethanone (800 mg).

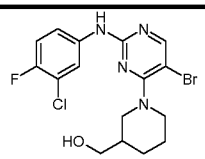
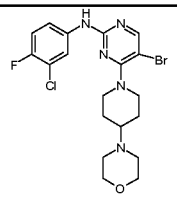
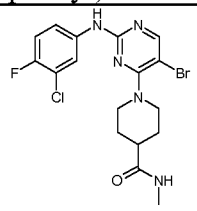
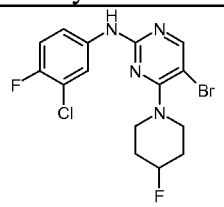
MS(ES): 442.7 (M) and 444 (M+2) for $C_{17}H_{18}BrClFN_5O$.

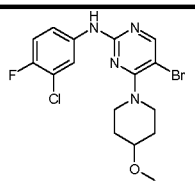
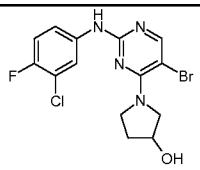
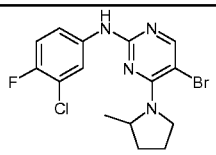
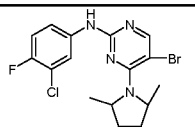
400 MHz, DMSO-d_6 : δ 1.4-1.75 (m, 2H), 1.83-1.88 (m, 2H), 2.02 (s, 3H), 2.6-2.63 (m, 1H), 3.11 (t, J = 12.00 Hz, 1H), 3.87-3.9 (m, 1H), 4.15-4.19 (m, 1H), 4.42-4.45 (m, 1H), 6.71 (d, J = 8.00 Hz, 1H), 7.32 (t, J = 9.04 Hz, 1H), 7.49-7.53 (m, 1H), 8.06 (s, 1H), 8.11 (dd, J = 6.86, 2.60 Hz, 1H), 9.50 (s, 1H).

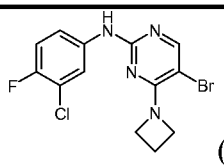
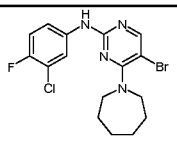
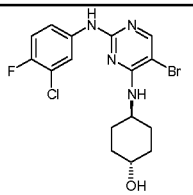
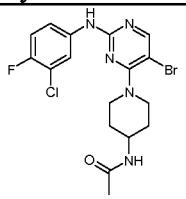
The following intermediates were prepared using the general method described above for **Intermediate 72** using 5- bromo-2-[N-(3-chloro-4-fluorophenyl)]-4-(methyl sulfonyl)pyrimidin-2-amine (**Intermediate 69**) and the starting material (SM) indicated.

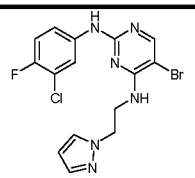
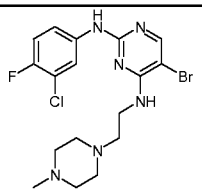
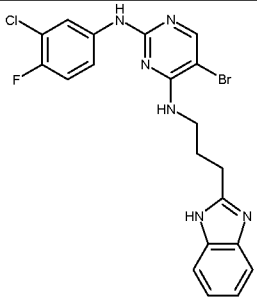
Int	Compound	Data	SM
73	 {2-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-ethyl}-carbamic acid *tert*-butyl ester	MS(ES): 461 (M+1) and 462(M+2) for $C_{17}H_{20}BrClFN_5O_2$. 400 MHz, DMSO-d_6 : δ1.34 (s, 9H), 3.17-3.2 (m, 2H), 3.41-3.44 (m, 2H), 6.91 (t, J = 5.04 Hz, 1H), 7.01 (t, J = 5.00 Hz, 1H), 7.28 (t, J = 8.96 Hz, 1H), 7.60 (s, 1H), 8-8.03 (m, 2H), 9.43 (s, 1H).	(2-Amino-ethyl)-carbamic acid tert-butyl ester
74	 5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(3-morpholin-4-yl-propyl)-pyrimidine-2,4-diamine	MS (ES): 444(M) and 446(M+2) for $C_{17}H_{20}BrClFN_5O$. 400 MHz, DMSO-d_6 : δ 1.72-1.77 (m, 2H) 2.33-2.38 (m, 6H), 3.42-3.46 (m, 2H), 3.55-3.57 (t, *J* = 9.04 Hz, 4H), 7.22-7.30 (m, 2H), 7.53 (ddd, *J* = 8.98, 4.16, 2.76 Hz, 1H), 8.02 (s, 1H), 8.13 (dd, *J* = 6.88, 2.60 Hz, 1H), 9.43 (s, 1H).	3-Morpholin-4-yl-propylamine

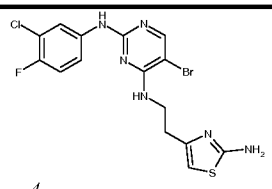
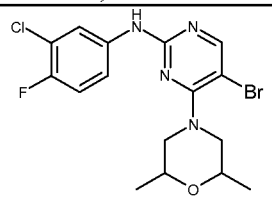
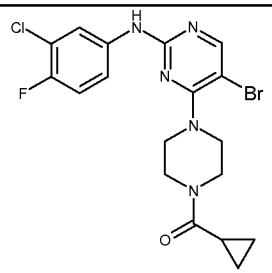
Int	Compound	Data	SM
75	 5-Bromo-N2-(3-chloro-4-fluoro-phenyl)-N4-(tetrahydrofuran-2-ylmethyl)-pyrimidine-2,4-diamine	MS(ES):401 (M) for $C_{15}H_{15}BrClFN_4O$. 400 MHz DMSO-d_6: δ 1.56 (m, 1H), 1.78 (m, 3H), 2.49 (t, *J* = 1.56 Hz, 2H), 3.43-3.63 (m, 1H), 3.73 (q, *J* = 6.64 Hz, 1H), 4.1 (m, 1H), 7.38 (t, *J* = 9 Hz, 1H), 7.47 (m, 1H) 7.95 (q, *J* = 2.48, 6.76 Hz, 1H), 8.15 (br s, 1H), 8.23 (s, 1H), 10.5 (br s, 1H).	C-(Tetrahydro-furan-2-yl)-methylamine
76	 [5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-acetic acid ethyl ester	The compound was taken to the next step on the basis of ^{1}H NMR. 400 MHz DMSO-d_6 δ : 1.13 (t, *J* = 7.08 Hz, 3H), 4.06 (q, *J* = 7.12 Hz, 2H), 4.11 (d, *J* = 6.00 Hz, 2H), 7.25 (t, *J* = 9.08 Hz, 1H), 7.44 (t, *J* = 6.00 Hz, 1H), 7.50 (dt, *J* = 8.57, 4.08 Hz, 1H), 7.94 (dd, *J* = 6.80, 2.56 Hz, 1H), 8.10 (s, 1H), 9.47 (s, 1H).	Amino-acetic acid ethyl ester
77	 5-Bromo-N2-(3-chloro-4-fluoro-phenyl)-N4-(5-methyl-pyrazin-2-ylmethyl)-pyrimidine-2,4-diamine	MS(ES): 423 (M+2) for $C_{16}H_{13}BrClFN_6$ The compound was taken to the next step on the basis of mass spectrum.	C-(5-Methyl-pyrazin-2-yl)-methylamine
78	 1-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-yl]-piperidin-4-ol	MS(ES):401 (M) and 402(M+1) for $C_{15}H_{15}BrClFN_4O$. 400 MHz, DMSO-d_6 : δ 1.6 (m, 2H), 1.8 (m, 2H), 3.2 (m, 2H), 3.8 (m, 1H), 3.9 (m, 2H), 7.31 (t, 1H), 7.5 (m, 1H), 8.1 (d, 1H), 8.2 (s, 1H).	Piperidin-4-ol

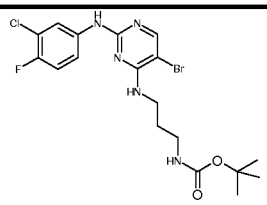
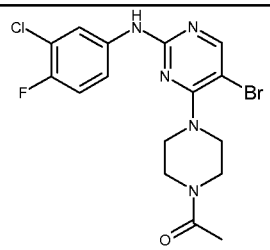
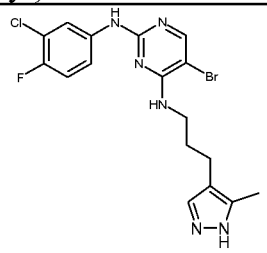
Int	Compound	Data	SM
79	 {1-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-yl]-piperidin-3-yl}-methanol	MS(ES): 415 (M) and 417(M+2) for $C_{16}H_{17}BrClFN_4O$. 300 MHz DMSO-d_6 δ : 1.2 (m, 1H), 1.5-1.7 (m, 3H), 2.73 (t, *J* = 10.47 Hz, 1H), 2.92 (t, *J* = 10.53 Hz, 1H), 4.12 (d, *J* = 13.02 Hz, 1H), 4.24 (d, *J* = 13.11 Hz, 1H), 7.29(t, *J* = 9.12 Hz, 1H), 7.55-7.59(m, 1H), 8.04 (dd, *J* = 2.58, 6.84 Hz, 1H), 8.19 (s, 1H), 9.61 (s, 1H).	Piperidin-3-yl-methanol
80	 [5-Bromo-4-(4-morpholin-4-yl-piperidin-1-yl)-pyrimidin-2-yl]-(3-chloro-4-fluoro-phenyl)-amine	MS(ES):471 (M+1) and 472(M+2) for $C_{19}H_{22}BrClFN_5O$. 300 MHz $CDCl_3$: δ 2.0 (br s, 2H), 2.6 (br s, 4H), 2.94 (br s, 2H), 3.74 (br s, 4H), 4.41–4.45 (br s, 2H), 6.86 (s, 1H), 7.1(t, *J* = 8.7 Hz, 1H), 7.17 (m, 1H), 7.95 (dd, *J* = 3, 6.6 Hz, 1H), 8.12 (s, 1H).	4-Piperidin-4-yl-morpholine
81	 1-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid methylamide	MS(ES):441.9 (M) and 444 (M+2) for $C_{17}H_{18}BrClFN_5O$. 400 MHz DMSO-d_6: δ 1.64 (m, 2H), 1.77 (m, 2H), 2.38 (m, 1H), 2.55 (d, *J* = 4.52 Hz, 3H), 2.95 (t, *J* = 11.6 Hz, 2H), 4.26 (d, *J* = 13.04 Hz, 2H), 7.30 (t, *J* = 9.12 Hz, 1H), 7.52 (m, 1H), 7.77 (d, *J* = 4.6 Hz, 1H), 8.08 (dd, *J* = 2.48, 6.84 Hz, 1H), 8.21(s, 1H), 9.64 (s, 1H).	Piperidine-4-carboxylic acid methylamide
82	 [5-Bromo-4-(4-fluoro-piperidin-1-yl)-pyrimidin-2-yl]-(3-chloro-4-fluoro-phenyl)-amine	MS(ES):403(M) for $C_{15}H_{14}BrClF_2N_4$. 300 MHz DMSO-d_6 : δ 1.82 (m, 2H), 1.94-2.04 (m, 2H), 3.56-3.68 (m, 4H), 4.92 (d, *J* = 48.6 Hz, 1H), 7.31 (t, *J* = 9.12 Hz, 1H), 7.51-7.56 (m, 1H), 8.06 (dd, *J* = 6.81, 2.49 Hz, 1H), 8.24 (s, 1H), 9.67 (br s, 1H).	4-Fluoro-piperidine

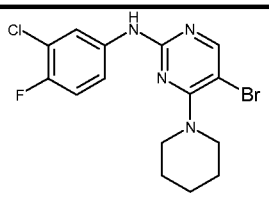
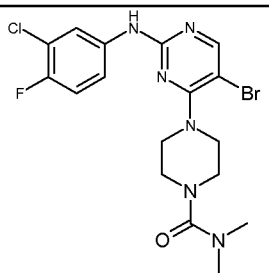
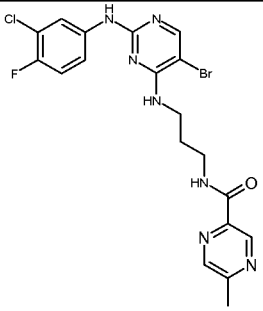
Int	Compound	Data	SM
83	 [5-Bromo-4-(4-methoxy-piperidin-1-yl)-pyrimidin-2-yl]-(3-chloro-4-fluoro-phenyl)-amine	MS(ES):415(M) and 417(M+2) for $C_{16}H_{17}BrClFN_4O$. 400 MHz DMSO-d_6: δ 1.48-1.57 (m, 2H), 1.88-1.96 (m, 2H), 3.24-3.30 (m, 4H), 3.42-3.46 (m, 1H), 3.87-3.90 (m, 2H), 7.3 (t, *J* = 9.12 Hz, 1H), 7.50-7.54 (m, 1H), 8.08 (dd, *J* = 6.86, 2.56 Hz, 1H), 8.21 (s, 1H), 9.64 (s, 1H).	4- methoxy-piperidine
84	 1-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-yl]-pyrrolidin-3-ol	MS(ES): 387 (M) and 389(M+2) for $C_{14}H_{13}BrClFN_4O$. 400 MHz DMSO-d_6: δ 1.87-1.95 (m, 2H), 3.65 (d, *J* = 11.44 Hz, 1H), 3.78-3.85 (m, 3H), 4.35 (s, 1H), 5.03 (d, *J* = 3.40 Hz, 1H), 7.30 (t, *J* = 9.12 Hz, 1H), 7.56 (ddd, *J* = 9.06, 4.24, 2.72 Hz, 1H), 8.08 (s, 1H), 8.11 (dd, *J* = 6.90, 2.68 Hz, 1H), 9.48 (s, 1H).	Pyrrolidin-3-ol
85	 [5-Bromo-4-(2-methyl-pyrrolidin-1-yl)-pyrimidin-2-yl]-(3-chloro-4-fluoro-phenyl)-amine	MS(ES): 385(M) and 387 (M+2) for $C_{15}H_{15}BrClFN_4$. 300 MHz DMSO-d_6: δ 1.2 (d, 3H), 1.6 (m, 1H), 1.8 (m, 1H), 1.9-2.1 (m, 2H), 3.68 (m, 1H), 3.87-3.96 (m, 1H), 4.55 (m, 1H), 7.29(t, *J* = 9.09 Hz, 1H), 7.50 (dt, *J* = 2.76, 9.12 Hz, 1H), 8.09-8.12 (m, 2H), 9.5 (s, 1H).	2-Methyl-pyrrolidine
86	 [5-Bromo-4-(2,5-dimethyl-pyrrolidin-1-yl)-pyrimidin-2-yl]-(3-chloro-4-fluoro-phenyl)-amine	MS(ES): 399(M) and 401 (M+2) for $C_{16}H_{17}BrClFN_4$. 400 MHz DMSO-d_6: δ 1.30 (d, 6H), 1.74 (m, 2H), 2.03 (m, 2H), 4.62 (br s, 2H), 7.29 (t, *J* = 9.08 Hz, 1H), 7.46 (ddd, *J* = 8.98, 4.12, 2.80 Hz, 1H), 8.08-8.11 (m, 2H), 9.43 (s, 1H).	2,5-Dimethyl-pyrrolidine

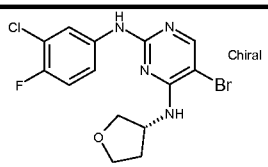
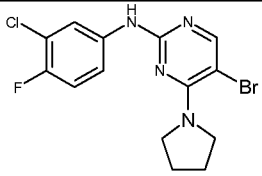
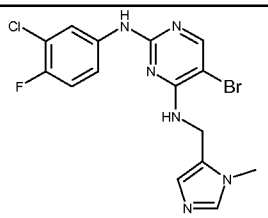
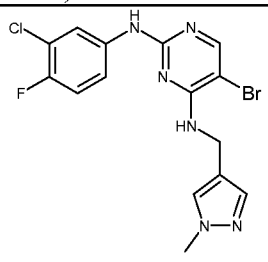
Int	Compound	Data	SM
87	 (4-Azetidin-1-yl-5-bromo-pyrimidin-2-yl)-(3-chloro-4-fluoro-phenyl)-amine	MS(ES):356.9 (M) and 359 (M+2) for $C_{13}H_{11}BrClFN_4$ 400 MHz, DMSO-d_6 :δ : 2.32 (q, *J* = 7.64 Hz, 2H), 4.40 (s, 4H), 7.34 (t, *J* = 9.12 Hz, 1H), 7.52 (ddd, *J* = 9.04, 4.24, 2.68 Hz, 1H), 8.04 (dd, *J* = 6.84, 2.60 Hz, 1H), 8.10 (s, 1H), 9.96 (s, 1H).	Azetidine
88	 (4-Azepan-1-yl-5-bromo-pyrimidin-2-yl)-(3-chloro-4-fluoro-phenyl)-amine	MS(ES):399 (M) and 401 (M+2) for $C_{16}H_{17}BrClFN_4$. 400 MHz, DMSO-d_6 : δ 1.51-1.52 (m, 4H), 1.79 (m, 4H), 3.83 (t, J = 6.04 Hz, 4H), 7.30 (t, J = 9.08 Hz, 1H), 7.47 (ddd, J = 9.09, 4.24, 2.72 Hz, 1H), 8.08 (dd, J = 6.90 , 2.68 Hz, 1H), 8.10 (s, 1H), 9.48 (s, 1H).	Azepane
89	 *Trans*-4-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-cyclohexanol	MS(ES): 415 (M) and 417(M+2) for $C_{16}H_{17}BrClFN_4O$. 300 MHz, DMSO-d_6 : δ 1.27-1.34 (m, 2H) 1.42-1.49 (m, 2H), 1.83-1.86 (br s, 4H), 3.89 (br s, 1H), 4.57 (d, *J* = 4.35 Hz, 1H), 6.48(d, *J* = 8.07 Hz, 1H), 7.28 (t, *J* = 8.94 Hz, 1H), 7.48 (m, 1H), 8.03 (s, 1H), 8.14 (dd, *J* = 2.43, 6.9 Hz, 1H), 9.45 (s, 1H).	4-Amino-cyclohexanol
90	 N-{1-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-yl]-piperidin-4-yl}-acetamide	MS(ES): 442 (M) and 444(M+2) for $C_{17}H_{18}BrClFN_5O$. 400 MHz, DMSO-d_6 δ : 1.49 (d, *J* = 7.28 Hz, 3H), 3.60 (s, 3H), 4.69 (m, 1H), 7.11 (d, *J* = 7.36 Hz, 1H), 7.27 (t, *J* = 9.08 Hz, 1H), 7.52 (ddd, *J* = 9.06, 4.18, 2.72 Hz, 1H), 7.93 (dd, *J* = 6.80, 2.56 Hz, 1H), 8.12 (s, 1H), 9.47 (s, 1H).	N-Piperidin-4-yl-acetamide

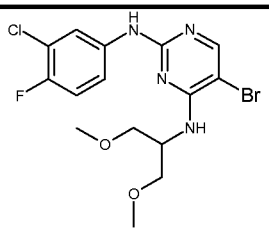
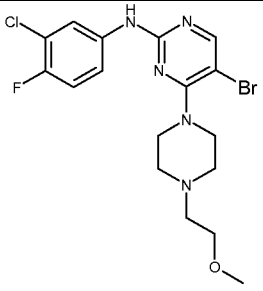
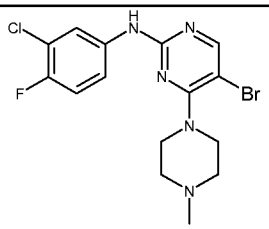
Int	Compound	Data	SM
91	 5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-[2-(1*H*-pyrazol-1-yl)ethyl]pyrimidine-2,4-diamine	MS(ES): 411 (M) and 413 (M+2) for $C_{15}H_{13}BrClFN_6$. 400 MHz, DMSO-d_6: δ 3.78 (q, *J* = 6.12 Hz, 2H), 4.36 (t, *J* = 6.40 Hz, 2H), 6.23 (t, *J* = 1.92 Hz, 1H), 7.13 (t, *J* = 5.52 Hz, 1H), 7.29 (t, *J* = 9.12 Hz, 1H), 7.46 (d, *J* = 1.68 Hz, 1H), 7.63-7.67 (m, 2H), 8.00 (dd, *J* = 2.28, 6.90 Hz, 1H), 8.06 (d, *J* = 2.12 Hz, 1H), 9.47 (s, 1H).	2-(1*H*-pyrazol-1-yl)ethanamine
92	 5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-[2-(4-methylpiperazin-1-yl)ethyl]pyrimidine-2,4-diamine	MS(ES): 443 (M) and 445 (M+2) for $C_{17}H_{21}BrClFN_6$. 400 MHz, DMSO-d_6: δ 2.30 (br s, 4H), 2.44 (br s, 4H), 2.69 (s, 3H), 3.30 (t, *J* = 6.92 Hz, 2H),, 3.50 (q, *J* = 6.16 Hz, 2H), 6.89 (t, *J* = 5.20 Hz, 1H), 7.27 (t, *J* = 9.08 Hz, 1H), 7.58 (ddd, *J* = 2.52, 4.26, 9.02 Hz, 1H), 8.04-8.07 (m, 2H), 9.44 (s, 1H).	2-(4-methylpiperazin-1-yl)ethanamine
93	 N^4-(3-(1*H*-benzo[d]imidazol-2-yl)propyl)-5-bromo-N^2-(3-chloro-4-fluorophenyl)pyrimidine-2,4-diamine	MS(ES): 475 (M) 477 (M+2) for $C_{20}H_{17}BrClFN_6$ 1H NMR (300 MHz, DMSO-*d6*) δ ppm 2.02 - 2.22 (m, 2 H) 2.89 (t, J=7.54 Hz, 2 H) 3.52 (q, J=6.22 Hz, 2 H) 6.98 - 7.15 (m, 2 H) 7.24 (t, J=9.14 Hz, 1 H) 7.29 - 7.46 (m, 2 H) 7.44 - 7.72 (m, 2 H) 8.04 (s, 1 H) 8.11 (dd, J=6.78, 2.64 Hz, 1 H) 9.46 (s, 1 H) 12.19 (s, 1 H)	3-(1*H*-benzo[d]imidazol-2-yl)propan-1-amine

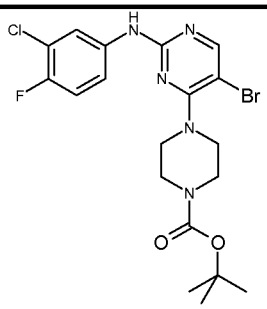
Int	Compound	Data	SM
94	 N^4-(2-(2-aminothiazol-4-yl)ethyl)-5-bromo-N^2-(3-chloro-4-fluorophenyl)pyrimidine-2,4-diamine	MS(ES): 445 (M+2) for $C_{15}H_{13}BrClFN_6S$ 1H NMR (300 MHz, DMSO- *d* 6) d ppm 2.21 (s, 3 H) 2.31 - 2.44 (m, 4 H) 3.15 - 3.35 (m, 4 H) 7.33 (t, J=9.04 Hz, 1 H) 7.61 (dd, J=4.90, 3.20 Hz, 1 H) 8.00 - 8.25 (m, 2 H) 8.30 (s, 1 H) 8.86 (d, J=1.32 Hz, 1 H) 8.98 (s, 1 H) 9.72 (s, 1 H)	4-(2-aminoethyl)thiazol-2-amine dihydrochloride
95	 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(2,6-dimethylmorpholino)pyrimidin-2-amine	MS(ES): 415 (M) 417 (M+2) for $C_{16}H_{17}BrClFN_4O$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 1.14 (d, 6 H) 2.55 - 2.77 (m, 2 H) 3.59 - 3.78 (m, 2 H) 4.15 (d, *J*=12.62 Hz, 2 H) 7.32 (t, *J*=9.04 Hz, 1 H) 7.48 (ddd, *J*=8.95, 4.14, 2.73 Hz, 1 H) 8.10 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.26 (s, 1 H) 9.70 (s, 1 H)	2,6-dimethyl-morpholine
96	 (4-(5-bromo-2-(3-chloro-4-fluorophenylamino)pyrimidin-4-yl)piperazin-1-yl)(cyclopropyl)methanone	MS(ES): 454 (M) 456 (M+2) for $C_{18}H_{18}BrClFN_5O$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 0.60 - 0.90 (m, 4 H) 1.91 - 2.11 (m, 1 H) 3.45 - 3.98 (m, 8 H) 7.33 (t, *J*=9.14 Hz, 1 H) 7.58 (ddd, *J*=9.04, 4.14, 2.64 Hz, 1 H) 8.03 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.28 (s, 1 H) 9.71 (s, 1 H)	1-(cyclopropyl-carbonyl)-piperazine

Int	Compound	Data	SM
97	 *tert*-Butyl 3-(5-bromo-2-(3-chloro-4-fluorophenylamino) pyrimidin-4-ylamino)propylcarbamate	MS(ES): 474 (M) 476 (M+2) for $C_{18}H_{22}BrClFN_5O_2$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 1.36 (s, 9 H) 1.57 - 1.80 (m, 2 H) 2.99 (q, *J*=6.47 Hz, 2 H) 3.35 - 3.51 (m, 2 H) 6.87 (t, *J*=5.46 Hz, 1 H) 7.11 (t, *J*=5.93 Hz, 1 H) 7.31 (t, *J*=9.14 Hz, 1 H) 7.59 (dd, *J*=9.42, 3.58 Hz, 1 H) 7.94 - 8.21 (m, 2 H) 9.46 (s, 1 H)	*N*-(3-Amino-propyl)carbamic acid *tert*-butyl ester
98	 1-{4-[5-bromo-2-(3-chloro-4-fluorophenylamino) pyrimidin-4-yl]piperazin-1-yl}ethanone	MS(ES): 428(M) 430 (M+2) for $C_{16}H_{16}BrClFN_5O$ 1H NMR (300 MHz, DMSO- *d*6) δ ppm 2.03 (s, 3 H) 3.43 - 3.78 (m, 8 H) 7.32 (t, *J*=9.14 Hz, 1 H) 7.46 - 7.66 (m, 1 H) 8.01 (dd, *J*=6.88, 2.54 Hz, 1 H) 8.27 (s, 1 H) 9.70 (s, 1 H)	1-Acetyl-piperazine
99	 5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-(5-methyl-1*H*-pyrazol-4-yl)propyl)pyrimidine-2,4-diamine	MS(ES): 441 (M+2) for $C_{17}H_{17}BrClFN_6$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 1.57 - 1.95 (m, 2 H) 2.08 (br. s., 3 H) 2.40 (t, *J*=7.54 Hz, 2 H) 3.36 - 3.53 (m, 2 H) 6.96 - 7.73 (m, 4 H) 7.87 - 8.30 (m, 2 H) 9.44 (s, 1 H) 11.94 - 12.38 (m, 1 H)	3-(5-Methyl-1*H*-pyrazol-4-yl)propylamine

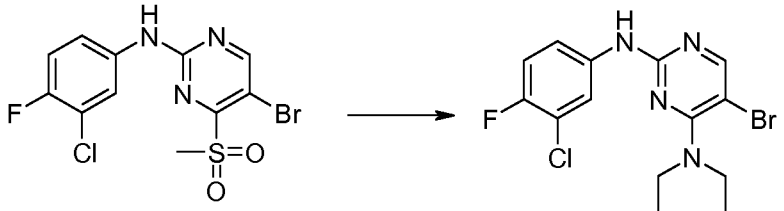
Int	Compound	Data	SM
100	 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(piperidin-1-yl)pyrimidin-2-amine	MS(ES): 385 (M) 387 (M+2) for $C_{15}H_{15}BrClFN_4$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 1.63 (br. s., 6 H) 3.57 (br. s., 4 H) 7.32 (t, *J*=9.04 Hz, 1 H) 7.54 (ddd, *J*=9.09, 4.19, 2.73 Hz, 1 H) 8.11 (dd, *J*=6.88, 2.54 Hz, 1 H) 8.21 (s, 1 H) 9.64 (s, 1 H)	Piperidine
101	 4-(5-bromo-2-(3-chloro-4-fluorophenylamino)pyrimidin-4-yl)-*N,N*-dimethylpiperazine-1-carboxamide	MS(ES): 457 (M) 459 (M+2) for $C_{17}H_{19}BrClFN_6O$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 2.77 (s, 6 H) 3.12 - 3.30 (m, 4 H) 3.51 - 3.73 (m, 4 H) 7.33 (t, *J*=9.14 Hz, 1 H) 7.57 (ddd, *J*=9.04, 4.14, 2.83 Hz, 1 H) 8.04 (dd, *J*=6.88, 2.54 Hz, 1 H) 8.27 (s, 1 H) 9.70 (s, 1 H)	piperazine-1-carboxylic acid dimethylamide
102	 *N*-(3-(5-bromo-2-(3-chloro-4-fluorophenylamino)pyrimidin-4-ylamino)propyl)-5-methylpyrazine-2-carboxamide	MS(ES): 494 (M) 496 (M+2) for $C_{19}H_{18}BrClFN_7O$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 1.77 - 1.95 (m, 2 H) 2.58 (s, 3 H) 3.37 (q, *J*=6.03 Hz, 2 H) 3.47 (q, *J*=5.97 Hz, 2 H) 7.30 (t, *J*=9.14 Hz, 1 H) 7.43 - 7.66 (m, *J*=4.52, 4.52, 4.24, 2.73 Hz, 2 H) 7.96 - 8.20 (m, 2 H) 8.59 (d, *J*=0.94 Hz, 1 H) 8.89 - 9.13 (m, 2 H) 9.65 (s, 1 H)	3-[(5-Methylpyrazine-2-carbonyl)amino]propylamine hydrochloride

Int	Compound	Data	SM
103	 (R)-5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(tetrahydrofuran-3-yl)pyrimidine-2,4-diamine	MS(ES): 387(M) 389 (M+3) for $C_{14}H_{13}BrClFN_4O$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 1.90 - 2.13 (m, 1 H) 2.13 - 2.33 (m, 1 H) 3.57 - 3.81 (m, 2 H) 3.81 - 4.05 (m, 2 H) 4.42 - 4.72 (m, 1 H) 6.86 (d, *J*=6.22 Hz, 1 H) 7.31 (t, *J*=9.14 Hz, 1 H) 7.52 (ddd, *J*=9.14, 4.24, 2.64 Hz, 1 H) 8.03 - 8.21 (m, 2 H) 9.51 (s, 1 H)	R(+)-3-Aminotetrahydrofuran
104	 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(pyrrolidin-1-yl)pyrimidin-2-amine	MS(ES): 371 (M) 373 (M+2) for $C_{14}H_{13}BrClFN_4$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 1.75 - 2.04 (m, 4 H) 3.74 (t, *J*=6.40 Hz, 4 H) 7.30 (t, *J*=9.14 Hz, 1 H) 7.57 (ddd, *J*=9.04, 4.24, 2.73 Hz, 1 H) 7.99 - 8.21 (m, 2 H) 9.48 (s, 1 H)	Pyrrolidine
105	 5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-((1-methyl-1*H*-imidazol-5-yl)methyl)pyrimidine-2,4-diamine	MS(ES): 411 (M) 413 (M+2) for $C_{15}H_{13}BrClFN_6$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 3.62 (s, 3 H) 4.57 (d, *J*=5.65 Hz, 2 H) 6.79 (s, 1 H) 7.29 (t, *J*=9.14 Hz, 1 H) 7.40 - 7.67 (m, 3 H) 8.02 (dd, *J*=6.88, 2.54 Hz, 1 H) 8.09 (s, 1 H) 9.45 (s, 1 H)	(1-Methyl-1*H*-imidazol-5-yl)methanamine
106	 5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-((1-methyl-1H-pyrazol-4-yl)methyl)pyrimidine-2,4-diamine	MS(ES): 411 (M) 413 (M+2) for $C_{15}H_{13}BrClFN_6$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 3.75 (s, 3 H) 4.42 (d, *J*=5.84 Hz, 2 H) 7.30 (t, *J*=9.14 Hz, 1 H) 7.36 (s, 1 H) 7.44 (t, *J*=5.75 Hz, 1 H) 7.50 - 7.66 (m, 2 H) 7.97 - 8.19 (m, 2 H) 9.45 (s, 1 H)	(1-Methyl-1H-pyrazol-4-yl)methanamine

Int	Compound	Data	SM
107	 5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(1,3-dimethoxypropan-2-yl)pyrimidine-2,4-diamine	MS(ES): 419(M) 421 (M+2) for $C_{15}H_{17}BrClFN_4O_2$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 3.27 (s, 6 H) 3.38 - 3.64 (m, 4 H) 4.33 - 4.70 (m, 1 H) 6.46 (d, *J*=8.48 Hz, 1 H) 7.28 (t, *J*=9.14 Hz, 1 H) 7.55 (ddd, *J*=9.04, 4.24, 2.73 Hz, 1 H) 7.96 - 8.17 (m, 2 H) 9.48 (s, 1 H)	2-Amino-1,3-dimethoxy-propane
108	 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[4-(2-methoxyethyl)piperazin-1-yl]pyrimidin-2-amine	MS(ES):444 (M) 446 (M+2) for $C_{17}H_{20}BrClFN_5O$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 2.52 - 2.64 (m, 6 H) 3.24 (s, 3 H) 3.46 (t, *J*=5.65 Hz, 2 H) 3.58 - 3.56 (m, 4 H) 7.32 (t, *J*=9.14 Hz, 1 H) 7.55 (dt, *J*=9.04, 3.39 Hz, 1 H) 8.07 (dd, *J*=6.88, 2.54 Hz, 1 H) 8.24 (s, 1 H) 9.68 (s, 1 H)	1-(2-Methoxyethyl)piperazine
109	 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(4-methylpiperazin-1-yl)pyrimidin-2-amine	MS(ES):400 (M) 402 (M+2) for $C_{15}H_{16}BrClFN_5$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 2.22 (s, 3 H) 2.31 - 2.47 (m, 4 H) 3.47 - 3.70 (m, 4 H) 7.32 (t, *J*=9.04 Hz, 1 H) 7.54 (ddd, *J*=9.04, 4.14, 2.64 Hz, 1 H) 8.08 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.24 (s, 1 H) 9.69 (s, 1 H)	1-Methylpiperazine

Int	Compound	Data	SM
110	 *tert*-butyl 4-[5-bromo-2-(3-chloro-4-fluorophenylamino) pyrimidin-4-yl]piperazine-1-carboxylate	MS(ES): 486 (M) 488 (M+2) for $C_{19}H_{22}BrClFN_5O_2$ 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.41 (s, 9 H) 3.36 - 3.72 (m, 8 H) 7.33 (t, *J*=9.14 Hz, 1 H) 7.45 - 7.70 (m, 1 H) 8.02 (dd, *J*=6.88, 2.54 Hz, 1 H) 8.27 (s, 1 H) 9.70 (s, 1 H)	*tert*-butyl piperazine-1-carboxylate

Intermediate 111: 5-Bromo-N-(3-chloro-4-fluorophenyl)-4-morpholin-4-ylpyrimidin-2-amine



Intermediate 69

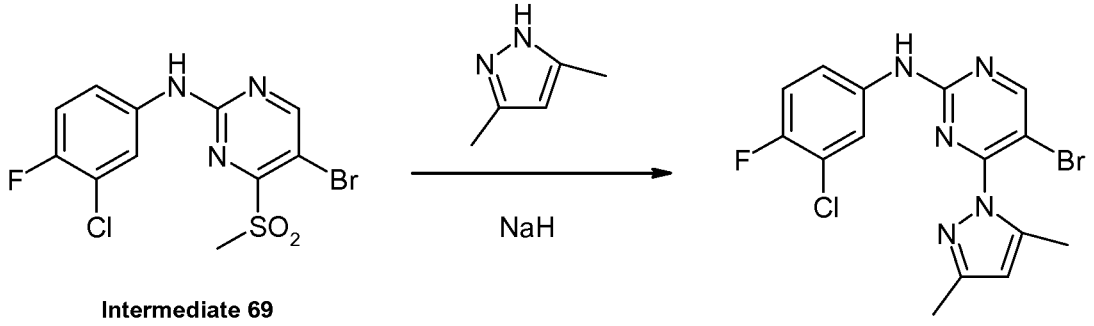
Intermediate 111

5-Bromo-2-[N-(3-chloro-4-fluorophenyl)]-4-(methylsulfonyl)pyrimidin-2-amine (**Intermediate 69**, 15.7 mmol, 6 g) was suspended in NMP (30 mL) and treated with N,N-diisopropylethylamine (23.6 mmol, 4 mL) and morpholine (18.9 mmol, 1.64 g) in a 100 mL round-bottomed flask. The reaction was heated to 90 °C for 45 min. The reaction mixture was added to water and stirred for 15 min. The precipitated solid was filtered and washed successively with water, diethyl ether and hexanes and dried to afford 4.96 g of the title compound (12.56 mmol, 80 %).

MS(ES): 387 (M) and 389 (M+2) for $C_{14}H_{13}BrClFN_4O$.

^{1}H NMR 400 MHz DMSO-d_6: δ 3.57-3.59 (m, 4H), 3.71-3.73 (m, 4H), 7.32 (t, J = 9.08 Hz, 1H), 7.55 (ddd, J = 9.00, 4.18, 2.68 Hz, 1H), 8.04 (dd, J = 6.86, 2.64 Hz, 1H), 8.26 (d, J = 1.20 Hz, 1H), 9.71 (s, 1H).

Intermediate 112: 5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyrimidin-2-amine

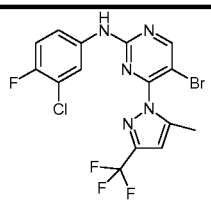
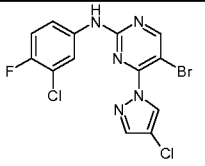
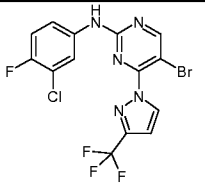


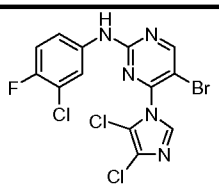
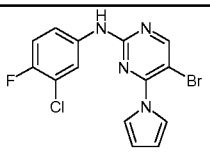
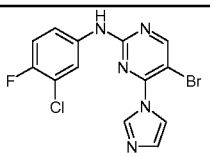
Intermediate 69

Intermediate 112

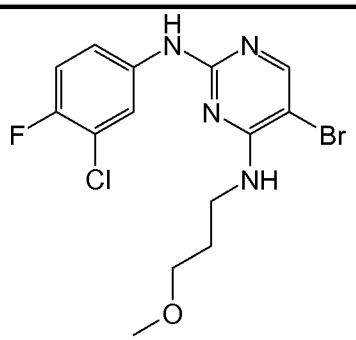
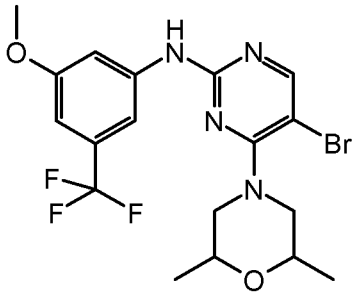
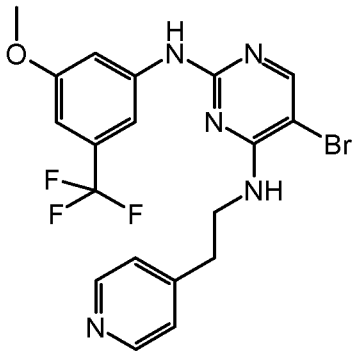
A solution of 3,5-dimethyl-1*H*-pyrazole (554 mg, 5.78 mmol) in DMF (1 ml) was added slowly to a suspension of sodium hydride (60%, 208 mg, 5.52 mmol) in DMF (1 ml) at 0 °C and the resultant mixture was stirred for 25 min. A solution of 5-bromo-N-(3-chloro-4-fluorophenyl)-4-(methylsulfonyl)pyrimidin-2-amine (Intermediate 69, 1.0 g, 2.63 mmol) in DMF (2 mL) was added slowly to the reaction mixture, and the mixture was stirred for 1 h. Water was added to the reaction mixture (~6 mL) and the solid that formed was filtered and dried to yield 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyrimidin-2-amine (800 mg).
MS(ES): 396 (M) and 398 (M+2) for $C_{15}H_{12}BrClFN_5$
400 MHz, DMSO-d_6: δ 2.19 (s, 3H), 2.34 (s, 3H), 6.14 (s, 1H), 7.38 (t, J = 9.08 Hz, 1H), 7.54-7.58 (m, 1H), 7.96 (dd, J = 2.48, 6.68 Hz, 1H), 8.83 (s, 1H), 10.24 (s, 1H).

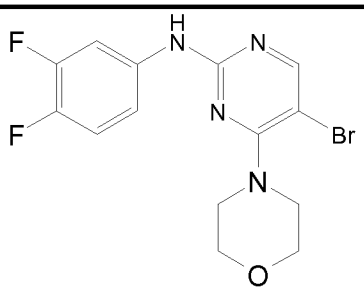
The following intermediates were prepared using the general method described above for **Intermediate 112** using 5- bromo-2-[N-(3-chloro-4-fluorophenyl)]-4-(methyl sulfonyl)pyrimidin-2-amine (**Intermediate 69**), sodium hydride and the starting material (SM) indicated.

Int	Compound	Data	SM
113	 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 450 (M) for $C_{15}H_9BrClF_4N_5$. 300 MHz, $CDCl_3$: δ 2.45 (s, 3H), 6.51 (s, 1H), 7.14 (t, *J* = 8.70 Hz, 1H), 7.27-7.30 (m, 1H), 7.75 (dd, *J* = 2.61, 6.39 Hz, 1H), 8.70 (s, 1H).	(5-Methyl-3-trifluoromethyl-1*H*-pyrazole)
114	 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(4-chloro-1*H*-pyrazol-1-yl)pyrimidin-2-amine	MS(ES): 404 (M+2) for $C_{13}H_7BrCl_2FN_5$. 400 MHz $CDCl_3$: δ 7.16 (d, *J* = 8.56 Hz 1H), 7.32-7.36 (m, 1H), 7.78 (m, 2H), 8.38 (s, 1H), 8.65 (s, 1H).	4-Chloro-1*H*-pyrazole
115	 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS (ES): 436(M) and 438(M+2) for $C_{14}H_7BrClF_4N_5$. 300 MHz DMSO-d_6 : δ 7.14 (s, 1H), 7.28 (t, *J* = 9.06 Hz 1H), 7.61 (d, *J* = 8.64 Hz 1H), 8.00 (br s, 1H), 8.62 (br s, 1H), 8.91 (br s, 1H), 10.83 (br s, 1H).	3-Trifluoromethyl-1*H*-pyrazole

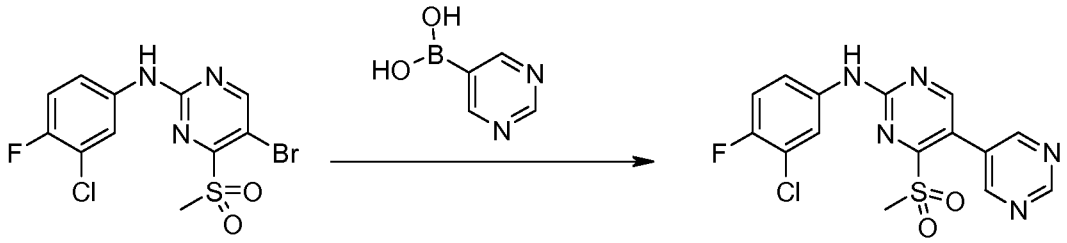
Int	Compound	Data	SM
116	 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(4,5-dichloro-1*H*-imidazol-1-yl)pyrimidin-2-amine	MS(ES): 436 (M) and 438 (M+2) for $C_{13}H_6BrCl_3FN_5$. 300 MHz DMSO-d_6 : δ 7.39 (t, *J* = 9.06 Hz, 1H), 7.57-7.60 (m, 1H), 7.92 (d, *J* = 5.85 Hz 1H), 8.28 (s, 1H), 9.0 (s, 1H), 10.55 (br s, 1H).	4,5-Dichloro-1*H*-imidazole
117	 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(1*H*-pyrrol-1-yl)pyrimidin-2-amine	MS(ES): 367 (M) for $C_{14}H_9BrClFN_4$. 300 MHz DMSO-d_6 : δ 6.36 (s, 2H), 7.37 (t, *J* = 9.12 Hz, 1H), 7.60 (br s, 3H), 8.01 (dd, *J* = 6.69, 2.37 Hz, 1H), 8.75 (s, 1H), 10.18 (s, 1H).	1*H*-Pyrrole
118	 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(1*H*-imidazol-1-yl)pyrimidin-2-amine	MS(ES): 368 (M) for $C_{13}H_8BrClFN_5$. 1H NMR (300 MHz, DMSO-D6) δ ppm 7.18 (s, 1 H) 7.40 (t, *J*=9.14 Hz, 1 H) 7.55 - 7.69 (m, 1 H) 7.82 (s, 1 H) 7.98 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.39 (s, 1 H) 8.86 (s, 1 H) 10.33 (s, 1 H).	1*H*-Imidazole

The following intermediates were prepared using the general method described above for **Intermediate 112** using sodium hydride and the starting materials (SM) indicated.

Int	Compound	Data	SM
119	 5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)pyrimidine-2,4-diamine	MS: ES+ 390 for $C_{14}H_{15}BrClFN_4O$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 1.75 - 1.90 (m, 2 H) 3.24 (s, 3 H) 3.37 - 3.53 (m, 4 H) 7.11 (t, *J*=5.56 Hz, 1 H) 7.28 (t, *J*=9.14 Hz, 1 H) 7.57 (ddd, *J*=9.09, 4.29, 2.64 Hz, 1 H) 8.04 (s, 1 H) 8.11 (dd, *J*=6.97, 2.64 Hz, 1 H) 9.45 (s, 1 H)	3-methoxy propylamine and **Intermediate 69**
120	 5-bromo-4-(2,6-dimethylmorpholino)-N-(3-methoxy-5-(trifluoro methyl)phenyl) pyrimidin-2-amine	MS: ES+ 462 for $C_{18}H_{20}BrF_3N_4O_2$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 1.12 (d, *J*=6.22 Hz, 6 H) 2.54 - 2.70 (m, 2 H) 3.67 (dd, *J*=8.29, 6.41 Hz, 2 H) 3.79 (s, 3 H) 4.13 (d, *J*=12.62 Hz, 2 H) 6.79 (s, 1 H) 7.51 (s, 1 H) 7.84 (s, 1 H) 8.24 - 8.28 (m, 1 H) 9.82 (s, 1 H)	2,6-dimethyl morpholine and **Intermediate 70**
121	 5-bromo-N^2-(3-methoxy-5-(trifluoromethyl)phenyl)-N^4-(2-(pyridin-4-yl) ethyl)pyrimidine-2,4-diamine	MS: ES+ 469 for $C_{19}H_{17}BrF_3N_5O$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 2.91 (t, *J*=7.35 Hz, 2 H) 3.60 - 3.72 (m, 2 H) 3.75 (s, 3 H) 6.76 (s, 1 H) 7.13 - 7.27 (m, 3 H) 7.63 (s, 1 H) 7.76 (s, 1 H) 8.07 (s, 1 H) 8.39 - 8.47 (m, 2 H) 9.56 (s, 1 H)	2-(pyridine -4-yl)ethan amine and **Intermediate 70**

Int	Compound	Data	SM
122	 5-bromo-N-(3,4-difluorophenyl)-4-morpholinopyrimidin-2-amine	MS: ES+ 372 for $C_{14}H_{13}BrF_2N_4O$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 3.53 - 3.61 (m, 4 H) 3.67 - 3.76 (m, 4 H) 7.21 - 7.45 (m, 2 H) 7.86 (ddd, *J*=14.03, 7.44, 2.45 Hz, 1 H) 8.26 (s, 1 H) 9.71 (s, 1 H)	Morpholine and **Intermediate 71**

Intermediate 123: N-(3-chloro-4-fluorophenyl)-4-methylsulfonyl-5-pyrimidin-5-ylpyrimidin-2-amine



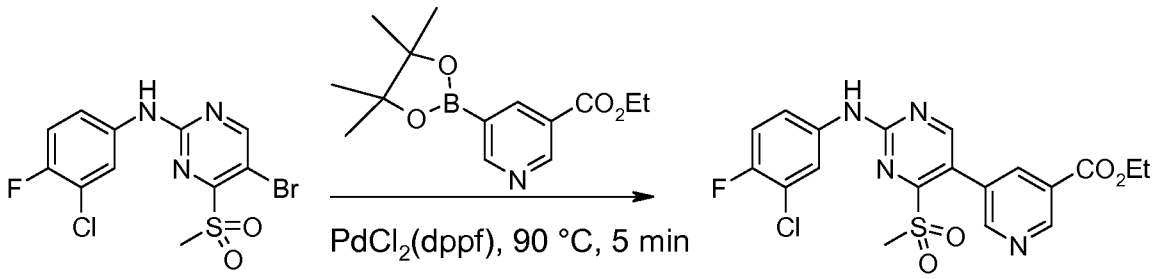
Intermediate 69 **Intermediate 123**

A suspension of **Intermediate 69** (1.05mmol, 400 mg), pyrimidine-5-boronic acid (1.68mmol, 208 mg), tris(dibenzyledeneacetone)dipalladium(0) (10 mol %, 0.1 mmol, 96 mg), 2-dicyclohexyl phosphino-2',4',6'-triiso-propyl-1,1'-biphenyl (30 mol %, 0.3 mmol, 148 mg) and sodium carbonate (1.05 mmol, 112 mg) in acetonitrile/water (4:1) was heated to 90° C for 30 min in an oil bath. The reaction mixture was diluted with ethyl acetate (10 mL) and the organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude compound was purified by silica gel column chromatography using chloroform:methanol (9:1) as an eluent in 20% yield.

MS(ES): 380 (M+1) for $C_{15}H_{11}ClFN_5O_2S$.

300 MHz DMSO-d_6 : δ 3.4 (s, 3H), 7.44 (t, *J* = 9.2 Hz, 1H), 7.63 (brs, 1H), 8.0 (br s, 1H), 8.86 (s, 1H), 8.89 (s, 2H), 9.21(s, 1H), 10.63 (s, 1H).

Intermediate 124: Ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}pyridine-3-carboxylate



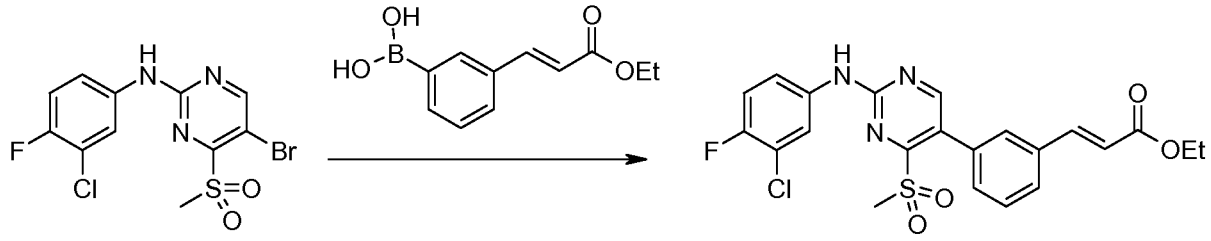
Intermediate 69 **Intermediate 124**

A suspension of **Intermediate 69** (1.31 mmol, 0.5 g), ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (1.38 mmol, 382 mg), [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium (II) complex with CH_2Cl_2 (10 mol %, 0.13 mmol, 107 mg), 2-dicyclohexyl phosphino-2',4',6'-triisopropyl-1,1'-biphenyl (30 mol %, 0.394 mmol, 188 mg) and sodium carbonate (2.62 mmol, 279 mg) in acetonitrile/water (20 mL : 5 mL) was heated to 90 °C for 5 min in an oil bath under inert atmosphere. After completion of the reaction, as monitored by TLC, the reaction mixture was diluted with EtOAc (30 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography using hexane: ethyl acetate (3:2) as an eluent. The title compound was obtained in 51 % combined yield (0.30 g, 1.33 mmol).

MS (ES) : 451 (M+1) for $C_{19}H_{16}ClFN_4O_4S$.

^{1}H NMR (300 MHz, DMSO-d_6) : δ 1.34 (t, J = 7.08 Hz, 3H), 3.38 (s, 3H), 4.37 (q, J = 7.0 Hz, 2H), 7.44 (t, J = 8.97 Hz, 1H), 7.64 (m, 1H), 8.0-8.01 (m, 1H), 8.39 (s, 1H), 8.83 (s, 1H), 8.87 (d, J = 2.01 Hz, 1H), 9.11 (d, J = 1.83 Hz, 1H), 10.59 (s, 1H).

Intermediate 125: Ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}phenyl)prop-2-enoate



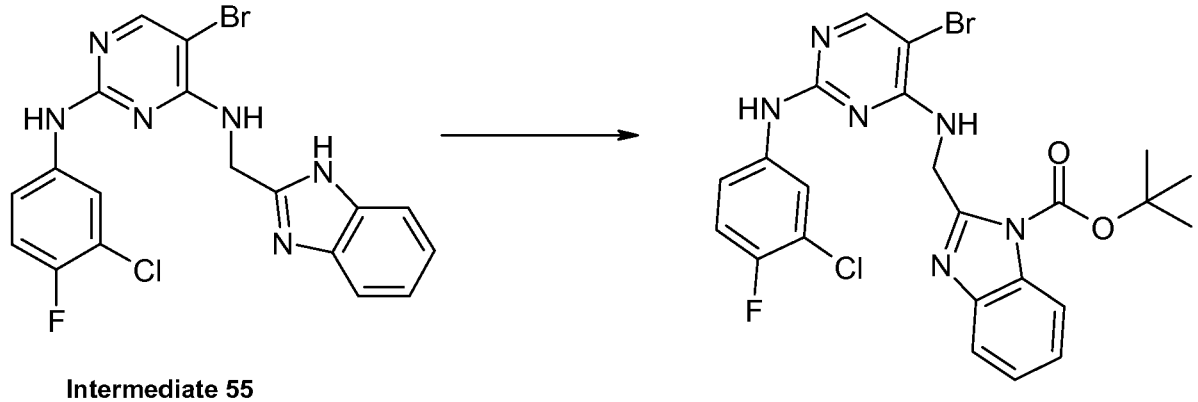
Intermediate 69 **Intermediate 125**

A suspension of **Intermediate 69** (2.11 mmol, 800 mg), {3-[(1*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]phenyl}boronic acid (2.32 mmol, 510 mg), tris(dibenzylideneacetone)dipalladium(0) (10 mol %, 0.21 mmol, 192 mg), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (30 mol %, 0.63 mmol, 300 mg) and sodium carbonate (3.15 mmol, 330 mg) in acetonitrile/water (40 mL; 4:1 mixture) was heated to 90 °C for 15-20 min in an oil bath. Acetonitrile was evaporated from the reaction mixture and water was added. The mixture was extracted with ethyl acetate (10 mL), and the organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude compound was purified by silica gel column chromatography using hexane-ethyl acetate (13:7) as an eluent to yield the title compound as a pale yellow solid in 52 % yield (0.52 g, 1.08 mmol).

MS(ES): 476 (M+1) for $C_{22}H_{19}ClFN_3O_4S$

^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.26 (t, J = 7.04 Hz, 3H), 3.36 (s, 3H), 4.20 (q, J = 7.08 Hz, 2H), 6.68 (d, J = 16.04 Hz, 1H), 7.43 (t, J = 9.08 Hz, 1H), 7.50 (t, J = 7.64 Hz, 1H), 7.56 (d, J = 7.76 Hz, 1H), 7.64 (ddd, J = 2.72, 4.12, 9.05 Hz, 1H), 7.69 (d, J = 16.04 Hz, 1H), 7.77 (d, J = 7.68 Hz, 1H), 7.84 (s, 1H), 8.02 (dd, J = 2.48, 6.72 Hz, 1H), 8.80 (s, 1H), 10.51 (s, 1H).

Intermediate 126: *Tert*-butyl 2-[[[5-bromo-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-4-yl]amino]methyl]benzimidazole-1-carboxylate



Intermediate 55

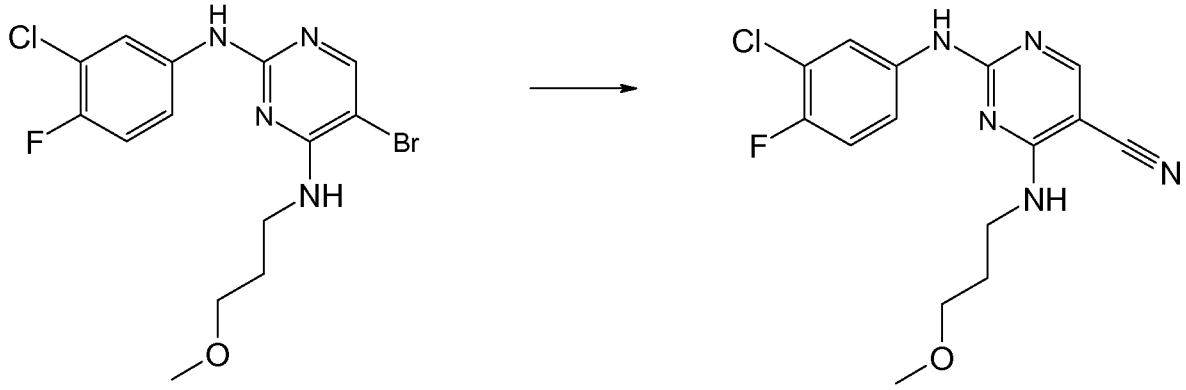
Intermediate 126

To a stirred solution of **Intermediate 55** (1g, 2.23 mmol) and triethylamine (1.24 mL, 8.93 mmol) in dichloromethane (20 mL) under nitrogen atmosphere was added di-*t*-butyldicarbonate(1.46g, 6.7 mmol) at 5-10°C. The reaction mixture was stirred overnight at room temperature, then diluted with water (20 mL) and extracted with dichloromethane (2 x 20 mL). The combined extracts were washed with water (2 x 20 mL), brine solution, dried over sodium sulfate, filtered and concentrated to give the title compound as a white solid in 83 % yield (1.2g, 1.85 mmol).

MS(ES): 547 (M) and 549 (M+2) for $C_{23}H_{21}BrClFN_6O_2$.

^{1}H NMR (300 MHz) DMSO-d_6 : δ 1.67 (s, 9H), 5.01 (d, J = 5.46 Hz, 2H), 7.05 (t, J = 9.12 Hz, 1H), 7.27-7.36 (m, 3H), 7.57 (t, J = 4.5 Hz, 1H), 7.66 (d, J = 7.44 Hz, 1H), 7.78 (t, J = 2.4 Hz, 1H), 7.92 (d, J = 7.59 Hz, 1H), 8.14 (s, 1H), 9.44 (s, 1H).

Intermediate 127: 2-(3-Chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidine-5-carbonitrile



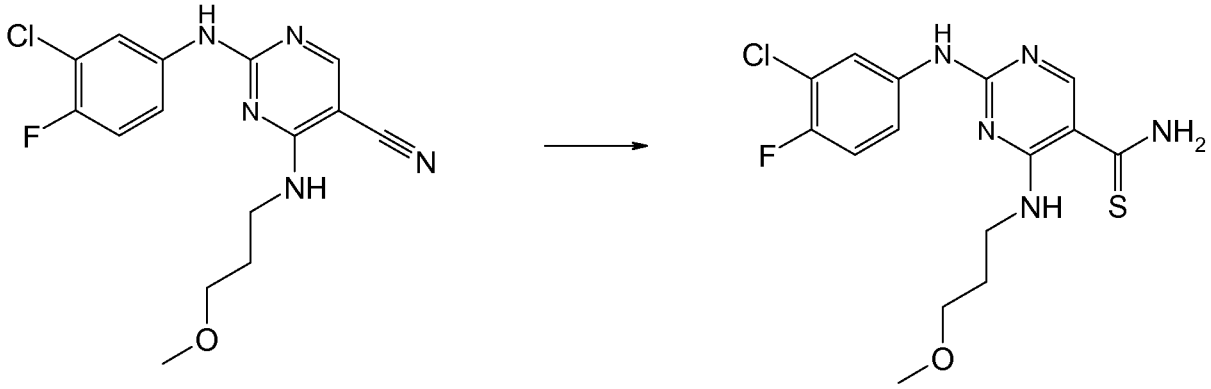
Intermediate 119 Intermediate 127

A stirred suspension of **Intermediate 119** (4.01 g, 10.3 mmol), zinc powder (168 mg, 2.57 mmol), zinc cyanide (784 mg, 6.67 mmol), tris(dibenzylideneacetone)dipalladium (0) (188 mg, 0.210 mmol), 1,1'-bis(diphenylphosphino)ferrocene (230 mg, 0.410 mmol), and zinc acetate (75 mg, 0.41 mmol) in degassed N,N-dimethylformamide (25 mL) was prepared. The vessel was purged with nitrogen gas for one minute. The mixture was placed under an atmosphere of nitrogen atmosphere and heated to 100 degrees C. A check of progress by LCMS after about an hour indicated complete conversion to desired product. Stirring continued while the mixture was allowed to cool to room temperature; the mixture was then diluted with small volumes of water. The dark solution became cloudy with addition of water. Larger volumes were added until a maximum of precipitation was reached. Stirring continued for ten minutes. The solid was collected and washed with water. Normal-phase chromatography (0-3% methanol in methylene chloride) was used to isolate the pure product (3.3 g, 95%).

MS: ES+ 336 for $C_{15}H_{15}ClFN_5O$.

1H NMR (300 MHz, DMSO-d_6) δ ppm 1.74 - 1.90 (m, *J*=6.76, 6.76, 6.64, 6.40 Hz, 2 H) 3.22 (s, 3 H) 3.39 (t, *J*=6.22 Hz, 2 H) 3.46 (q, *J*=6.53 Hz, 2 H) 7.33 (t, *J*=9.04 Hz, 1 H) 7.60 (ddd, *J*=9.04, 4.24, 2.73 Hz, 1 H) 7.86 (br. s., 1 H) 8.11 (dd, *J*=6.78, 2.45 Hz, 1 H) 8.36 (s, 1 H) 9.99 (br. s., 1 H)

Intermediate 128: 2-(3-Chloro-4-fluorophenylamino)-4-(3-methoxy propylamino)pyrimidine-5-carbothioamide



Intermediate 127

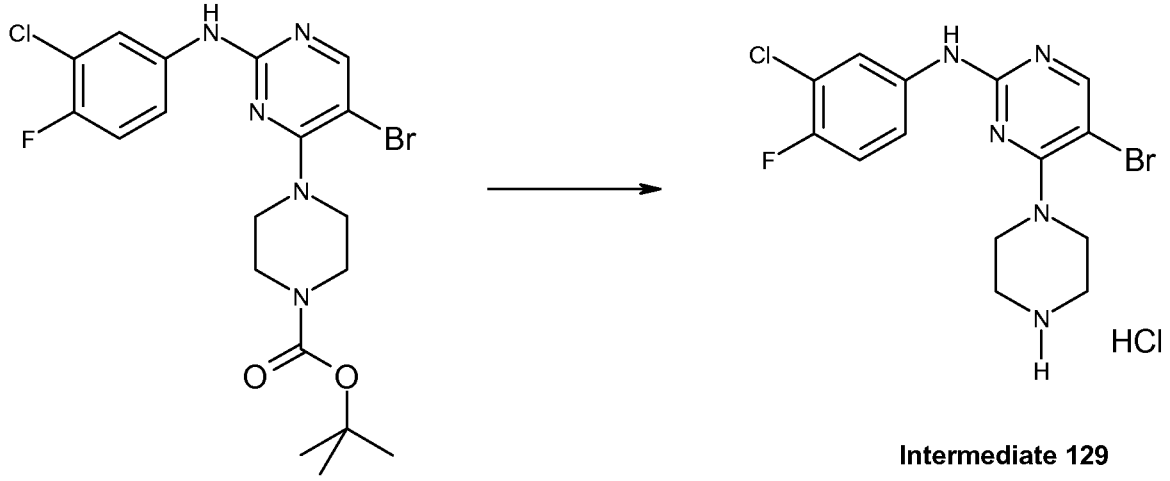
Intermediate 128

A stirred solution of **Intermediate 127** (750 mg, 2.2 mmol) in methanol (4 mL) and N,N-dimethylformamide (4 mL) was prepared under ambient conditions. The reaction vessel was purged with nitrogen, and the contents were placed under an atmosphere of nitrogen. The mixture was heated to 90 degrees C. At that time 1 mL of a 22 wt% aqueous solution of ammonium sulfide (about 3 mmol ammonium sulfide) was added slowly by syringe. Volumes of a similar size were added every thirty minutes until conversion to desired product was complete as monitored by LCMS. The mixture was allowed to cool to room temperature with stirring. Water (5 mL) was then added very slowly with stirring, precipitating a grey solid. This was collected, washed with water and dried to yield the title compound (768 mg, 93%).

MS: ES+ 369 for $C_{15}H_{17}ClFN_5OS$.

1H NMR (300 MHz, DMSO-d_6) δ ppm 1.84 (qd, *J*=6.22, 6.03 Hz, 2 H) 3.24 (s, 3 H) 3.44 (t, *J*=6.03 Hz, 2 H) 3.52 (q, *J*=5.90 Hz, 2 H) 7.32 (t, *J*=9.04 Hz, 1 H) 7.52 - 7.70 (m, 1 H) 8.22 (d, *J*=4.90 Hz, 1 H) 8.36 (s, 1 H) 9.27 (br. s., 1 H) 9.39 (br. s., 1 H) 9.64 (br. s., 1 H) 9.80 (br. s., 1 H).

Intermediate 129: 5-bromo-N-(3-chloro-4-fluorophenyl)-4-(piperazin-1-yl)pyrimidin-2-amine hydrochloride



Intermediate 110

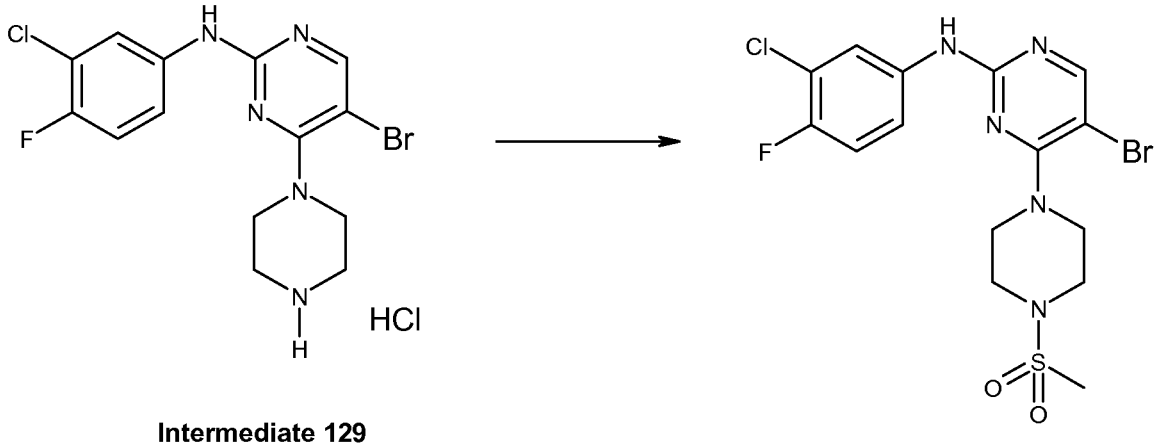
Intermediate 129

To a stirred solution of **Intermediate 110** (500mg, 1.30 mmol) in 1,4- dioxane (10 mL) under nitrogen atmosphere was added 4N hydrochloric acid in 1,4–dioxane (3 mL) dropwise. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated to give the hydrochloride salt title compound as a white solid (320 mg).

MS(ES): 386 (M) 388 (M+2) for $C_{14}H_{14}BrClFN_5$

1H NMR (300 MHz, DMSO- *d*6) δ ppm 3.22 (s, 4 H) 3.67 - 3.91 (m, 4 H) 7.33 (t, *J*=9.04 Hz, 1 H) 7.41 - 7.63 (m, 1 H) 8.00 (d, *J*=6.03 Hz, 1 H) 8.33 (s, 1 H) 9.34 (d, *J*=20.91 Hz, 1 H) 9.83 (s, 1 H).

Intermediate 130: 5-Bromo-N-(3-chloro-4-fluorophenyl)-4-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-2-amine



Intermediate 129

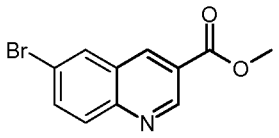
Intermediate 130

A solution of methanesulfonyl chloride (30mg, 0.26 mmol) was added to **Intermediate 129** (100 mg, 0.26 mmol), triethylamine (0.054ml, 0.39 mmol) and methylene chloride (1.5 ml) under nitrogen. The resultant mixture was stirred for 1h and concentrated under vacuum. The residue was chromatographed using 40-70% ethyl acetate/ hexane to yield the title compound (88 mg).

MS(ES): 386 (M) 388 (M+2) for $C_{15}H_{16}BrClFN_5O_2S$

1H NMR (300 MHz, DMSO- *d*6) δ ppm 2.92 (s, 3 H) 3.12 - 3.30 (m, 4 H) 3.55 - 3.84 (m, 4 H) 7.33 (t, *J*=9.14 Hz, 1 H) 7.47 - 7.71 (m, 1 H) 7.93 - 8.11 (m, 1 H) 8.30 (s, 1 H) 9.74 (s, 1 H).

Intermediate 131: Methyl 6-bromoquinoline-3-carboxylate

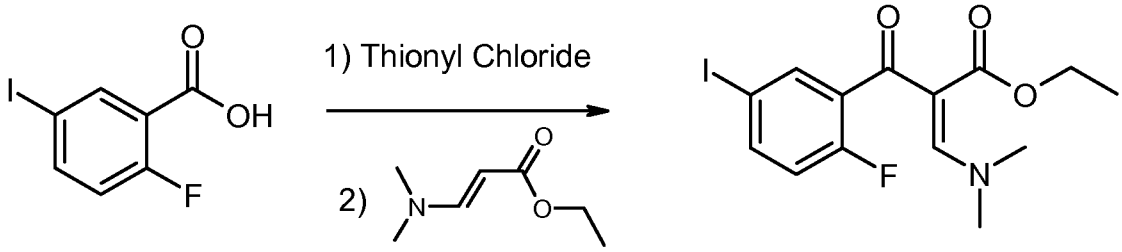


6-Bromoquinoline-3-carboxylic acid (2.5 g, 9.92 mmol) was suspended in methyl alcohol (40.2 ml, 991.81 mmol) and treated with sulfuric acid (2.64 ml, 49.59 mmol). The reaction was refluxed overnight. TLC analysis of a small aliquot showed complete reaction. The reaction was cooled to room temperature and concentrated at reduced pressure. The residue was diluted with EtOAc and carefully neutralized with a solution of sodium carbonate. The biphasic suspension was diluted with EtOAc/DCM until all solid dissolved. The layers were then separated, and the organic was washed with brine and dried over sodium sulfate. The solvent was removed at reduced to afford the desired product with good purity. It was used without further purification.

MS(ES): 266 (M), 268 (M+2) for $C_{11}H_8BrNO_2$

1H NMR (300 MHz, DMSO-D6) δ ppm 3.95 (s, 3 H) 8.03 (d, *J*=1.13 Hz, 2 H) 8.52 (s, 1 H) 8.99 (d, *J*=2.07 Hz, 1 H) 9.31 (d, *J*=2.07 Hz, 1 H).

Intermediate 132: (Z)-ethyl 3-(dimethylamino)-2-(2-fluoro-5-iodobenzoyl)acrylate

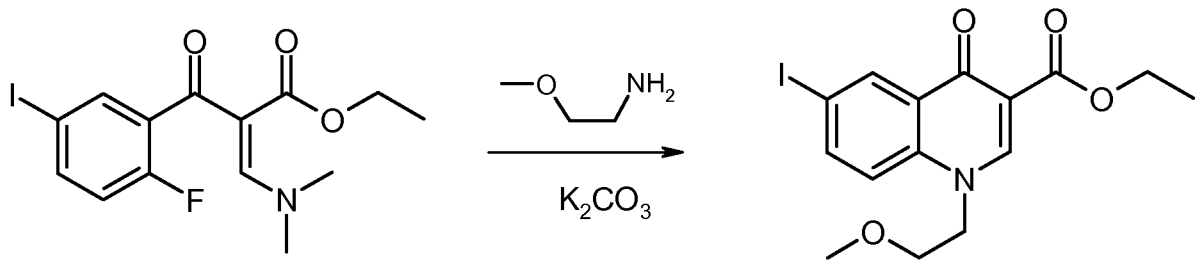


Intermediate 132

2-Fluoro-5-iodobenzoic acid (3.76 mmol, 1 g) was treated with thionyl chloride (3 mL) and DMF (2 drops). The reaction mixture was heated at 70°C for 1.5 h to form the acid chloride, then cooled and concentrated under reduced pressure. Toluene was added, and the mixture was concentrated again. The crude acid chloride was dissolved in toluene and treated with triethylamine (3.76 mmol, 0.524 mL) and ethyl 3-(dimethylamino)acrylate (4.89 mmol, 0.700 g). The reaction mixture was heated to 90 °C for 1.5 h. The reaction mixture was filtered and the resulting solution was purified using flash column chromatography (silica, 2.5:1 hexanes/ethyl acetate) to give the desired product in 47 % yield. (1.79 mmol, 0.7 g) MS(ES): 391.9 (M+1) for $C_{14}H_{15}FINO_3$.

^{1}H NMR (300 MHz) DMSO-d_6 δ : 0.95 (t, *J* = 7.14 Hz, 3H), 2.89 (br s, 3H), 3.33 (br s, 3H), 4.0(q, *J* = 7.08 Hz, 2H), 6.80 (t, *J* = 1.17 Hz, 1H), 7.64-7.69(m, 1H), 7.79 (m, 1H), 7.87 (br s, 1H).

Intermediate 133: Ethyl 6-iodo-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate

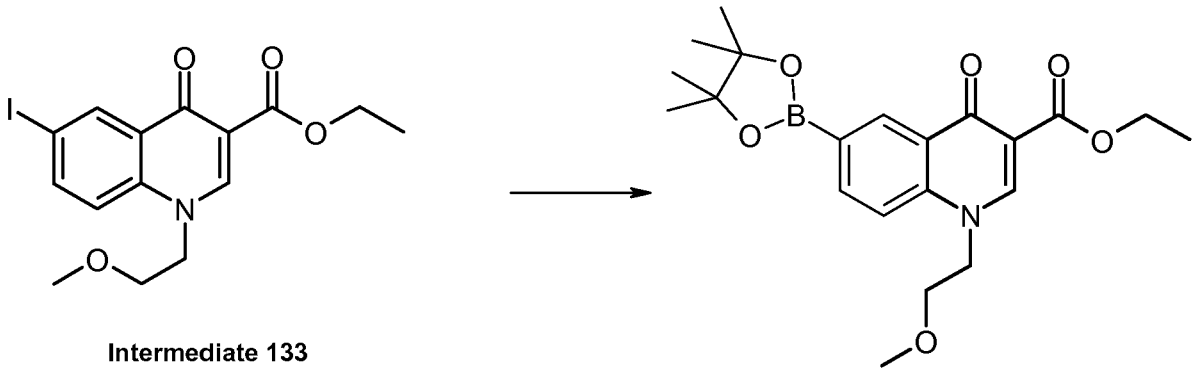


Intermediate 132 **Intermediate 133**

A suspension of (Z)-ethyl 3-(dimethylamino)-2-(2-fluoro-5-iodobenzoyl)acrylate **Intermediate 132** (1.79 mmol, 0.7 g) in ethanol (3 mL) at room temperature was treated with 2-methoxyethylamine (2.26 mmol, 0.17 mL). The reaction mixture was stirred until a yellow solution resulted and concentrated under reduced pressure after 1 h. Potassium carbonate (2.69 mmol, 0.372 g) and DMF (2 mL) were added. The reaction mixture was heated to 70 °C for 3 h, then cooled to room temperature and allowed to stand overnight. The reaction mixture was poured into water. The solid that formed was collected by filtration, washed with water and dried under vacuum for 4 h to give desired product in 80 % yield (1.44mmol, 0.580 g). MS(ES): 402 (M+1) for $C_{15}H_{16}INO_4$.

^{1}H NMR (400MHz) DMSO-d_6 δ : 1.27 (t, *J* = 7.08 Hz, 3H), 3.32 (s, 3H), 3.64 (t, *J* = 4.84 Hz, 2H), 4.22 (q, *J* = 7.08 Hz, 2H), 4.54 (t, *J* = 4.92 Hz, 2H), 7.68 (d, *J* = 9.00 Hz, 1H), 8.05 (dd, *J* = 8.94, 2.16 Hz, 1H), 8.49 (d, *J* = 2.16 Hz, 1H), 8.59 (s, 1H).

Intermediate 134: Ethyl 1-(2-methoxyethyl)-4-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydroquinoline-3-carboxylate



Intermediate 133

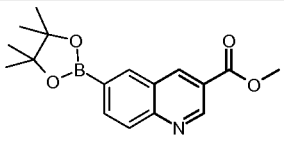
Intermediate 134

Ethyl 6-iodo-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (**Intermediate 133**, 400 mg, 1.00 mmol) was suspended in dioxane (4 mL) and degassed with nitrogen for 10 minutes at which time bis(pinacolato)diboron (506 mg, 1.99 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride (41.0 mg, 0.05 mmol), and potassium acetate (294 mg, 2.99 mmol) were added. After the reaction was heated at 90 °C overnight, LC/MS showed completion of the reaction. The reaction was then cooled to room temperature, diluted with DCM and filtered through a pad of diatomaceous earth. The filtrate was concentrated at reduced pressure and quickly purified by silica gel chromatography with 8% MeOH in DCM to yield the title compound.

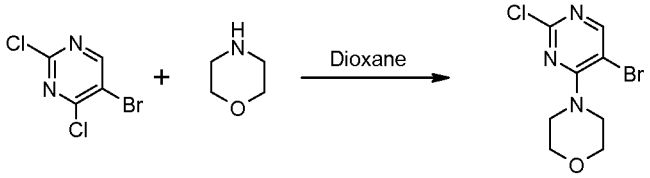
MS(ES): 402 (M+1) for $C_{21}H_{28}BNO_6$

1H NMR (300 MHz, DMSO-D6) δ ppm 1.20 - 1.45 (m, 15 H) 3.17 - 3.27 (s, 3 H) 3.67 (t, *J*=4.71 Hz, 2 H) 4.24 (q, *J*=6.97 Hz, 2 H) 4.57 (t, *J*=4.71 Hz, 2 H) 7.75 - 7.91 (m, 1 H) 7.90 - 8.04 (m, 1 H) 8.49 - 8.74 (m, 2 H).

The following intermediate was prepared using the general method described above for **Intermediate 134** using bis(pinacolato)diboron, 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride, potassium acetate and the starting material (SM) indicated.

Int	Compound	Data	SM
135	 Methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline-3-carboxylate	^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.34 (s, 12 H) 3.95 (s, 3 H) 8.08 (s, 2 H) 8.58 (s, 1 H) 9.10 (d, *J*=1.88 Hz, 1 H) 9.35 (d, *J*=2.07 Hz, 1 H)	**Intermediate 131**

Intermediate 136: 4-(5-Bromo-2-chloro-pyrimidin-4-yl)-morpholine

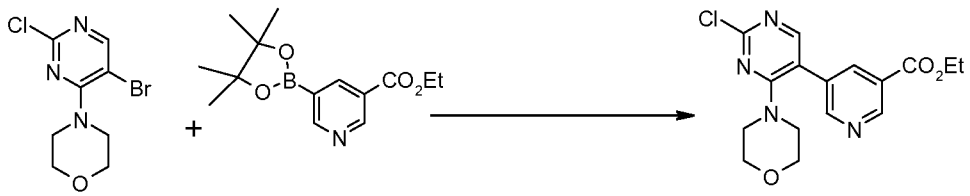


To a stirred solution of 2, 4-dichloro-5-bromopyrimidine (22 mmol, 5 g) in dioxane (100 mL), at room temperature under nitrogen atmosphere, was added morpholine (29.2 mmol, 2.54 g). The reaction mixture was stirred overnight at room temperature, diluted with ethyl acetate (50 mL) and the resulting white solid formed was removed by filtration. The filtrate was concentrated and the resulting residue was purified by column chromatography (using 60-120 mesh silica gel and 4% of ethyl acetate in petroleum ether) to yield the title compound. (4.7 g).

MS(ES): 278 (M) and 280 (M+2) for $C_8H_9BrClN_3O$.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 8H), 8.27 (s, 1H).

Intermediate 137: 5-(2-Chloro-4-morpholin-4-yl-pyrimidin-5-yl)-nicotinic acid ethyl ester



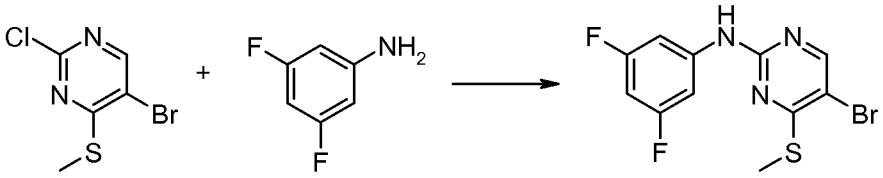
A suspension of **Intermediate 136** (3.5 mmol, 1 g), 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-nicotinic acid ethyl ester (3.6 mmol, 1.01 g), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (10 mol %, 0.35 mmol, 285 mg) and sodium carbonate (3.5 mmol, 370 mg) in acetonitrile/water (20 mL:5

mL) was degassed and heated to 90 °C for 20 min under an inert atmosphere. The solvent was removed in vacuo and the crude mixture was taken in $CHCl_3$ (30 mL). It was then washed with water and brine. The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude material was purified by silica gel column chromatography, using Hexane: Ethyl Acetate (3:1) as eluent to get **Intermediate 137** (0.69 g).

MS (ES) : 349 (M+1) for $C_{16}H_{17}ClN_4O_3$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ 0.81 (t, *J* = 6.54 Hz, 3H), 3.24-3.25 (m, 4H), 3.49-3.50 (m, 4H), 4.37 (q, *J* = 7.05 Hz, 2H), 8.20 (s, 1H), 8.37 (s, 1H), 8.91 (d, *J* = 1.98 Hz, 1H), 9.07 (d, *J* = 1.80 Hz, 1H).

Intermediate 138: (5-Bromo-4-methylsulfanyl-pyrimidin-2-yl)-(3,5-difluoro-phenyl)-amine

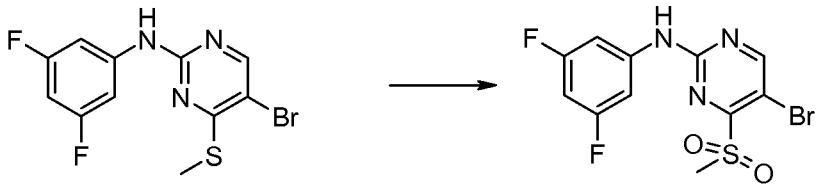


5-Bromo-2-chloro-4-(methylthio)pyrimidine (8.3 mmol, 2 g) was suspended in n-BuOH (20 mL) and treated with 3,5-difluoroaniline (9.1 mmol, 1.18 g), HCl in dioxane (4 mL) was added under nitrogen atmosphere and the mixture was refluxed at 100 °C for 3 h. The reaction was cooled to room temperature, diluted with diethyl ether and the solid was filtered and dried to afford **Intermediate 138.**

MS(ES): 333.8 (M+2) for $C_{11}H_8BrF_2N_3S$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.58 (s, 3H), 6.78 (tt, *J* = 2.32, 9.27 Hz, 1H), 7.50 (dd, *J* = 2.20, 10.36 Hz, 2H), 8.40 (s, 1H), 10.19 (s, 1H).

Intermediate 139: (5-Bromo-4-methanesulfonyl-pyrimidin-2-yl)-(3,5-difluoro-phenyl)-amine



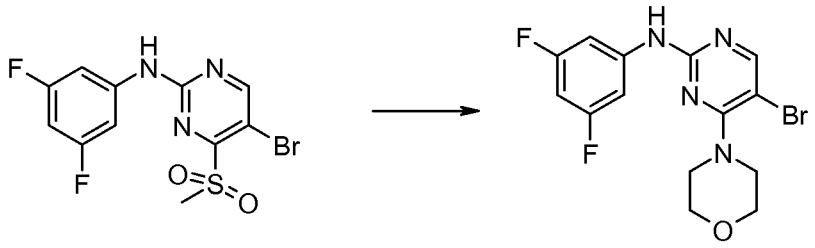
Intermediate 138 (3 mmol, 1 g) was suspended in acetone (10 mL), cooled to 0 °C and 3-chloroperoxybenzoic acid (15 mmol, 2.59 g) was added portion wise. The suspension

became a clear solution after stirring at 0 °C for 30 min. The reaction mixture was then allowed to warm up slowly to room temperature and stirred for 5 h. The reaction mixture pH was raised to 8 with the addition of aq. $NaHCO_3$ solution (50 mL), extracted with ethyl acetate (3x10 mL), combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated to get crude **Intermediate 139** (1 g).

MS(ES): 363.9 (M) and 365 (M+1) for $C_{11}H_8BrF_2N_3O_2S$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.54 (s, 3H), 6.86 (t, J = 9.24 Hz, 1H), 7.44 (d, J = 8.82 Hz, 2H), 8.99 (s, 1H), 10.72 (s, 1H).

Intermediate 140: (5-Bromo-4-morpholin-4-yl-pyrimidin-2-yl)-(3,5-difluoro-phenyl)-amine

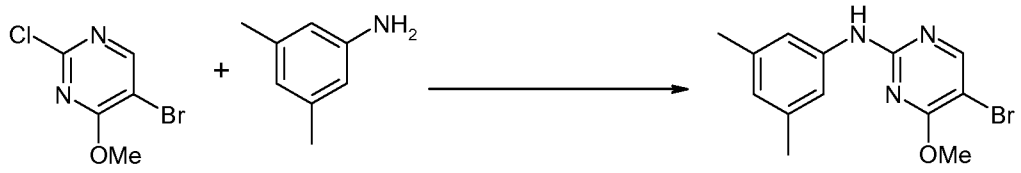


Intermediate 139 (2.7 mmol, 1 g) was suspended in NMP (10 mL), treated with N,N-diisopropylethylamine (3.4 mmol, 0.56 mL), morpholine (30 mmol, 263 mg) in a sealed tube. The reaction was heated at 90 °C for 30 min then cooled to room temperature, added to water and stirred for 15 min. The precipitate was filtered and dried to afford **Intermediate 140**.

MS(ES): 371 (M) and 373 (M+2) for $C_{14}H_{13}BrF_2N_4O$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.59 (d, J = 3.93 Hz, 4H), 3.72 (s, 4H), 6.72 (t, J = 9.36 Hz, 1H), 7.45 (d, J = 10.32 Hz, 2H), 8.30 (s, 1H), 9.91 (s, 1H).

Intermediate 141: (5-Bromo-4-methoxy-pyrimidin-2-yl)-(3,5-dimethyl-phenyl)-amine



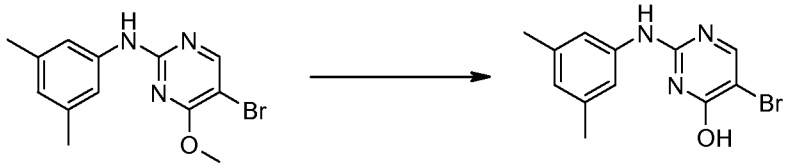
To a stirred solution of 5-bromo-2-chloro-4-methoxypyrimidine (17.9 mmol, 4 g) and 3,5-dimethylaniline (18.8 mmol, 2.2 g) in acetonitrile (50 mL), 4 M HCl in 1,4-dioxane (5 mL) was added drop wise. The resulting solution was refluxed at 100 °C with constant stirring. The solvent was removed in vacuo and basified with 10% $NaHCO_3$ solution,

extracted with EtOAc (2x150 mL). The combined organic layer was washed with water and brine, dried over sodium sulfate and concentrated under vacuo to yield **Intermediate 141** as a white solid (9.7 mmol, 3 g, 54%).

MS(ES): 310 (M+2) for $C_{13}H_{14}BrN_3O$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 6H), 3.99 (d, J = 1.84 Hz, 3H), 6.62 (s, 1H), 7.34 (s, 2H), 8.35 (d, J = 2.0 Hz, 1H), 9.63 (s, 1H).

Intermediate 142: 5-Bromo-2-(3,5-dimethyl-phenylamino)-pyrimidin-4-ol

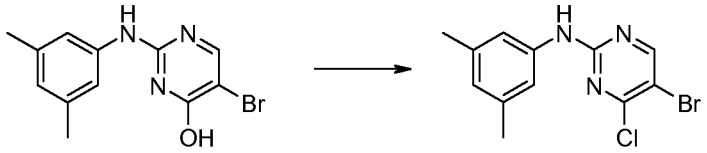


A mixture of **Intermediate 141** (9.7 mmol, 3 g) and aq. sodium thiomethoxide (38.9 mmol, 18 mL, 21% w/v,) and DMF (75 mL) was heated at 60 °C for 2 h; cooled to room temperature, poured into water (150 mL) and acidified with 1.5 N HCl solution. The precipitated solid was filtered to yield **Intermediate 142** as off-white solid (2.5 g).

MS(ES): 294 (M) and 296 (M+2) for $C_{12}H_{12}BrN_3O$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 6H), 6.69 (s, 1H), 7.14 (s, 2H), 8.04 (s, 1H), 8.79 (br s, 1H), 11.33 (br s, 1H).

Intermediate 143: (5-Bromo-4-chloro-pyrimidin-2-yl)-(3,5-dimethyl-phenyl)-amine

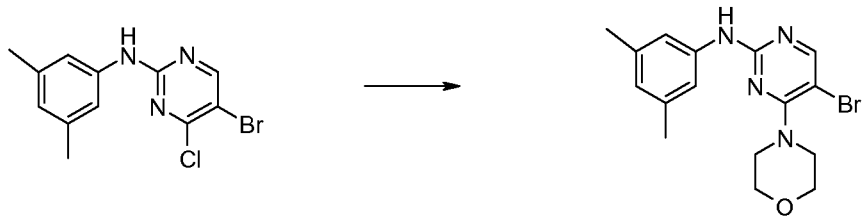


A solution of **Intermediate 142** (8.4 mmol, 2.5 g) in phosphorus oxychloride (13 mL) was heated to reflux for 45 min, cooled to RT, poured carefully onto a mixture of ice (100 mL) and saturated aq. $NaHCO_3$ solution (20 mL) with constant stirring. It was further extracted with ethyl acetate (2x150 mL). The combined organic layer was washed with water and brine, dried over sodium sulfate and concentrated under vacuo to yield **Intermediate 143** (1.7 g).

MS(ES): 312 (M) and 314 (M+2) for $C_{12}H_{11}BrClN_3$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 6H), 6.67 (s, 1H), 7.27 (s, 2H), 8.66 (s, 1H), 10.05 (s, 1H).

Intermediate 144: (5-Bromo-4-morpholin-4-yl-pyrimidin-2-yl)-(3,5-dimethyl-phenyl)-amine

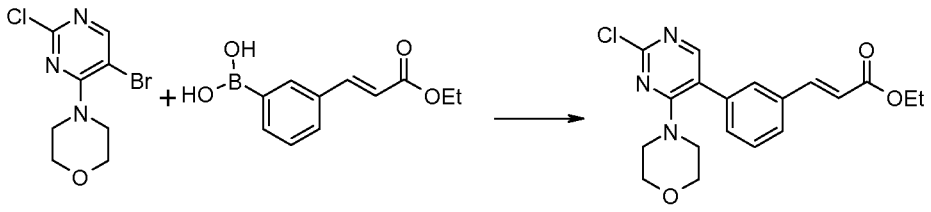


A mixture of **Intermediate 143** (5.4 mmol, 1.7 g) and morpholine (10.8 mmol, 0.94 g) in dioxane (40 mL) was stirred at room temperature for 18 h. Then the reaction mixture was concentrated under vacuo to yield white solid. The solid was dissolved in ethyl acetate (150 mL) and washed with water, brine and dried over sodium sulfate. The solvent was concentrated under vacuo to yield **Intermediate 144** as a white solid (1.5 g).

MS(ES): 365 (M+2) for $C_{16}H_{19}BrN_4O$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 6H), 3.57-3.59 (m, 4H), 3.72-3.73 (m, 4H), 6.57 (s, 1H), 7.32 (s, 2H), 8.21 (d, J = 1.2 Hz, 1H), 9.35 (s, 1H).

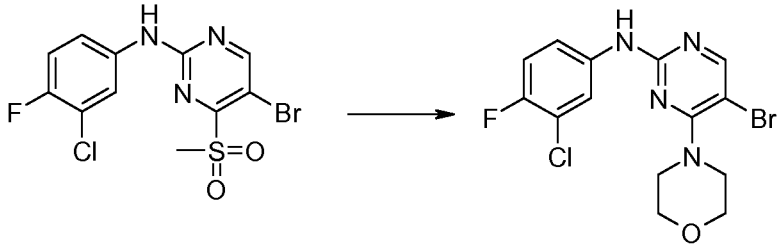
Intermediate 145: 3-[3-(2-Chloro-4-morpholin-4-yl-pyrimidin-5-yl)-phenyl]-acrylic acid ethyl ester



A suspension of 4-(5-Bromo-2-chloro-pyrimidin-4-yl)-morpholine **Intermediate 136** (3.5 mmol, 1 g), ethyl boronocinnamate (3.95 mmol, 0.87 g), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (0.35 mmol, 285 mg) and sodium carbonate (3.5 mmol, 370 mg) in acetonitrile/water (20 mL : 5 mL) was degassed and heated to 90 °C for 15-20 min under inert atmosphere. The solvent was removed in vacuo and the crude mixture was taken in $CHCl_3$ (30 mL). It was then washed with water and brine. The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude material was purified by 60-120 mesh silica gel column chromatography using Hexane:Ethylacetate (91:9) to get 3-[3-(2-Chloro-4-morpholin-4-yl-pyrimidin-5-yl)-phenyl]-acrylic acid ethyl ester **Intermediate 145** (0.63 g). MS (ES) : 374 (M+1) for $C_{19}H_{20}ClN_3O_3$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.25 (t, J = 7.05 Hz, 3H), 3.25-3.32 (m, 4H), 3.49-3.50 (m, 4H), 4.19 (q, J = 7.05 Hz, 2H), 6.74 (d, J = 16.05 Hz, 1H), 7.50-7.59 (m, 2H), 7.69 (d, J = 16.14 Hz, 1H), 7.73 (br s, 1H), 7.83 (s, 1H), 8.11 (s, 1H) .

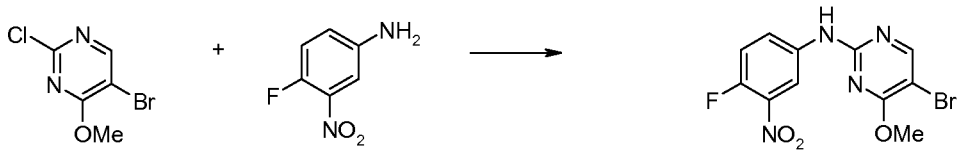
Intermediate 146: 5-bromo-N-(3-chloro-4-fluorophenyl)-4-morpholinopyrimidin-2-amine



5-Bromo-2-[N-(3-chloro-4-fluorophenyl)]-4-(methylsulfonyl)pyrimidin-2-amine **Intermediate 69** (15.7 mmol, 6 g) was suspended in NMP (30 mL) and treated with N,N-diisopropylethylamine (23.6 mmol, 4 mL) and morpholine (18.9 mmol, 1.64 g) in a 100 mL round-bottomed flask. The reaction was refluxed at 90 °C for 45 min. The reaction mixture was added to water and stirred for 15 min. The precipitated solid was filtered and washed successively with water, diethyl ether and hexanes and dried to afford 4.96 g of **Intermediate 146** (12.56 mmol, 80 %). MS(ES): 387 (M) and 389 (M+2) for $C_{14}H_{13}BrClFN_4O$.

^{1}H NMR 400 MHz DMSO-d_6: δ 3.57-3.59 (m, 4H), 3.71-3.73 (m, 4H), 7.32 (t, J = 9.08 Hz, 1H), 7.55 (ddd, J = 9.00, 4.18, 2.68 Hz, 1H), 8.04 (dd, J = 6.86, 2.64 Hz, 1H), 8.26 (d, J = 1.20 Hz, 1H), 9.71 (s, 1H).

Intermediate 147: 5-bromo-*N*-(4-fluoro-3-nitrophenyl)-4-methoxypyrimidin-2-amine



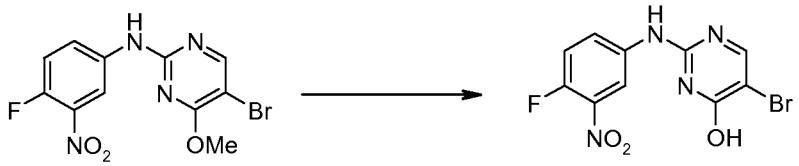
To a stirred solution of 5-bromo-2-chloro-4-methoxypyrimidine (8.96 mmol, 2 g) and (4-fluoro-3-nitrophenyl)amine (9.41 mmol, 1.47 g) in butanol (40 mL), 4 M HCl in 1,4-dioxane (2.5 mL) was added dropwise. The resulting solution was refluxed at 100 °C with constant stirring. The solvent was removed in vacuo and basified with 10% $NaHCO_3$ solution. It was further extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with water and brine, dried over sodium sulfate and concentrated under vacuum to yield 5-bromo-

N-(4-fluoro-3-nitrophenyl)-4-methoxypyrimidin-2-amine **Intermediate 147** as a white solid (2 g).

MS(ES): 343 (M)and 345 (M+2) for $C_{11}H_8BrFN_4O_3$.

^{1}H-NMR (400 MHz, DMSO-d_6 : δ 4.04 (s, 3H), 7.53 (dd, *J* = 9.28, 11.02 Hz, 1H), 7.92-7.96 (m, 1H), 8.45 (s, 1H), 8.79 (dd, *J* = 2.56, 6.76 Hz, 1H), 10.24 (br s, 1H).

Intermediate 148: 5-bromo-2-[(4-fluoro-3-nitrophenyl)amino]pyrimidin-4-ol

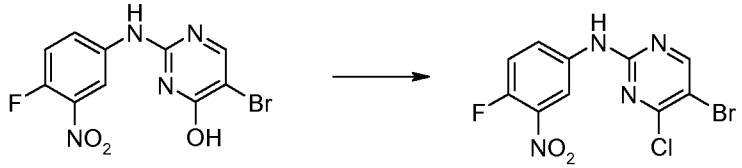


A mixture of 5-bromo-*N*-(4-fluoro-3-nitrophenyl)-4-methoxypyrimidin-2-amine **Intermediate 147** (5.82 mmol, 2 g) and HBr in AcOH (12 mL) and aq. HBr (6 mL) was heated at 100 °C for 3 h; The reaction mixture was cooled to RT, extracted with ethyl acetate (2 x 100mL), washed with brine, dried over Na_2SO_4 and concentrated to yield 1.3 g of 5-bromo-2-[(4-fluoro-3-nitrophenyl)amino]pyrimidin-4-ol **Intermediate 148** as an off-white solid.

MS(ES): 329 (M) and 331 (M+2) for $C_{10}H_6BrFN_4O_3$.

^{1}H-NMR (400 MHz, DMSO-d6): δ 7.55 (dd, *J* = 9.16, 11.04 Hz, 1H), 7.87-7.89 (m, 1H), 8.12 (s, 1H), 8.47 (dd, *J* = 2.80, 6.74 Hz, 1H), 9.39 (br s, 1H), 11.8 (br s, 1H).

Intermediate 149: 5-bromo-4-chloro-N-(4-fluoro-3-nitrophenyl)pyrimidin-2-amine

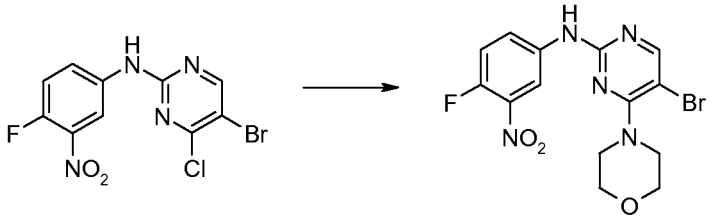


A solution of 5-bromo-2-[(4-fluoro-3-nitrophenyl)amino]pyrimidin-4-ol **Intermediate 148** (3.95 mmol, 1.3 g) in phosphorus oxychloride (6 mL) was heated to reflux for 45 minutes, cooled to RT, poured carefully onto a mixture of ice (100 mL) and sat. $NaHCO_3$ (20 mL) with constant stirring. It was further extracted with EtOAc (2 x 150 mL). The combined organic layers were washed with water and brine, dried over sodium sulfate and concentrated under vacuum to yield 5-bromo-4-chloro-*N*-(4-fluoro-3-nitrophenyl)pyrimidin-2-amine **Intermediate 149** (1 g).

MS(ES): 347 (M) and 349 (M+2) for $C_{10}H_5BrClFN_4O_2$.

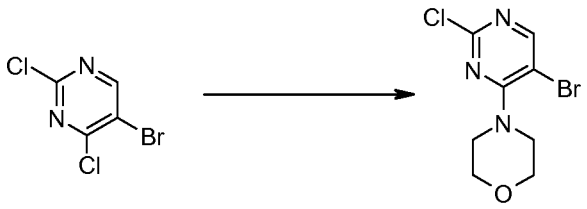
^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.57 (dd, J = 9.24, 11.05 Hz, 1H), 7.93-7.98 (m, 1H), 8.57 (dd, J = 2.73, 6.73 Hz, 1H), 8.77 (s, 1H), 10.63 (br s, 1H).

Intermediate 150: 5-bromo-N-(4-fluoro-3-nitrophenyl)-4-morpholin-4-ylpyrimidin-2-amine



A mixture of 5-bromo-4-chloro-*N*-(4-fluoro-3-nitrophenyl)pyrimidin-2-amine **Intermediate 149** (2.88 mmol, 1 g) and morpholine (3.45 mmol, 0.3 g) was stirred at room temperature for 18 h. Then the reaction mixture was concentrated under vacuum to yield white solid. The solid was dissolved in EtOAc (100 mL) and washed with water, brine and dried over sodium sulfate. The solvent was concentrated under vacuum to yield 5-bromo-*N*-(4-fluoro-3-nitrophenyl)-4-morpholin-4-ylpyrimidin-2-amine **Intermediate 150** as a white solid (1 g).
MS(ES): 398 (M) and 400 (M+2) for $C_{14}H_{13}BrFN_5O_3$.
400 MHz, DMSO-d_6: δ 3.62-3.63 (m, 4H), 3.71-3.72 (m, 4H), 7.50 (t, J = 10.24 Hz, 1H), 7.83-7.86 (m, 1H), 8.30 (s, 1H), 8.81 (d, J = 6.24 Hz, 1H), 10.04 (s, 1H).

Intermediate 151: 4-(5-Bromo-2-chloro-pyrimidin-4-yl)-morpholine

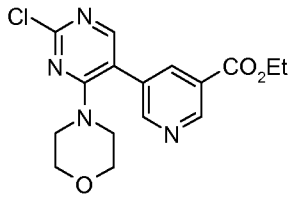


To a stirred solution of 2,4-dichloro-5-bromopyrimidine (22 mmol, 5 g) in dioxane (50 mL), at room temperature under nitrogen atmosphere was added morpholine (29.2 mmol, 2.54 g). Further dilution with dioxane (50 mL) became necessary as the reaction progressed. The reaction mixture was stirred overnight at room temperature, then diluted with ethyl acetate (50 mL) and white solid formed was removed by filtration. The filtrate was concentrated and the resulting residue was purified by column chromatography (using 60-120 mesh silica gel and 4 % of ethylacetate in petroleum ether) to give 4-(5-Bromo-2-chloro-pyrimidin-4-yl)-morpholine **Intermediate 151** (4.7 g).

MS (ES): 278 (M) and 280 (M+2) for $C_8H_9BrClN_3O$.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 8H), 8.27 (s, 1H).

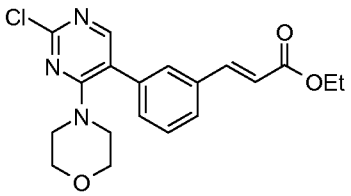
Intermediate 152: 5-(2-Chloro-4-morpholin-4-yl-pyrimidin-5-yl)-nicotinic acid ethyl ester



A suspension of 4-(5-Bromo-2-chloro-pyrimidin-4-yl)-morpholine **Intermediate 151** (3.5 mmol, 1 g), 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-nicotinic acid ethyl ester (3.6 mmol, 1.01 g), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)complex with CH_2Cl_2 (10 mol %, 0.35 mmol, 0.285 g) and sodium carbonate (3.5 mmol, 0.370 g) were taken in acetonitrile/water (20 mL : 5 mL), degassed and heated to 90 °C for 15-20 min under inert atmosphere. The solvent was removed in vacuo and the crude mixture was taken in $CHCl_3$ (30 mL). It was then washed with water and brine. The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude material was purified by silica gel column chromatography. The product eluted with Hexane: Ethyl Acetate (3 : 1) eluent mixture. The title compound **Intermediate 152** was obtained (0.69 g). MS (ES) : 349 (M+1) for $C_{16}H_{17}ClN_4O_3$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ 0.81 (t, J = 6.54 Hz, 3H), 3.24-3.25 (m, 4H), 3.49-3.50 (m, 4H), 4.37 (q, J = 7.05 Hz, 2H), 8.20 (s, 1H), 8.37 (s, 1H), 8.91 (d, J = 1.98 Hz, 1H), 9.07 (d, J = 1.80 Hz, 1H).

Intermediate 153: 3-[3-(2-Chloro-4-morpholin-4-yl-pyrimidin-5-yl)-phenyl]-acrylic acid ethyl ester



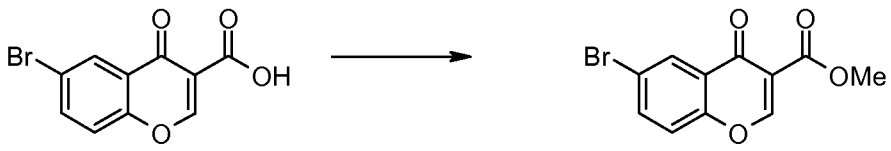
A suspension of 4-(5-Bromo-2-chloro-pyrimidin-4-yl)-morpholine **Intermediate 151** (3.5 mmol, 1 g), ethyl boronocinnamate (3.95 mmol, 0.87 g), [1,1′-bis(diphenyl-phosphino)ferrocene]dichloropalladium(II)complex with CH_2Cl_2 (10 mol %, 0.35 mmol,

0.285 g) and sodium carbonate (3.5 mmol, 0.370 g) in acetonitrile/water (20 mL : 5 mL) was degassed and heated to 90 °C for 15-20 min under inert atmosphere. Completion of the reaction was monitored by TLC. The solvent was removed in vacuo and the crude mixture was taken in $CHCl_3$ (30 mL). It was then washed with water and brine. The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude material was purified by silica gel column chromatography. The product eluted with Hexane : Ethyl Acetate (91 : 9) eluent mixture. The title compound **Intermediate 153** was obtained (0.63 g).

MS (ES) : 374 (M+1) for $C_{19}H_{20}ClN_3O_3$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.25 (t, *J* = 7.05 Hz, 3H), 3.25-3.32 (m, 4H), 3.49-3.50 (m, 4H), 4.19 (q, *J* = 7.05 Hz, 2H), 6.74 (d, *J* = 16.05 Hz, 1H), 7.50-7.59 (m, 2H), 7.69 (d, *J* = 16.14 Hz, 1H), 7.73 (br s, 1H), 7.83 (s, 1H), 8.11 (s, 1H) .

Intermediate 154: methyl 6-bromo-4-oxo-4*H*-chromene-3-carboxylate

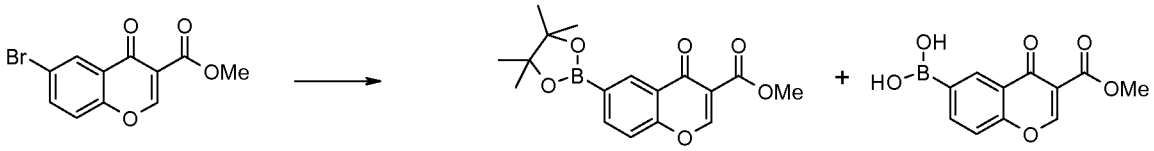


To a solution of 6-bromo-4-oxo-4*H*-chromene-3-carboxylic acid (3.7 mmol, 1 g) in methanol (15 mL) was added thionyl chloride (5 mL) slowly at 0 °C. The reaction mixture was then refluxed at 70 °C for 2 h and then cooled to room temperature. Methanol was removed in vacuo and the residue was poured on to ice water (25 mL), extracted with ethyl acetate (2 x10 mL). The combined organic extracts were washed with 10 % sodium bicarbonate solution (2 x10 mL), brine, dried over anhydrous sodium sulphate, filtered and concentrated to get methyl 6-bromo-4-oxo-4*H*-chromene-3-carboxylate **Intermediate 154** as yellow solid (900 mg).

MS(ES): 283 (M) and 285.2 (M+2) for $C_{11}H_7BrO_4$.

^{1}H-NMR(400 MHz, DMSO-d_6): δ 3.80 (s, 3H), 7.74 (d, *J* = 8.80 Hz, 1H), 8.03 (dd, *J* = 2.80, 9.00 Hz, 1H), 8.16 (d, *J* = 2.40 Hz, 1H), 9.01 (s, 1H).

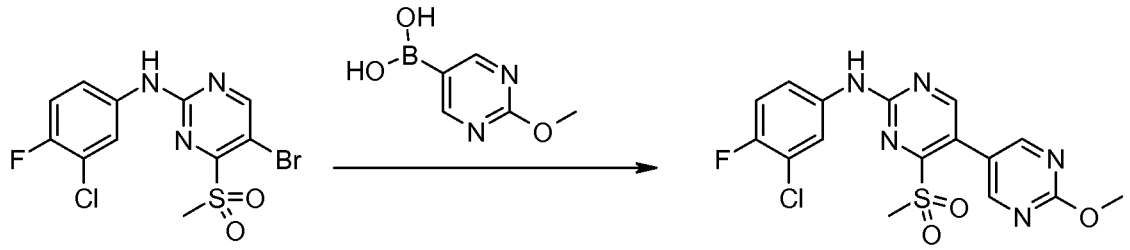
Intermediate 155: methyl 4-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4*H*-chromene-3-carboxylate and [3-(methoxycarbonyl)-4-oxo-4*H*-chromen-6-yl]boronic acid



A mixture of methyl 6-bromo-4-oxo-4*H*-chromene-3-carboxylate **Intermediate 154** (1.41 mmol, 400 mg), bis(pinacolato)diboron (3.94 mmol, 1 g), 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (20 mol%, 0.28 mmol, 135 mg), palladium acetate (4 mol%, 0.06 mmol, 16 mg) and triethylamine (5.6 mmol, 570 mg) in dioxane (20 mL) was degassed and then refluxed at 100 °C for 20 min under nitrogen atmosphere. The solvent was removed in vacuo, residue diluted with dichloromethane (20 mL), washed with water (2x 20 mL), brine. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated and the resulting residue was then recrystallized with dichloromethane-hexane to get 300 mg of a mixture of methyl 4-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4*H*-chromene-3-carboxylate and [3-(methoxycarbonyl)-4-oxo-4*H*-chromen-6-yl]boronic acid, **Intermediate 155**.

MS(ES): 249.2 (M+1) for $C_{11}H_9BO_6$. LC = 58.64 % of boronic acid and 331.2 (M+1) for $C_{17}H_{19}BO_6$ LC = 36.05 % for pinacol boronate.

Intermediate 156: 3-Chloro-4-fluoro-phenyl)-(4-methanesulfonyl-2'-methoxy-[5,5']bipyrimidinyl-2-yl)-amine

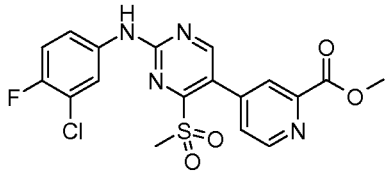


A suspension of sulfone **Intermediate 69** (7.8 mmol, 3 g), methoxypyrimidineboronic acid (8.6 mmol, 1.38 g), dichlorobis(triphenyl-phosphine)palladium(II) (0.6 mmol, 437 mg) and sodium carbonate (7.8 mmol, 826 mg) in dioxane (20 mL)-water (5 mL) was degassed and refluxed at 100 °C for 15-20 minutes. Dioxane was removed under vacuum and the residue taken in chloroform (50 mL), washed with water (50 mL) and brine. The layers were separated and the organic layer was dried over sodium sulphate, filtered and concentrated.

The resulting residue was then purified by column chromatography using 230-400 mesh silica gel and 2% of methanol in chloroform as eluent. The solid thus obtained was stirred with acetonitrile for 15 minutes. The solid was filtered and dried under vacuum to yield the title compound as solid (1.4 g). MS(ES): 410.2 (M+1) for $C_{16}H_{13}ClFN_5O_3S$.

^{1}H-NMR(300 MHz, DMSO-d_6): δ 3.39 (s, 3H), 3.96 (s, 3H), 7.43 (t, J = 9.09 Hz, 1H), 7.60-7.65 (m, 1H), 8.00 (dd, J = 2.40, 6.61 Hz, 1H), 8.67 (s, 2H), 8.81 (s, 1H), 10.57 (s, 1H).

Intermediate 157: methyl 4-{2-[(3-chloro-4-fluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}pyridine-2-carboxylate



A mixture of methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-carboxylate (1.1 eq, 0.289 mmol, 0.076 g) and 2,8,9-Triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane (0.1 eq, 0.024 mmol, 8.1 mg) was stirred for 20 min under N_2 in acetonitrile (3 mL). [Flask I]

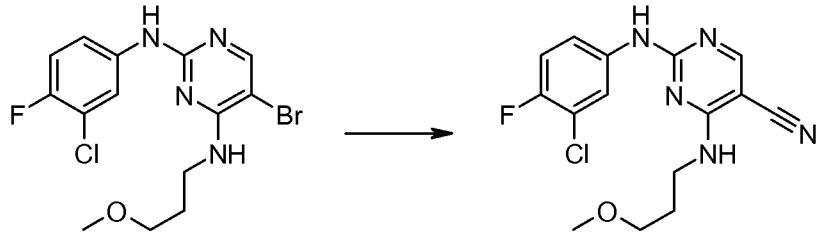
In a separate flask, 5-bromo-N-(3-chloro-4-fluorophenyl)-4-(methylsulfonyl)pyrimidin-2-amine, (Intermediate **69)** (1 eq, 0.263 mmol, 100 mg) was mixed with [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)complex with CH_2Cl_2 (10 mol%, 21.5 mg) and stirred for 10 min under N_2 in acetonitrile (3 mL). [Flask II]

The contents of [Flask I] were quickly transferred to [Flask II]. Water (1.5 mL) was added and the mixture was heated at 90 °C for 20-25 minutes then concentrated *in vacuo*. The resulting slurry was taken in EtOAc and washed with water and brine. The organic layer was separated, dried over sodium sulfate, filtered and concentrated.

The reaction was repeated on the same scale using the above procedure. The crude materials from both batches were combined and purified by silica gel column chromatography (60-120 mesh) using ethyl acetate/hexanes (2:3 to 3: 2) as an eluent. The title compound was thus obtained (0.09 g). MS(ES): 437 (M+1) for $C_{18}H_{14}ClFN_4O_4S$.

400 MHz, DMSO-d_6: δ 3.38 (s, 3H), 3.90 (s, 3H), 7.44 (t, J = 9.08 Hz, 1H), 7.64 (ddd, J = 2.72, 4.10, 9.03 Hz, 1H), 7.75 (dd, J = 1.76, 4.94 Hz, 1H), 8.00 (dd, J = 2.40, 6.66 Hz, 1H), 8.19 (d, J = 1.12 Hz, 1H), 8.78 (d, J = 4.96 Hz, 1H), 8.82 (s, 1H), 10.63 (s, 1H).

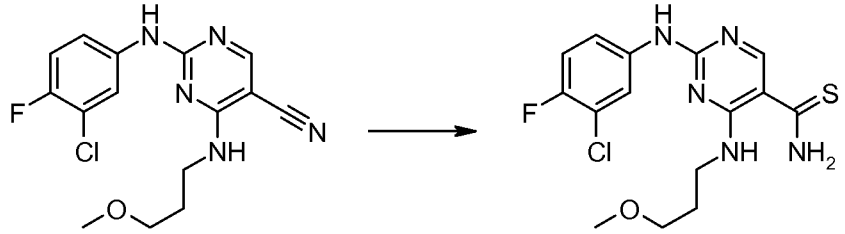
Intermediate 158: 2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidine-5-carbonitrile



To a stirred suspension of 5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)pyrimidine-2,4-diamine, **Intermediate 119** (7.7 mmol, 3 g, 1 eq), zinc acetate (0.306 mmol, 0.056 g, 0.04 eq), zinc (1.9 mmol, 0.124 g, 2.5 eq), tris(dibenzylideneacetone)-dipalladium (0) (0. 15 mmol, 0. 135 g, 0.02 eq) and 1,1'-bis(diphenylphosphino)ferrocene (0.3 mmol, 0. 168 g, 0.04 eq) in degassed DMF (30 mL) was added zinc cyanide (0. 580 g, 4.9 mmol). The vessel was evacuated and backfilled with argon; this process was repeated once. The mixture was placed under an atmosphere of nitrogen, stirred, and heated to 100 °C for 3 hours. The stirring was continued while the mixture was allowed to cool to room temperature; the mixture was then diluted with small volumes of water. The dark solution became cloudy with addition of water. Larger volumes were added until a maximum of precipitation was reached. The stirring was continued for ten minutes. The solid was collected and washed with water to give the title compound (2.1 g). MS(ES): 336 (M+1) for $C_{15}H_{15}ClFN_5O$.

300 MHz, DMSO-d_6: δ 1.76-1.85 (m, 2H), 3.21 (s, 3H), 3.38 (t, J = 6.15 Hz, 2H), 3.41-3.47 (m, 2H), 7.33 (t, J = 9.09 Hz, 1H), 7.57-7.62 (m, 1H), 7.87 (br s, 1H), 8.09-8.12 (m, 1H), 8.36 (s, 1H), 9.99 (br s, 1H).

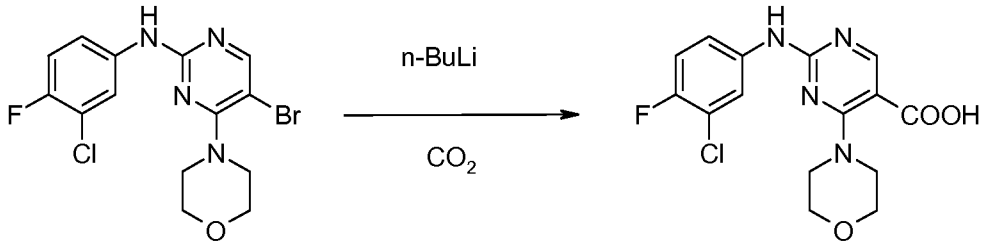
Intermediate 159: 2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidine-5-carbothioamide



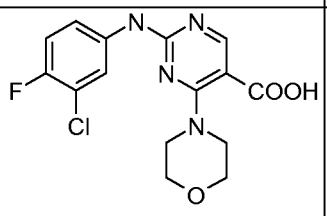
To 2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidine-5-carbonitrile, **Intermediate 158** (6.8 mmol, 2.3 g) in 5 mL DMF, ammonium sulfide, (20 % aq solution, 14 mL, 41 mmol) was added and heated at 70 °C in a sealed tube for 4 h. The reaction mixture was quenched with water and the solid was filtered to give the title compound (2 g). MS(ES): 368 (M-1) for $C_{15}H_{17}ClFN_5OS$.

400 MHz, DMSO-d_6: δ 1.80-1.87 (m, 2H), 3.32 (s, 3H), 3.43 (t, J = 6.12 Hz, 2H), 3.52 (q, J = 6.56 Hz, 2H), 7.32 (t, J = 9.08 Hz, 1H), 7.59-7.63 (m, 1H), 8.21 (dd, J = 2.48, 6.84 Hz, 1H), 8.35 (s, 1H), 9.26 (br s, 1H), 9.37 (br s, 1H), 9.63 (br s, 1H), 9.79 (br s, 1H).

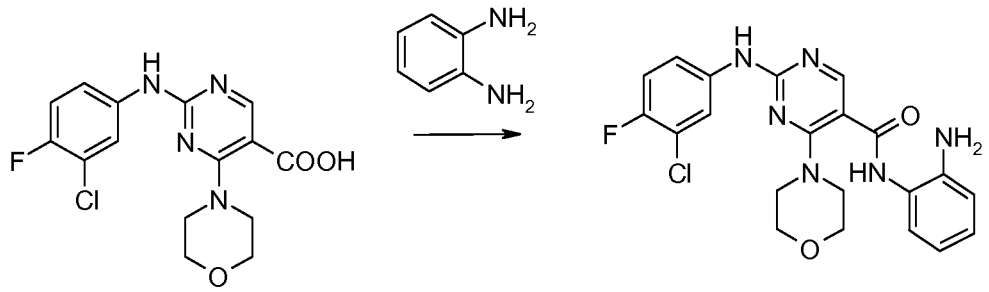
Intermediate 160: 2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidine-5-carboxylic acid



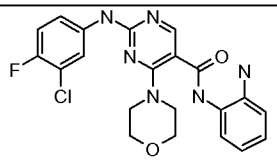
To 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(morpholin-4-yl)pyrimidin-2-amine **Intermediate 146**, 0.51 mmol, 0.2 g) in dry THF at-78° C under nitrogen atmosphere, n-BuLi (1.6 M in Hexanes, 1.02 mmol, 0.64 mL) was added dropwise and stirred for 20 min. Carbon dioxide gas was passed into the reaction mixture for 10 min with constant stirring. The solvent was evaporated and the residue was dissolved in water followed by washing with ethyl acetate. The aqueous layer was acidified with 1 N HCl and the precipitate formed was filtered and dried to yield 45 mg of 2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidine-5-carboxylic acid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 160	 2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidine-5-carboxylic acid	MS(ES): 353 (M+1) for $C_{15}H_{14}ClFN_4O_3$. 400 MHz, DMSO-d_6: δ 3.51-3.52 (m, 4H), 3.66-3.68 (m, 4H), 7.33 (t, J = 9.12 Hz, 1H), 7.56-7.60 (m, 1H), 8.03 (dd, J = 2.60, 6.84 Hz, 1H), 8.54 (s, 1H), 9.86 (br s, 1H), 12.58 (br s, 1H).	**Intermediate 146**

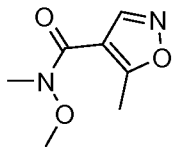
Intermediate 161: *N*-(2-aminophenyl)-2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidine-5-carboxamide



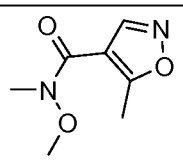
To a mixture of 2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidine-5-carboxylic acid (**Intermediate 160**, 0.85 mmol, 0.3 g) and (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (1 mmol, 442 mg) in DMF at 0° C, Et_3N (2.14 mmol, 216 mg, 0.3 mL) was added and stirred for 5 min. 1,2-phenylenediamine (1 mmol, 110 mg) in DMF was added drop wise to the reaction mixture and stirred at RT for 4-5 h. Water was added to the mixture and stirred overnight. The solid thus obtained was filtered and purified by column chromatography using methanol: chloroform (3: 97) to yield the title compound (70 mg).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 161	 *N*-(2-aminophenyl)-2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidine-5-carboxamide	MS(ES): 443 (M+1) for $C_{21}H_{20}ClFN_6O_2$. 400 MHz, DMSO-d_6: δ 3.55-3.56 (m, 4H), 3.65-3.67 (m, 4H), 4.95 (br s, 2H), 6.57 (t, J = 7.60 Hz, 1H), 6.74 (d, J = 7.96 Hz, 1H), 6.92 (t, J = 7.36 Hz, 1H), 7.29 (d, J = 7.68 Hz, 1H), 7.33 (t, J = 9.12 Hz, 1H), 7.60 (dd, J = 2.56, 8.38 Hz, 1H), 8.08 (d, J = 4.52 Hz, 1H), 8.35 (s, 1H), 9.52 (s, 1H), 9.71 (s, 1H).	**Intermediate 160** 2-[(3-chloro-4-fluorophenyl) amino]-4-(morpholin-4-yl)pyrimidine -5-carboxylic acid

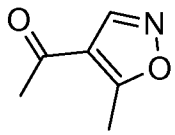
Intermediate 162: *N*-methoxy-*N*,5-dimethylisoxazole-4-carboxamide



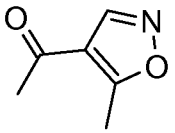
To a mixture of 5-methylisoxazole-4-carboxylic acid (3.5 mmol, 500 mg), triethylamine (11.8 mmol, 1.19 g, 1.6 mL) and *N*,*O*-Dimethylhydroxylamine hydrochloride (5.1 mmol, 498 mg) in DCM, was added T3P (50 % in EtOAc, 3.3 mL, 6 mmol) slowly at 0 °C. The reaction mixture was slowly raised to room temperature and stirred for 12 h. Reaction mixture was then diluted with dichloromethane (12 mL) and the dichloromethane layer was successively with water (2x50 mL), 10% aq sodium bicarbonate solution (50 mL) and brine. The organic layer was dried over sodium sulphate, filtered and concentrated. The residue was further purified using column chromatography (60-120 mesh; product eluted at 15% ethyl acetate/hexanes) to yield 480 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 162	 *N*-methoxy-*N*,5-dimethylisoxazole-4-carboxamide	MS(ES): 171 (M+1) for $C_7H_{10}N_2O_3$. 300 MHz, $CDCl_3$: δ 2.71 (s, 3H), 3.34 (s, 3H), 3.69 (s, 3H), 8.54 (s, 1H).	5-methylisoxazole -4-carboxylic acid

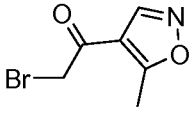
Intermediate 163: 1-(5-methylisoxazol-4-yl)ethanone



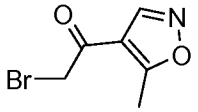
To 480 mg of *N*-methoxy-*N*,5-dimethylisoxazole-4-carboxamide (**Intermediate 162**, 2.8 mmol) taken in dry ether at 0 °C, was added drop wise a solution of methyl magnesium bromide (3 M in ether) (2.8 mL, 8.4 mmol, 3 eq). The contents of the flask were then slowly brought to room temperature and stirred for 3 h. The reaction was quenched with saturated ammonium chloride (2 x20 mL) and extracted with Et_2O. The organic layer was dried over sodium sulphate, filtered and concentrated to yield 200 mg of the title compound.

Compound	Structure	Mass spectrum and ^1H NMR	SM
Intermediate 163	 1-(5-methylisoxazol-4-yl)ethanone	MS(ES): 126 (M+1) (84 % purity) for $C_6H_7NO_2$ 300 MHz, $CDCl_3$: δ 2.47 (s, 3H), 2.73 (d, *J* = 0.45 Hz, 3H), 8.48 (d, *J* = 0.48 Hz, 1H).	**Intermediate 162** *N*-methoxy-*N*,5-dimethylisoxazole-4-carboxamide

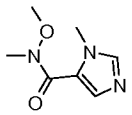
Intermediate 164: 2-bromo-1-(5-methylisoxazol-4-yl)ethanone



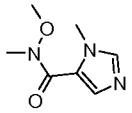
To 340 mg of 1-(5-methylisoxazol-4-yl)ethanone (**Intermediate 163**, 2.7 mmol) taken in dry THF at room temperature, was added phenyltrimethylammonium tribromide (3 mmol, 1.12 g) and refluxed for 2 h. The reaction was quenched with water (2 x20 mL) and extracted with ethyl acetate. The organic layer was dried over sodium sulphate, filtered and concentrated. The resulting residue was purified by silica gel column chromatography (60-120 mesh; product eluted at 15% ethyl acetate/hexanes) to afford 100 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 164	 2-bromo-1-(5-methylisoxazol-4-yl)ethanone	MS(GC): 110 (100 %), 123, 203 (M) and 205 (M+2)for $C_6H_6BrNO_2$. 300 MHz, $CDCl_3$: δ 2.76 (s, 3H), 4.14 (s, 2H), 8.58 (s, 1H).	**Intermediate 163** 1-(5-methylisoxazol-4-yl)ethanone

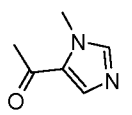
Intermediate 165: *N*-methoxy-*N*,1-dimethyl-1*H*-imidazole-5-carboxamide



To a mixture of 1-methyl-1*H*-imidazole-5-carboxylic acid (7.93 mmol, 1 g), triethylamine (19.83 mmol, 2.77 mL) and *N*,*O*-Dimethylhydroxylamine hydrochloride (9.52 mmol, 928 mg) in DCM, was added T3P (50 % in EtOAc, 11.89 mol, 7.57 mL) slowly at 0 °C. The reaction mixture was slowly raised to room temperature and stirred overnight. Reaction mixture was then diluted with dichloromethane (12 mL), washed the dichloromethane solution successively with water (2x50 mL), 10% aq sodium bicarbonate solution (50 mL) and brine. The organic layer was dried over sodium sulphate, filtered and concentrated. The residue was further purified using column chromatography (hexane-ethyl acetate as the eluent) to yield the title compound (1.13 g).

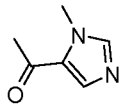
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 165	 *N*-methoxy-*N*,1-dimethyl-1*H*-imidazole-5-carboxamide	MS(ES): 170 (M+1) for $C_7H_{11}N_3O_2$. 400 MHz, MeOD: δ 3.34 (s, 3H), 3.74 (s, 3H), 3.93 (br s, 3H), 7.74 (br s, 1H), 7.91 (s, 1H).	1-methyl-1*H*-imidazole-5-carboxylic acid

Intermediate 166: 1-(1-methyl-1*H*-imidazol-5-yl)ethanone

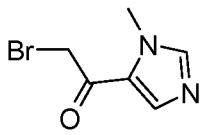


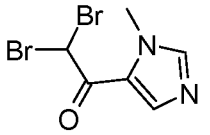
To 1.3 g of *N*-methoxy-*N*,1-dimethyl-1*H*-imidazole-5-carboxamide (**Intermediate 165**, 7.68

mmol) taken in dry ether at 0 °C, was added drop wise a solution of methyl magnesium bromide (3 M in ether) (7.69 mL, 23 mmol). The contents of the flask were then slowly brought to room temperature and stirred for 3 h. The reaction was quenched with 1.5 N HCl (2 x20 mL) and extracted with Et_2O. The organic layer was dried over sodium sulphate, filtered and concentrated to yield 800 mg of the title compound.

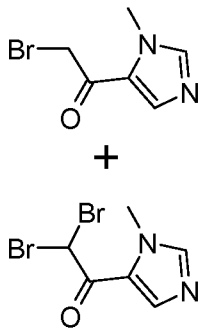
Compound	Structure	Mass spectrum and ^1H NMR	SM
Intermediate 166	 1-(1-methyl-1*H*-imidazol-5-yl)ethanone	MS(GC): 125 (M+1), 124 (M), 109 (M-15), 81 (M-43) for $C_6H_8N_2O$. 400 MHz, $CDCl_3$: δ 2.46 (s, 3H), 3.91 (s, 3H), 7.55 (br s, 1H), 7.76 (br s, 1H).	**Intermediate 165** *N*-methoxy-*N*,1-dimethyl-1*H*-imidazole-5-carboxamide

Intermediate 167: 2-bromo-1-(1-methyl-1*H*-imidazol-5-yl)ethanone and 2,2-dibromo-1-(1-methyl-1*H*-imidazol-5-yl)ethanone

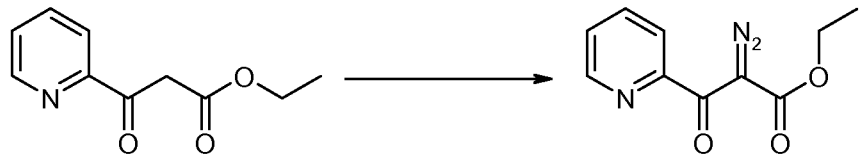




1-(1-methyl-1*H*-imidazol-5-yl)ethanone (2.89 mmol, 0.36 g) was dissolved in 5 mL of 48 % hydrogen bromide. To the stirred solution at 25 °C was added over a 5 min period bromine (3.19 mmol, 0.163 mL, 0.51 g) dissolved in 5 mL of 48 % hydrogen bromide. The reaction mixture was heated at 70 °C for 2.5 h and then concentrated *in vacuo* to a dark oil. A mixture of isopropyl alcohol/diethyl ether was added, and trituration of the oil gave a solid. This was collected by filtration and washed with diethyl ether to give 0.28 g of a mixture of 2-bromo-1-(1-methyl-1*H*-imidazol-5-yl)ethanone and 2,2-dibromo-1-(1-methyl-1*H*-imidazol-5-yl)ethanone.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 167	 2-bromo-1-(1-methyl-1*H*-imidazol-5-yl)ethanone and 2,2-dibromo-1-(1-methyl-1*H*-imidazol-5-yl)ethanone	Obtained as a mixture of monobromo and dibromo ketones. MS(GC) for the monobromoketone: 202 and 204 for $C_6H_7BrN_2O$. 1H NMR for the dibromoketone 400 MHz, DMSO-d_6: δ 3.98 (s, 3H), 7.56 (s, 1H), 8.77 (s, 1H), 9.17 (s, 1H).	**Intermediate 166** 1-(1-methyl-1*H*-imidazol-5-yl)ethanone

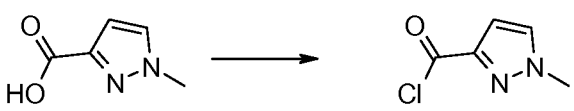
Intermediate 168: [1-ethoxy-1,3-dioxo-3-(pyridin-2-yl)propan-2-ylidene]diazenium



To a mixture of ethyl 3-oxo-3-(pyridin-2-yl)propanoate (0.52 mmol, 100 mg), *p*-Acetamidobenzene sulfonyl azide (0.52 mmol, 114 mg) in dry acetonitrile (5 mL) was added triethyl amine (1.56 mmol, 157 mg) slowly at 0 °C. The reaction mixture was slowly raised to room temperature and stirred for 2-3 h. The solvent was removed *in vacuo* and the resulting residue was stirred with petroleum ether: diethyl ether (1:1) mixture for 0.5 h and filtered. The filtrate was concentrated to yield 100 mg of the title compound as brownish liquid, which was used in the next step without further purification.

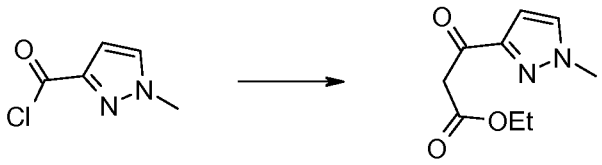
MS(ES): 220 (M+1) for $C_{10}H_9N_3O_3$.

Intermediate 169: 1-methyl-1H-pyrazole-3-carbonyl chloride

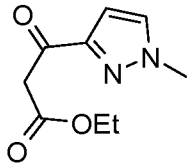


To a suspension of 1-methyl-1*H*-pyrazole-3-carboxylic acid (0.3 g, 2.38 mmol) in dichloromethane (10 mL) was added oxalyl chloride (0.3 mL, 3.6 mmol) dropwise at 0 °C. The resulting mixture was stirred at room temperature for 1 h and then heated to 70 °C for 2 h. After cooling to room temperature, the excess oxalyl chloride and solvent was removed by rotary evaporator (with water bath temperature below 40 °C) to afford the title compound as a gum, which was used in the next step without further purification.

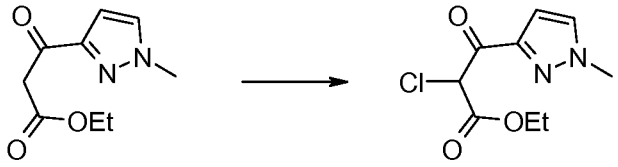
Intermediate 170: ethyl 3-(1-methyl-1*H*-pyrazol-3-yl)-3-oxopropanoate



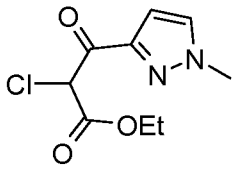
0.53 g of ethyl hydrogen malonate (4.05 mmol) was taken in anhydrous tetrahydrofuran (10 mL) in a 2-necked 100 mL round bottom flask equipped with a nitrogen inlet. After cooling to -78 °C, n-butyl lithium (2.7 mL, 8.1 mmol, 3 M solution in hexanes) was added through a syringe while the temperature was allowed to rise to approximately -10 °C. The heterogeneous solution was recooled to -75 °C and acid chloride, **Intermediate 169**, prepared above in anhydrous THF (5 mL) was added over 10-15 minutes. The resulting mixture was stirred for 3 hours and then poured into a 100 mL separatory funnel containing ethyl acetate (50 mL) and ice-cold 1N HCl (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (50 mL x 2). The organic layers were combined and washed with saturated aqueous sodium bicarbonate solution (2 x 50 mL) and brine (50 mL). The solvent was removed under vacuum to afford a purple solid, which was purified by RP-HPLC (Symmetry C18 column(19 x 300 mm, 7μm); using a binary solvent mixture of 10 mM NH_4OAc (A)/CH_3CN (B) (0-20 min: 0-40% B, 20-30 min: 40% B and 30-40 min: 40-100% B; flow rate of 15 mL/min; Separation was monitored at 254 nm) to get the title compound as a semi-solid (100 mg).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 170	 ethyl 3-(1-methyl-1*H*-pyrazol-3-yl)-3-oxopropanoate	MS(ES): 197 (M+1) for $C_9H_{12}N_2O_3$. 300 MHz, $CDCl_3$: δ 1.27 (t, *J* = 7.14 Hz, 3H), 3.97 (s, 3H), 4.02 (s, 2H), 4.21 (q, *J* = 7.11 Hz, 2H), 6.83 (d, *J* = 2.34 Hz, 1H), 7.39 (d, *J* = 2.34 Hz, 1H).	**Intermediate 169** 1-methyl-1H-pyrazole-3-carbonyl chloride

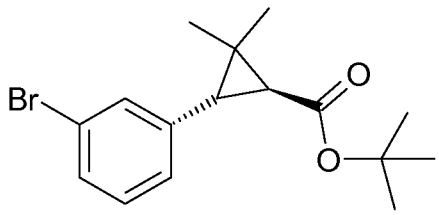
Intermediate 171: ethyl 2-chloro-3-(1-methyl-1*H*-pyrazol-3-yl)-3-oxopropanoate



To a solution of ethyl 3-(1-methyl-1*H*-pyrazol-3-yl)-3-oxopropanoate (**Intermediate 170**, 100 mg, 0.510 mmol) in ethyl acetate (5 mL) was added N-chlorosuccinimide (75 mg, 0.56 mmol, 1.1 equiv) and Amberlyst-15 resin (100 mg). The resulting mixture was stirred for 4 hours at room temperature. The solid was removed by filtration and the solvent was removed *in vacuo* to afford the title compound (100 mg) which was used for the next step without further purification.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 171	 ethyl 2-chloro-3-(1-methyl-1*H*-pyrazol-3-yl)-3-oxopropanoate	MS(ES): 231 (M+1) for $C_9H_{11}ClN_2O_3$. 300 MHz, $CDCl_3$: δ 1.28 (t, *J* = 7.11 Hz, 3H), 4.00 (s, 3H), 4.27 (q, *J* = 7.26 Hz, 2H), 5.91 (s, 1H), 6.91 (d, *J* = 2.40 Hz, 1H), 7.43 (d, *J* = 2.37 Hz, 1H).	**Intermediate 170** ethyl 3-(1-methyl-1*H*-pyrazol-3-yl)-3-oxopropanoate

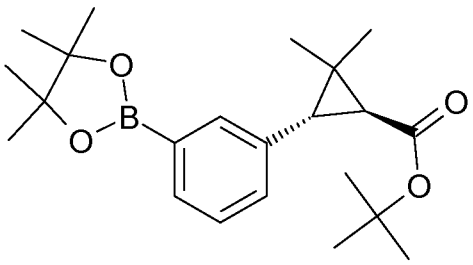
Intermediate 173: (1,3-*trans*)-tert-butyl 3-(3-bromophenyl)-2,2-dimethylcyclopropanecarboxylate



Isopropyltriphenylphosphonium iodide (1.621 g, 3.75 mmol) was suspended in THF (8 ml) and cooled to –78 °C. 2.4 M butyllithium in hexanes (1.563 mL, 3.75 mmol) was added dropwise over 2 minutes. The mixture was then stirred over an ice-water bath 30 min to give a clear dark red solution. The mixture was cooled to –78 °C and a solution of (E)-tert-butyl 3-(3-bromophenyl)acrylate (590 mg, 2.08 mmol) in THF (3 ml) was added. The mixture was cooled over an ice-water bath and allowed to slowly warm to room temperature overnight. Methyl iodide (0.6 mL, 9.60 mmol) was added to the mixture followed by stirring at room temperature 1 hour. The mixture was poured into 0.5M HCl, extracted with EtOAc, dried over $MgSO_4$ and evaporated. The residue was dissolved in dichloromethane and filtered over silica gel, rinsed with 200 ml 5% ethyl acetate in hexane. The filtrate was evaporated to give the crude product as a yellow oil: (550 mg).

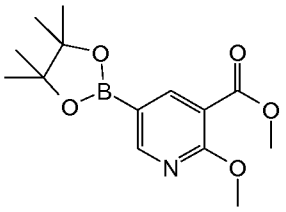
^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.90 (s, 3 H), 1.34 (s, 3 H), 1.48 (s, 9 H), 1.86 (d, 1 H), 2.56 (d, 1 H), 7.06 - 7.17 (m, 2 H), 7.29 - 7.35 (m, 2 H).

Intermediate 174: (1,3-*trans*)-tert-butyl 2,2-dimethyl-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropanecarboxylate

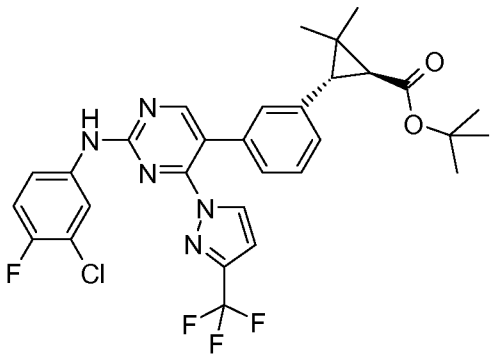


(1,3-*trans*)-tert-butyl 3-(3-bromophenyl)-2,2-dimethylcyclopropanecarboxylate) **Intermediate 173** (1.3 g, 4.00 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane (2.030 g, 7.99 mmol), potassium acetate (1.177 g, 11.99 mmol), PdCl2(dppf)-CH_2Cl_2 Adduct (0.326 g, 0.40 mmol) and dioxane (10 mL) were combined and degassed by bubbling an argon stream through the mixture for 10 minutes. The mixture was warmed over a 90 °C heating block 1h15m. The mixture was allowed to cool, diluted to ~40 ml with CH_2Cl_2, filtered and evaporated then applied to a 40g silica cartridge and eluted with 0 to 10% ethyl acetate / hexanes. The title compound was obtained as a thick clear oil (1.124 g) 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.89 (s, 3 H), 1.25 (s, 3 H), 1.34 (s, 12 H), 1.48 (s, 9 H), 1.93 (d, 1 H), 2.61 (d, 1H), 7.25 (d, 1 H), 7.28 (t, 1 H), 7.59 (s, 1 H), 7.64 (d, 1 H)

The intermediates in the table below were prepared using the procedure described above and the specified starting material.

Compound	**Structure**	**Mass spectrum and ^{1}H NMR**	**SM**
Intermediate 175	 methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) nicotinate	MS: ES+ 294 for $C_{14}H_{20}BNO_5$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 1.30 (s, 12 H) 3.81 (s, 3 H) 3.96 (s, 3 H) 8.30 (d, *J*=1.88 Hz, 1 H) 8.55 (d, *J*=2.07 Hz, 1 H)	Methyl 5-bromo -2-methoxy nicotinate

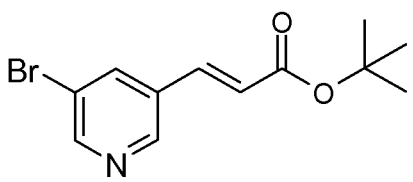
Intermediate 176: (1,3-trans)-tert-butyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenyl)-2,2-dimethylcyclopropanecarboxylate



(1S,3S)-tert-butyl 2,2-dimethyl-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropanecarboxylate **Intermediate 174** (300 mg, 0.81 mmol), 5-bromo-N-(3-chloro-4-fluorophenyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine [**Intermediate 115**] (200 mg, 0.46 mmol), Tris(dibenzylideneacetone)dipalladium(0) (41.9 mg, 0.05 mmol), 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (65.5 mg, 0.14 mmol), Na_2CO_3 (72.8 mg, 0.69 mmol), acetonitrile (3 mL) and water (0.750 mL) were combined and degassed with an argon stream for 10 min. The mixture was warmed at 80 °C 1h15m, allowed to cool, diluted with acetonitrile, filtered and adsorbed on 15 ml silica gel. Flash chromatography (40 g cartridge) 20 to 100% dichloromethane/hexane gave the pure title compound (35 mg). MS: ES+ 602 for $C_{30}H_{28}ClF_4N_5O_2$.

1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.86 (s, 3 H), 1.32 (s, 3 H), 1.46 (s, 9 H), 1.79 (d, 1 H), 2.57 (d, 1 H), 6.56 (s, 1 H), 6.92 (s, 1 H), 7.00 (d, 1 H), 7.09 - 7.21 (m, 2 H), 7.25 - 7.32 (m, 2 H), 7.35 - 7.41 (m, 1 H), 7.85 - 7.95 (m, 2 H), 8.52 (s, 1 H).

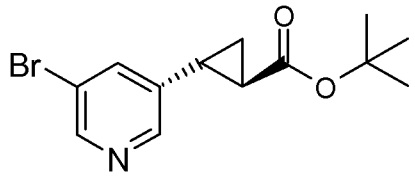
Intermediate 177: (E)-tert-butyl 3-(5-bromopyridin-3-yl)acrylate



tert-Butyl 2-(diethoxyphosphoryl)acetate (2.291 mL, 9.75 mmol) and tetrahydrofuran (5 mL) were combined and cooled over a dry-ice ethanol bath at -70 C then Sodium bis(trimethylsilyl)amide, 2M solution in THF (4.82 mL, 9.63 mmol) was added dropwise over

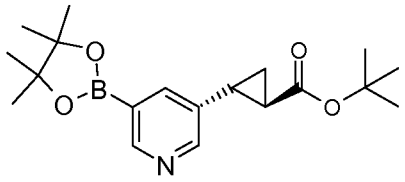
5 minutes to give a clear yellow solution. The mixture was stirred over the cold bath 30 minutes, then a solution of 5-bromonicotinaldehyde (1.629 g, 8.76 mmol) in 5 ml THF was added. The cold bath was removed and the mixture was stirred 20 minutes. The mixture was poured into 0.5M HCl and extracted ethyl acetate, washed with saturated sodium chloride, dried over MgSO4 and evaporated to give the title compound as a light yellow solid (2.78 g). 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.52 (s, 9 H), 6.44 (d, 1 H), 7.48 (d, 1 H), 7.98 (d, 1 H), 8.55 - 8.73 (m, 2 H)

Intermediate 178: (1,2-*trans*)-tert-butyl 2-(5-bromopyridin-3-yl)cyclopropanecarboxylate



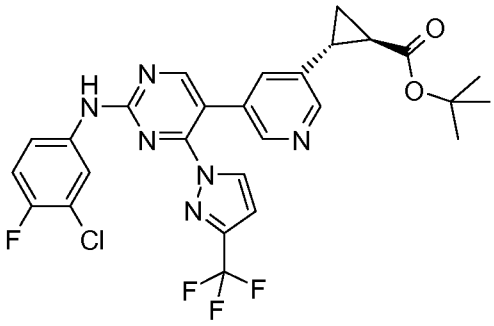
Trimethylsulfoxonium iodide (1.084 g, 4.93 mmol) was combined with dimethylsulfoxide (5 ml) and 60% sodium hydride dispersion in oil (0.183 g, 4.58 mmol) and stirred at room temperature for 50 minutes to give a clear solution, then (E)-tert-butyl 3-(5-bromopyridin-3-yl)acrylate **Intermediate 177** (1 g, 3.52 mmol) was added together with dimethylsulfoxide (1 ml) to give a yellow-orange suspension which was stirred at room temperature for 45 minutes. The mixture was poured into 50 ml water, extracted twice with ethyl acetate and the organic layer was dried over magnesium sulfate and evaporated to give a clear oil. Purification by flash chromatography, 0 to 15% ethyl acetate in hexane gave the title compound as a white solid (455 mg). 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.20 - 1.28 (m, 1 H), 1.47 (s, 9 H), 1.56 - 1.63 (m, 1 H), 1.82 - 1.90 (m, 1 H), 2.38 - 2.45 (m, 1 H),7.51 (s, 1 H), 8.35 (d, 1 H), 8.50 (d, 1 H).

Intermediate 179: (1,2-*trans*)-tert-butyl 2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)cyclopropanecarboxylate



(1,2-trans)-tert-butyl 2-(5-bromopyridin-3-yl)cyclopropanecarboxylate **Intermediate 178** (0.435 g, 1.46 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.741 g, 2.92 mmol), potassium acetate (0.430 g, 4.38 mmol), PdCl2(dppf)-dichloromethane adduct (0.119 g, 0.15 mmol) and dioxane (5 mL) were combined and degassed by bubbling and argon stream through the mixture for 10 minutes. The mixture was warmed at 90 °for 1.5 hours, allowed to cool and filtered. The solids were rinsed with dichloromethane and the filtrate was evaporated. The residue was filtered over 25 ml silica gel, eluting with dichloromethane (200 ml), then 25% ethyl acetate in dichloromethane (200 ml). The filtrate was discarded before the silica gel was further eluted with 200 ml 5% methanol in dichloromethane. Evaporation gave the title compound as a crude brown solid (270 mg). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.79 - 0.99 (m, 1 H), 1.34 (s, 12 H), 1.46 (s, 9 H), 1.51 - 1.59 (m, 1 H), 1.83 - 1.90 (m, 1 H), 2.38 - 2.47 (m, 1 H), 7.68 (s, 1 H), 8.49 (m, 1 H), 8.76 (m, 1 H).

Intermediate 180: (1,2-trans)-tert-butyl 2-(5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)pyridin-3-yl)cyclopropanecarboxylate

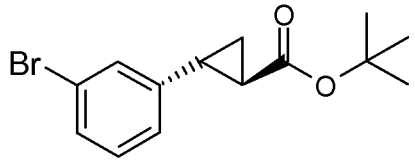


(1R,2R)-tert-butyl 2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)cyclopropanecarboxylate, **Intermediate 179** (270 mg, 0.55 mmol), 5-bromo-N-(3-chloro-4-fluorophenyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine [**Intermediate 115**] (159 mg, 0.36 mmol), Tris(dibenzylideneacetone) dipalladium(0) (33.4 mg, 0.04 mmol), 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (52.2 mg, 0.11 mmol), sodium

carbonate (58.0 mg, 0.55 mmol), acetonitrile (2 mL) and water (0.500 mL) were combined and degassed with an argon stream for 10 min. The mixture was warmed at 80 °C for 1 hour 15 minutes, allowed to cool, diluted with acetonitrile, filtered and adsorbed on silica gel. Purification by flash chromatography (25 g cartridge) 0.5 to 5% methanol in dichloromethane gave the solid title compound (110 mg). MS: ES+ 575 for $C_{27}H_{23}ClF_4N_6O_2$.

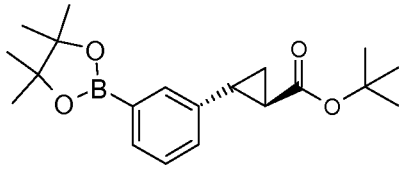
1H NMR (400 MHz, DMSO-D6) δ ppm 1.21 - 1.30 (m, 2 H), 1.41 (s, 9 H), 1.78 - 1.86 (m, 1 H), 2.33 - 2.42 (m, 1 H), 7.02 (d, 1 H), 7.23 (s,1 H), 7.41 (t, 1 H), 7.65 - 7.75 (m, 1 H), 8.08 (dd, 1 H), 8.21 (d, 1 H), 8.45 (d, 2 H), 8.81 (s, 1 H), 10.42 (s, 1 H).

Intermediate 181: (1,2-*trans*)- tert-butyl 2-(3-bromophenyl)cyclopropanecarboxylate



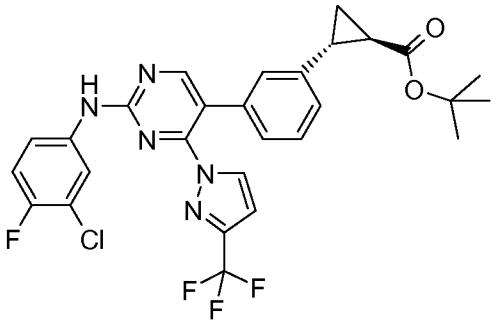
The title compound was prepared using the general method described above for **Intermediate 178** using (E)-tert-butyl 3-(3-bromophenyl)acrylate as a starting material. ^{1}H NMR (300 MHz, CHLOROFORM-D) δ ppm 0.76 - 0.94 (m, 1 H), 1.16 - 1.23 (m, 1 H), 1.46 (s, 9 H), 1.77 - 1.86 (m, 1 H), 2.33 - 2.43 (m, 1 H), 7.01 (d, 4 H), 7.12 (t, 1 H), 7.21 (s, 1 H), 7.31 (d, 1 H).

Intermediate 182: (1,2-trans)-tert-butyl 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropanecarboxylate



The title compound was prepared using the general method described above for **Intermediate 178** using **Intermediate 181** as a starting material. ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.80 - 0.93 (m, 1 H), 1.45 (s, 12 H), 1.45 (s, 9 H), 1.47 - 1.53 (m, 1 H), 1.79 - 1.89 (m, 1 H), 2.40 - 2.50 (m, 1 H), 7.17 (d, 1 H), 7.28 (d, 1 H), 7.52 (s, 1 H), 7.63 (d, 1 H).

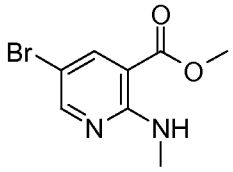
Intermediate 183: (1,2-trans)-tert-butyl 2-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenyl)cyclopropanecarboxylate



The title compound was prepared using the general method described above for **Intermediate 178** using **Intermediate 182** and **Intermediate 115** as starting materials. MS: ES+ 574 for $C_{27}H_{23}ClF_4N_6O_2$.

^{1}H NMR (400 MHz, DMSO-D6) δ ppm 1.17 - 1.22 (m, 1 H), 1.30 - 1.37 (m, 1 H), 1.40 (s, 9 H), 1.68 - 1.76 (m, 1 H), 2.23 - 2.33 (m, 1 H), 6.79 (s,1 H), 6.96 (d, 1 H), 7.00 (d, 1 H), 7.13 - 7.18 (m, 1 H), 7.24 (t, 1 H), 7.39 (t, 1 H), 7.65 - 7.73 (m, 1 H), 8.12 (dd, 1 H), 8.25 (s, 1 H), 8.79 (s, 1 H),10.38 (s, 1 H).

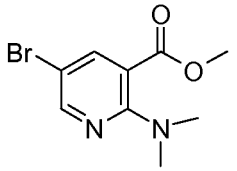
Intermediate 184: methyl 5-bromo-2-(methylamino)nicotinate



Methyl 5-bromo-2-chloronicotinate (1 g, 3.99 mmol) and methylamine, 2M solution in THF (4 ml, 8.00 mmol) were combined and warmed in a microwave reactor at 125 °C for 1 hour. The mixture was combined with 50 ml ethyl acetate, washed with 0.2M HCl, dried over magnesium sulfate and evaporated to give the title compound as an off-white solid (0.956 g).

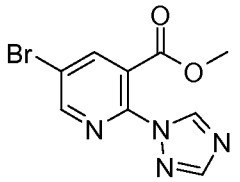
^{1}H NMR (300 MHz, DMSO-d6) δ ppm 2.93 (d, 3 H), 3.82 (s, 3 H), 7.87 (br. s., 1 H), 8.12 (d, 1 H), 8.39 (d, 1 H)

Intermediate 185: methyl 5-bromo-2-(dimethylamino)nicotinate



The title compound was prepared using the general method described above for **Intermediate 184** using dimethylamine, 2M solution in THF as a reagent. ^{1}H NMR (300 MHz, DMSO-d6) d ppm 2.92 (s, 6 H), 3.82 (s, 3 H), 7.97 (d, 1 H), 8.30 (d, 1 H)

Intermediate 186: methyl 5-bromo-2-(1H-1,2,4-triazol-1-yl)nicotinate

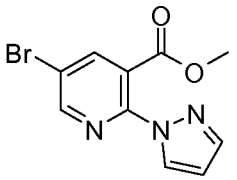


4H-1,2,4-triazole (0.4 g, 5.79 mmol) was dissolved in NMP (5 mL) then sodium hydride (60% dispesion in oil) (200 mg, 5.00 mmol) was added. The mixture was stirred at room temperature for 30 minutes, then methyl 5-bromo-2-chloronicotinate (1 g, 3.99 mmol) was added. The mixture was stirred for 2 hours, diluted with water, extracted with ethyl acetate, washed with saturated sodium chloride, dried over magnesium sulfate and evaporated. Purification of the residue by flash chromatography (25g cartridge, 20 to 60% ethyl acetae / hexanes) gave the title compound as an off-white solid (0.42 g).

MS: ES+ 284 for $C_9H_7BrN_4O_2$.

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 3.76 (s, 3 H), 8.29 (s, 1 H), 8.56 (d, 1 H), 8.89 (d, 1 H), 9.29 (s, 1 H).

Intermediate 187 methyl 5-bromo-2-(1H-pyrazol-1-yl)nicotinate

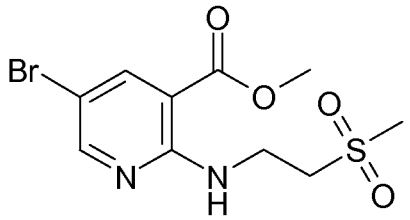


The title compound was prepared using the general method described above for Intermediate **186** using 1H-pyrazole as a reagent.

MS: ES+ 283 for $C_{10}H_8BrN_3O_2$.

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 3.75 (s, 3 H), 6.53 - 6.64 (m, 1 H), 7.81 (d, 1 H), 8.41 (d, 1 H), 8.51 (d, 1 H), 8.76 (d, 1 H).

Intermediate 188 methyl 5-bromo-2-(2-(methylsulfonyl)ethylamino)nicotinate

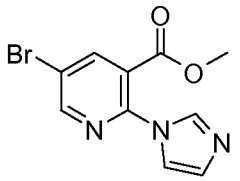


Methyl 5-bromo-2-chloronicotinate (800 mg, 3.19 mmol), 2-(methylsulfonyl)ethanamine hydrochloride (586 mg, 3.67 mmol), NMP (4 mL) and N,N-diisopropylethylamine (0.893 mL, 5.11 mmol) were combined and warmed over at 80 °for 18h, , diluted with water (50 ml) to give a solid precipitate which was collected and rinsed with water, then 1:1 ether/hexanes to give the title compound as a beige solid (0.687 g).

MS: ES+ 338 for $C_{10}H_{13}BrN_2O_4S$.

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 3.02 (s, 3 H), 3.40 (t, 2 H), 3.83 (s, 3 H), 3.90 (q, 2 H), 8.18 (d, 1 H), 8.16 (t, 1 H), 8.42 (d, 1 H)

Intermediate 189 methyl 5-bromo-2-(1H-imidazol-1-yl)nicotinate

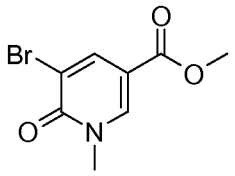


Methyl 5-bromo-2-chloronicotinate (1 g, 4 mmol) and imidazole (820 mg, 12 mmol) combined with NMP (5 mL) and warmed at 70 °C for 17 hours, then at 100 °C for 5 hours. The mixture was diluted with water, extracted with ethyl acetate, washed with saturated sodium chloride, dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography (25g cartridge, 10 to 40% acetonitrile in dichloromethane) to give the title compounds as an off-white solid: 236 mg .

MS: ES+ 283 for $C_{10}H_8BrN_3O_2$.

^{1}H NMR (400 MHz, DMSO-d6) δ ppm 3.78 (s, 3 H), 7.07 (s, 1 H), 7.50 (s, 1 H), 8.03 (s, 1 H), 8.58 (d, 1 H), 8.90 (d, 1 H)

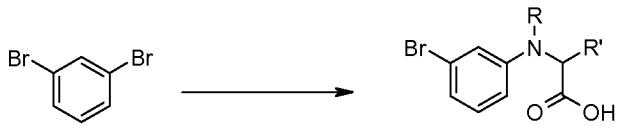
Intermediate 190: methyl 5-bromo-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate



Methyl 5-bromo-6-oxo-1,6-dihydropyridine-3-carboxylate (2 g, 8.62 mmol) was combined with DMF (20 mL) and triethylamine (3.60 mL, 25.86 mmol) to give a clear solution which was cooled over an ice-water bath. Dimethylsulfate (2.452 mL, 25.86 mmol) was added to the cold solution dropwise over several minutes. The clear solution was removed from the cold bath and stirred at room temperature for 1.5 hours to give a suspension. The mixture was diluted with 0.2M NaOH to 200 ml and the solids were filtered and rinsed with water to give the title compound as a white solid (0.84 g).

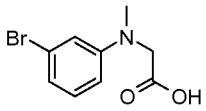
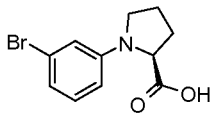
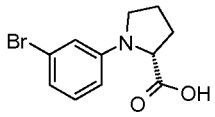
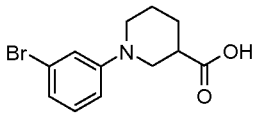
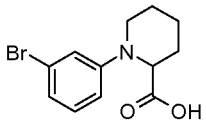
^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 3.68 (s, 3 H), 3.88 (s, 3 H), 8.19 (d, 1 H), 8.27 (d, 1 H).

General procedure for reaction of amino acids with 1,3-dibromobenzene:



A suspension of 1,3-dibromobenzene (1 eq), amino acid (2-2.5 eq), CuI (20 mol%) and potassium carbonate (3 eq) in DMF (5 mL) was taken in sealed tube, degassed and heated to 90 °C overnight under inert atmosphere. The reaction mixture was then cooled to RT and filtered through a celite bed. The filtrate was acidified with 1.5 N HCl. The solvent was removed under vacuum and the crude mixture taken in $CHCl_3$ (50 mL), washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using chloroform: methanol (9:1) as an eluent to give the product.

The compounds in the table below were prepared using this general procedure and the starting material specified.

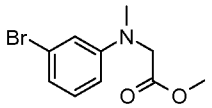
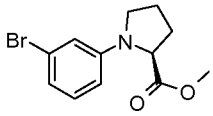
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 191	 *N*-(3-bromophenyl)-*N*-methylglycine	MS(ES): 244 (M) and 246 (M+2) for $C_9H_{10}BrNO_2$. 400 MHz, DMSO-d_6: δ 2.94 (s, 3H), 4.08 (s, 2H), 6.65 (t, *J* = 7.20 Hz, 1H), 6.78 (t, *J* = 3.60 Hz, 1H), 7.09 (t, *J* = 8.40 Hz, 1H), 7.95-8.07 (m, 1H), 12.71 (s, 1H).	*N*-methyl glycine
Intermediate 192	 1-(3-bromophenyl)-L-proline	Taken to the next step based on LCMS without further purification. MS(ES): 270 (M) and 272 (M+2) for $C_{11}H_{12}BrNO_2$.	L-proline
Intermediate 193	 1-(3-bromophenyl)-D-proline	Taken to the next step based on LCMS without further purification. MS(ES): 270 (M) and 272 (M+2) for $C_{11}H_{12}BrNO_2$. (74 % pure by LCMS)	D-proline
Intermediate 194	 1-(3-bromophenyl)piperidine-3-carboxylic acid	MS(ES): 284 (M) and 286 (M+2) for $C_{12}H_{14}BrNO_2$. 400 MHz, DMSO-d_6: δ 3.15 (d, *J* = 14.12 Hz, 1H), 3.28-3.29 (m, 2H), 3.55-3.71 (m, 5H), 7.37 (t, *J* = 12.16 Hz, 1H), 7.54-7.60 (m, 2H), 7.95 (q, *J* = 3.44 Hz, 1H), 8.74 (s, 1H), 10.29 (s, 1H).	piperidine-3-carboxylic acid
Intermediate 195	 1-(3-bromophenyl)piperidine-2-carboxylic acid	Taken to the next step based on LCMS without further purification. MS(ES): 284 (M) and 286 (M+2) for $C_{12}H_{14}BrNO_2$. (65 % pure by LCMS)	piperidine-2-carboxylic acid

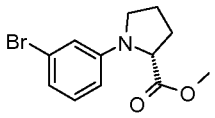
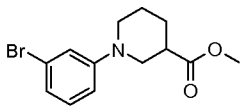
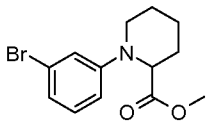
General procedure for esterification of *N*-aryl amino acids



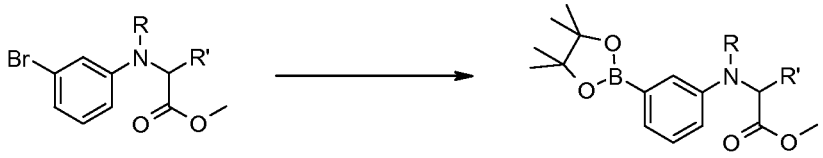
To a suspension of amino acid derivative (1.5 eq) taken in excess of MeOH at 0 °C, was added thionyl chloride (1 vol) slowly and the reaction mixture refluxed for 2 h. The solvent was removed under vacuum and the crude mixture was taken in EtOAc (30 mL), washed with aq. $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated. The crude material was taken to the next step as such without further purification.

The compounds in the table belowwere prepared using this general procedure and the starting material specified.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 196	 methyl *N*-(3-bromophenyl)-*N*-methylglycinate	Taken to the next step based on LCMS without further purification. MS(ES): 258 (M) and 260 (M+2) for $C_{10}H_{12}BrNO_2$.	*N*-(3-bromophenyl)-*N*-methylglycine **Intermediate 191**
Intermediate 197	 methyl 1-(3-bromophenyl)-L-prolinate	MS(ES): 284 (M) and 286 (M+2) for $C_{12}H_{14}BrNO_2$. 300 MHz, $CDCl_3$: δ 2.06-2.18 (m, 4H), 3.33-3.36 (m, 1H), 3.50-3.62 (m, 1H), 3.73 (s, 3H), 4.24 (dd, *J* = 2.37, 8.28 Hz, 1H), 6.43 (dd, *J* = 1.89, 8.32 Hz, 1H), 6.68 (t, *J* = 2.04 Hz, 1H), 6.81-6.84 (m, 1H), 7.06 (t, *J* = 8.13 Hz, 1H).	1-(3-bromophenyl)-L-proline **Intermediate 192**

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 198	 methyl 1-(3-bromophenyl)-D-prolinate	Taken to the next step based on LCMS without further purification. MS(ES): 284 (M) and 286 (M+2) for $C_{12}H_{14}BrNO_2$. (75 % pure by LCMS)	1-(3-bromophenyl)-D-proline **Intermediate 193**
Intermediate 199	 methyl 1-(3-bromophenyl)piperidine-3-carboxylate	MS(ES): 298 (M) and 300 (M+2) for $C_{13}H_{16}BrNO_2$. 300 MHz, DMSO-d_6: δ 1.42-1.73 (m, 3H), 1.85-1.90 (m, 1H), 2.57-2.60 (m, 1H), 2.75-2.92 (m, 1H), 2.96-3.03 (m, 1H), 3.40-3.58 (m, 1H), 3.61 (s, 3H), 3.37-3.72 (m, 1H), 6.89 (t, J = 7.74 Hz, 2H), 6.94 (d, J = 8.57 Hz, 1H), 7.03-7.12 (m, 1H).	1-(3-bromophenyl)piperidine-3-carboxylic acid **Intermediate 194**
Intermediate 200	 methyl 1-(3-bromophenyl)piperidine-2-carboxylate	Taken to the next step based on LCMS without further purification. MS(ES): 298 (M) and 300 (M+2) for $C_{13}H_{16}BrNO_2$.	1-(3-bromophenyl)piperidine-2-carboxylic acid **Intermediate 195**

General procedures for the preparation of boronate esters from aryl bromides



Method I:

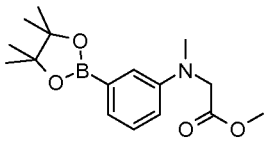
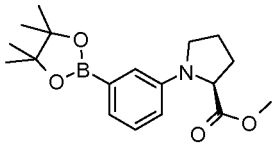
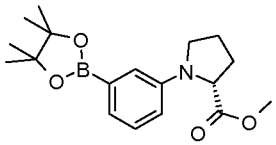
A suspension of aryl bromide (1 eq), bis(pinacolato)diboron (2 eq), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (20 mol%) and potassium acetate (3 eq) was taken in dioxane and it was degassed for 10 min. Then the reaction mixture was heated overnight at 90 °C. The reaction mixture was cooled to room temperature, filtered through a celite bed, washed with ethyl acetate twice and concentrated *in vacuo*. The residue was diluted with ethyl acetate (2x), washed with water (1x) and brine (1x),

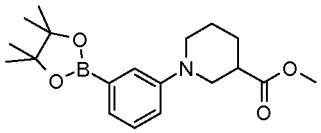
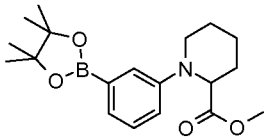
dried over Na_2SO_4 and concentrated *in vacuo*. The crude mass was purified by 60-120 silica gel column chromatography using ethyl acetate/hexanes and as eluent to give the product.

Method II:

A suspension of aryl bromide (1 eq), bis(pinacolato)diboron (3 eq), palladium(II) acetate (20-40 mol%), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (20 mol%) and triethylamine (3 eq) was taken in dioxane and it was degassed for 10 min. Then the reaction mixture was heated overnight at 90-100 °C. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate (2x). The organic layer was washed with water (1x) and brine (1x), dried over Na_2SO_4 and concentrated *in vacuo*. Then the crude mass was purified by 60-120 silica gel column chromatography using ethyl acetate/hexanes and as eluent to give the product.

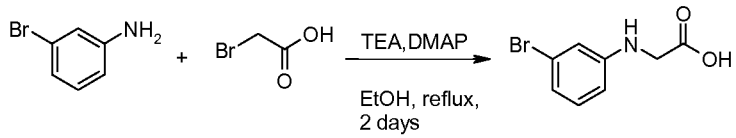
The compounds in the below table were prepared using this general procedure and the starting material specified.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 201[b)]	 methyl *N*-methyl-*N*-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]glycinate	The compound was taken to the next step on the basis of LCMS MS(ES): 306 (M+1) for $C_{16}H_{24}BNO_4$. (35 % purity by LCMS).	methyl *N*-(3-bromophenyl)-*N*-methylglycinate **Intermediate 196**
Intermediate 202[a)]	 methyl 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-L-prolinate	MS(ES): 332 (M+1) for $C_{18}H_{26}BNO_4$. 300 MHz, $CDCl_3$: δ 1.34 (s, 12H), 2.13-2.19 (m, 4H), 3.41-3.44 (m, 1H), 3.50-3.64 (m, 1H), 3.71 (s, 3H), 4.29-4.30 (m, 1H), 6.64 (d, *J* = 6.30 Hz, 1H), 7.04 (d, *J* = 5.64 Hz, 1H), 7.16-7.27 (m, 2H).	methyl 1-(3-bromophenyl)-L-prolinate **Intermediate 197**
Intermediate 203[a)]	 methyl 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-D-prolinate	MS(ES): 332 (M+1) for $C_{18}H_{26}BNO_4$. 300 MHz, DMSO-d_6: δ 1.15 (s, 12H), 2.26-2.31 (m, 2H), 2.35-2.42 (m, 2H), 3.62 (s, 3H), 4.00-4.20 (m, 2H), 4.31 (d, *J* = 7.95 Hz, 1H), 6.78 (d, *J* = 7.53 Hz, 1H), 6.95 (d, *J* = 7.32 Hz, 1H), 7.16-7.21 (m, 2H).	methyl 1-(3-bromophenyl)-D-prolinate **Intermediate 198**

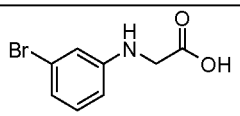
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 204[b)]	 methyl 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-3-carboxylate	Taken to the next step based on LCMS without further purification. MS(ES): 346 (M+1) for $C_{19}H_{28}BNO_4$. (40 % pure by LCMS)	methyl 1-(3-bromophenyl) piperidine-3-carboxylate **Intermediate 199**
Intermediate 205[b)]	 methyl 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-2-carboxylate	The compound was taken to the next step on the basis of LCMS. MS(ES): 346 (M+1) for $C_{19}H_{28}BNO_4$. (80 % pure by LCMS)	methyl 1-(3-bromophenyl) piperidine-2-carboxylate **Intermediate 200**

a) Method I; b) Method II

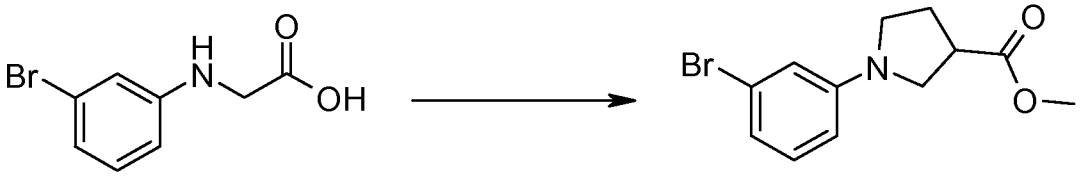
Intermediate 206: *N*-(3-bromophenyl)glycine



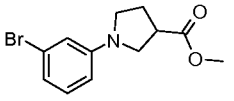
To a suspension of 3-bromoaniline (5.8 mmol, 1 g), and bromoacetic acid (8.7 mmol, 1.2 g) in ethanol (50 mL), was added triethylamine (17.3 mmol, 1.75 g) and 4-(Dimethylamino)pyridine (1.7 mmol, 0.2 g). The mixture was refluxed for 2 days. The reaction mixture was concentrated *in vacuo*, acidified with 1.5 N HCl and extracted with ethyl acetate (50 mL).The organic layer was washed with brine solution (25 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude mass was purified by 60-120 silica gel column chromatography using chloroform and methanol (2 %) as eluent to give the title compound (0.5 g). Taken for next step on basis of LCMS.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 206	 *N*-(3-bromophenyl) glycine	Taken to the next step based on LCMS without further purification. MS(ES): 230 (M) and 232 (M+2) for $C_8H_8BrNO_2$ (57% pure by LCMS).	3-bromoaniline and bromoacetic acid

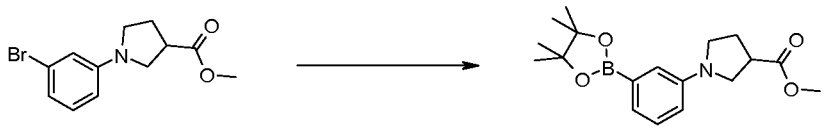
Intermediate 207: methyl 1-(3-bromophenyl)pyrrolidine-3-carboxylate



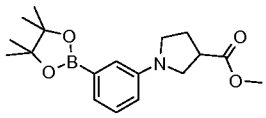
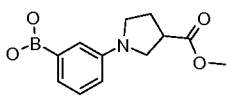
A suspension of *N*-(3-bromophenyl)glycine **Intermediate 206** (3.04 mmol, 0.7 g), 30% aq. formaldehyde solution (4.56 mmol, 0.14 g) and methyl acrylate (4.65 mmol, 0.4 g) in toluene (5 mL) was refluxed for 2 days. The reaction mixture was concentrated *in vacuo* and diluted with ethyl acetate (10 mL). The ethyl acetate layer was washed with water (5 mL), brine solution (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude mass was purified by 60-120 silica gel column chromatography using 8 % ethyl acetate/hexanes as eluent to give the title compound (0.15 g). Taken for next step on basis of LCMS.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 207	 methyl 1-(3-bromophenyl)pyrrolidine-3-carboxylate	Taken to the next step based on LCMS without further purification. MS(ES): 284 (M) and 286 (M+2) for $C_{12}H_{14}BrNO_2$ (65% pure by LCMS).	*N*-(3-bromophenyl)glycine **Intermediate 206**

Intermediate 208: methyl 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidine-3-carboxylate and {3-[3-(methoxycarbonyl)pyrrolidin-1-yl]phenyl}boronic acid

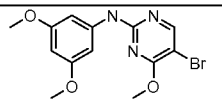


A suspension of methyl 1-(3-bromophenyl)pyrrolidine-3-carboxylate (**Intermediate 207**, 0.42 mmol, 120 mg), bis(pinacolato)diboron (0.84 mmol, 215 mg), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.084 mmol, 61 mg) and potassium acetate (1.26 mmol, 125 mg) was taken in dioxane (10 mL) and it was degassed for 10 min. Then the reaction mixture was heated overnight at 90 °C. The reaction mixture was cooled to room temperature, filtered through celite bed, washed with ethyl acetate twice and concentrated *in vacuo*. Then the residue was diluted with ethyl acetate (10 mL), washed with water (5 mL), brine solution (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude mass was purified by 60-120 silica gel column chromatography using 10 % ethyl acetate/hexanes and as eluent to give 0.1 g of a 72:19 mixture of methyl 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidine-3-carboxylate and {3-[3-(methoxycarbonyl)pyrrolidin-1-yl]phenyl}boronic acid which was taken for next step on basis of LCMS.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 208	 +  methyl 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidine-3-carboxylate and {3-[3-(methoxycarbonyl)pyrrolidin-1-yl]phenyl}boronic acid	Taken to the next step based on LCMS without further purification. MS(ES): 332 (M+1) for $C_{18}H_{26}BNO_4$ (72%) and 250 (M+1) for $C_{12}H_{16}BNO_4$ (19 %)	**Intermediate 207** methyl 1-(3-bromophenyl)pyrrolidine-3-carboxylate

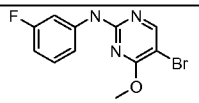
Intermediate 209: 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-methoxypyrimidin-2-amine

To a stirred solution of 5-bromo-2-chloro-4-methoxypyrimidine (53.81 mmol, 12 g,) and dimethoxyaniline (54.9 mmol, 8.4 g) in n-BuOH (150 mL) was added dioxane-HCl (12 mL) slowly. The reaction mixture was heated to 110 °C for 3 h. It was then cooled to room temperature, diethyl ether (150 mL) was added and the resulting solid was filtered to yield the title compound (15 g).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 209	 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-methoxypyrimidin-2-amine	MS (ES): 340 (M), 342 (M+2) for $C_{13}H_{14}BrN_3O_3$ ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.70 (s, 6H), 4.00 (s, 3H), 6.12 (s, 1H), 6.14 (s, 1H), 7.01 (s, 1H), 7.02 (s, 1H), 8.36 (s, 1H).	5-bromo-2-chloro-4-methoxypyrimidine and 3,5-dimethoxyaniline

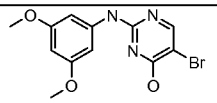
Intermediate 210: 5-bromo-*N*-(3-fluorophenyl)-4-methoxypyrimidin-2-amine

To a stirred solution of 5-bromo-2-chloro-4-methoxypyrimidine (11.21 mmol, 2.5 g) and 3-fluoroaniline (12.28 mmol, 1.37 g, 1.18 mL) in 2,2,2-trifluoroethanol (15 mL), trifluoroacetic acid (22.34 mmol, 2.55 g, 1.66 mL) was added and the solution was refluxed at 75 °C with constant stirring. After completion of the reaction, as monitored by TLC, water was added to the reaction mixture and extracted with EtOAc (2x50 mL). The organic layer was washed with water, 10% $NaHCO_3$ solution and brine, dried over sodium sulfate and concentrated *in vacuo* to yield the title compound (2.8 g).

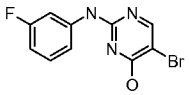
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 210	 5-bromo-*N*-(3-fluorophenyl)-4-methoxypyrimidin-2-amine	MS(ES): 298 (M) and 300 (M+2) for $C_{11}H_9BrFN_3O$. 400 MHz, DMSO-d_6: δ 4.01 (s, 3H), 6.77 (td, J = 2.48, 8.44 Hz, 1H), 7.30 (dd, J = 8.12, 15.34 Hz, 1H), 7.47 (d, J = 9.20 Hz, 1H), 7.73 (td, J = 2.16, 12.39 Hz, 1H), 8.41 (s, 1H), 9.96 (s, 1H).	5-bromo-2-chloro-4-methoxypyrimidine and 3-fluoroaniline

Intermediate 211: 5-bromo-2-[(3,5-dimethoxyphenyl)amino]pyrimidin-4-ol

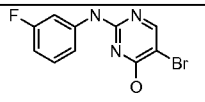
A solution of 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-methoxypyrimidin-2-amine (**Intermediate 209**, 14.7 mmol, 5 g) in n-BuOH (50 mL) and dioxane-HCl (15 mL) were heated to 110 °C in a sealed tube and stirred for 9 h. The reaction mixture was cooled to room temperature and BuOH was concentrated under vacuum. To the residue obtained, was added water (50 mL) and neutralized using 10% $NaHCO_3$ solution. The resulting solid was filtered to yield 3.5 g of 5-bromo-2-[(3,5-dimethoxyphenyl)amino]pyrimidin-4-ol as a white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 211	 5-bromo-2-[(3,5-dimethoxyphenyl)amino]pyrimidin-4-ol	MS (ES): 326 (M), 328 (M+2) for $C_{12}H_{12}BrN_3O_3$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.74 (s, 6H), 6.21 (s, 1H), 6.75 (s, 2H), 8.05 (s, 1H), 8.88 (s, 1H), 11.35 (s, 1H).	**Intermediate 209** 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-methoxypyrimidin-2-amine

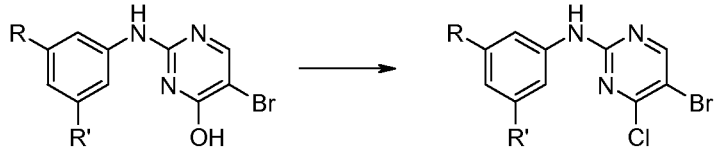
Intermediate 212: 5-bromo-2-[(3-fluorophenyl)amino]pyrimidin-4-ol



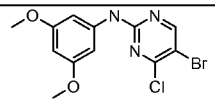
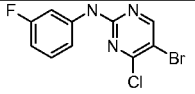
A solution of 5-bromo-*N*-(3-fluorophenyl)-4-methoxypyrimidin-2-amine (**Intermediate 210**, 5.03 mmol, 1.5 g) in n-BuOH (15 mL) and dioxane-HCl (4.5 mL) was heated to 110 °C in a sealed tube and stirred for 36 h. The reaction mixture was cooled to room temperature and BuOH was concentrated under vacuum. To the residue obtained, was added water (50 mL) and neutralized using 10% $NaHCO_3$ solution. The resulting solid was filtered to yield 0.6 g of 5-bromo-2-[(3-fluorophenyl)amino]pyrimidin-4-ol.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 212	 5-bromo-2-[(3-fluorophenyl)amino]pyrimidin-4-ol	MS(ES): 284 (M) and 286 (M+2) for $C_{10}H_7BrFN_3O$. 400 MHz, DMSO-d_6: δ 6.79 (td, J = 1.60, 8.40 Hz, 1H), 7.29-7.35 (m, 1H), 7.37 (d, J = 8.40 Hz, 1H), 7.79 (dt, J = 2.00, 12.40 Hz, 1H), 8.08 (s, 1H), 10.44 (br s, 1H), 13.20 (br s, 1H).	**Intermediate 210** 5-bromo-*N*-(3-fluorophenyl)-4-methoxypyrimidin-2-amine

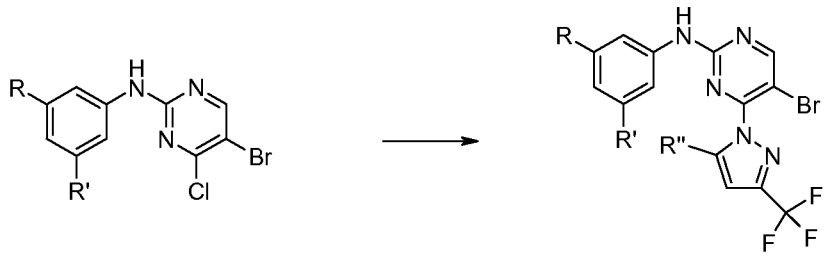
General procedure for the synthesis of 5-bromo-4-chloro-*N*-(aryl)pyrimidin-2-amine



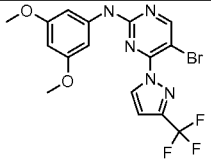
A solution of 5-bromo-2-[arylamino]pyrimidin-4-ol (**Intermediate 211** or **Intermediate 212**, 1 eq) in $POCl_3$ (15 eq) was heated to reflux for 1 h. The mixture was cooled to RT and $POCl_3$ was removed *in vacuo*. To the residue obtained, was added crushed ice with stirring, and the pH was adjusted to 7-8 using 10% sodium bicarbonate solution. The solid obtained was filtered and washed with chilled water to yield the title compound. The compounds in the below table were prepared using this method and the specified starting material.

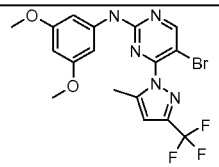
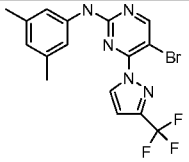
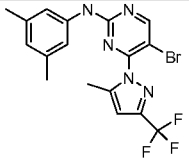
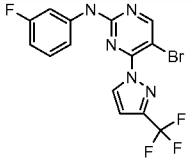
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 213	 5-bromo-4-chloro-*N*-(3,5-dimethoxyphenyl)pyrimidin-2-amine	MS (ES): 344 (M), 346 (M+2) for $C_{12}H_{11}BrClN_3O_2$. 300 MHz, DMSO-d_6: δ 3.77 (s, 6H), 6.19 (t, J = 2.13 Hz, 1H), 6.94 (d, J = 2.19 Hz, 2H), 8.68 (s, 1H), 10.13 (s, 1H).	**Intermediate 211** 5-bromo-2-[(3,5-dimethoxyphenyl)amino]pyrimidin-4-ol
Intermediate 214	 5-bromo-4-chloro-*N*-(3-fluorophenyl)pyrimidin-2-amine	MS(ES): 302 (M) and 304 (M+2) for $C_{10}H_6BrClFN_3$. 400 MHz, DMSO-d_6: δ 6.84 (t, J = 8.40 Hz, 1H), 7.33-7.37 (m, 1H), 7.42 (d, J = 8.48 Hz, 1H), 7.66 (d, J = 12.08 Hz, 1H), 8.74 (s, 1H), 10.43 (s, 1H).	**Intermediate 212** 5-bromo-2-[(3-fluorophenyl)amino]pyrimidin-4-ol

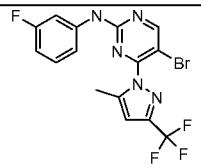
General procedure for 5-bromo-*N*-(aryl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine and 5-bromo-*N*-(aryl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine



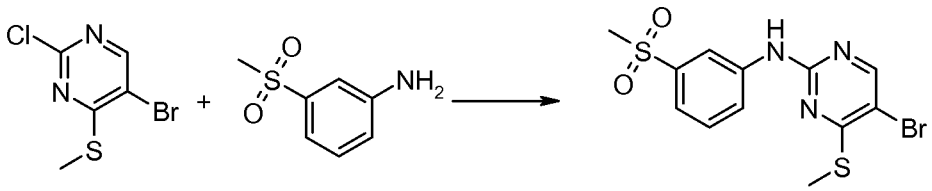
NaH (1.2 eq) was dissolved in 1 mL of NMP and stirred for about 5 min at 0 °C. Then either 3-(trifluoromethyl)-1*H*-pyrazole or 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole (1.1 eq) in NMP was added dropwise at 0 °C for about 10 min and stirring continued for about 20 min under N_2. Then the 5-bromo-4-chloro-*N*-(aryl)pyrimidin-2-amine starting material in NMP was added dropwise and the reaction was stirred at room temperature overnight. After completion of the reaction, water was added and the solid obtained was filtered, dried and purified by silica gel column chromatography using ethyl acetate/hexanes as eluent to yield the desired product. The compounds in the below table were prepared using this method and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 215	 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 444 (M) and 446 (M+2) for $C_{16}H_{13}BrF_3N_5O_2$. 300 MHz, DMSO-d_6: δ 3.71 (s, 6H), 6.18-6.19 (m, 1H), 7.01 (d, J = 2.13 Hz, 2H), 7.13-7.14 (m, 1H), 8.62 (br s, 1H), 8.88 (br s, 1H), 10.19 (br s, 1H), .	**Intermediate 213** 5-bromo-4-chloro-*N*-(3,5-dimethoxyphenyl)pyrimidin-2-amine

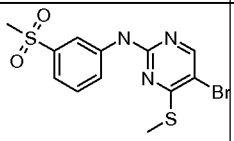
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 216	 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 458 (M) and 460 (M+2) for $C_{17}H_{15}BrF_3N_5O_2$. 400 MHz, DMSO-d_6: δ 2.38 (s, 3H), 3.71 (s, 6H), 6.20 (t, J = 2.80 Hz, 1H), 6.84 (s, 1H), 6.93 (d, J = 2.84 Hz, 2H), 8.91 (s, 1H), 10.21 (br s, 1H).	**Intermediate 213**
Intermediate 217	 5-bromo-*N*-(3,5-dimethylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	Taken to the next step based on LCMS without further purification. MS(ES): 412 (M) and 414 (M+2) for $C_{16}H_{13}BrF_3N_5$. (80 % pure by LCMS).	**Intermediate 143** 5-bromo-4-chloro-*N*-(3,5-dimethylphenyl)pyrimidin-2-amine
Intermediate 218	 5-bromo-*N*-(3,5-dimethylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	Taken to the next step based on LCMS without further purification MS(ES): 426 (M) and 428 (M+2) for $C_{17}H_{15}BrF_3N_5$. (61 % pure by LCMS).	**Intermediate 143** 5-bromo-4-chloro-*N*-(3,5-dimethylphenyl)pyrimidin-2-amine
Intermediate 219	 5-bromo-*N*-(3-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 402 (M) and 404 (M+2) for $C_{14}H_8BrF_4N_5$. 400 MHz, DMSO-d_6: δ 6.84 (td, J = 2.24, 8.34 Hz, 1H), 7.15 (d, J = 2.64 Hz, 1H), 7.35 (dd, J = 8.12, 15.20 Hz, 1H), 7.47 (d, J = 8.24 Hz, 1H), 7.70 (d, J = 12.08 Hz, 1H), 8.64 (br s, 1H), 8.93 (s, 1H), 10.46 (s, 1H).	**Intermediate 214** 5-bromo-4-chloro-*N*-(3-fluorophenyl)pyrimidin-2-amine

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 220	 5-bromo-*N*-(3-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 416 (M) and 418 (M+2) for $C_{15}H_{10}BrF_4N_5$. 400 MHz, DMSO-d_6: δ 2.40 (s, 3H), 6.83-6.87 (m, 2H), 7.35 (dd, J = 8.40, 15.20 Hz, 1H), 7.44 (d, J = 8.40 Hz, 1H), 7.65 (d, J = 12.00 Hz, 1H), 8.98 (s, 1H), 10.49 (s, 1H).	**Intermediate 214** 5-bromo-4-chloro-*N*-(3-fluorophenyl) pyrimidin-2-amine

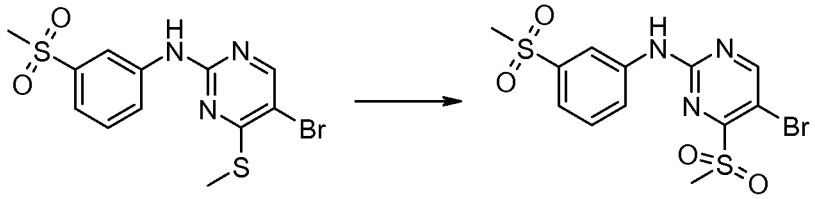
Intermediate 221: 5-bromo-4-(methylsulfanyl)-*N*-[3-(methylsulfonyl)phenyl]pyrimidin-2-amine



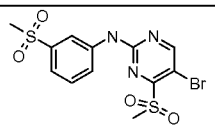
To 6 g of 5-bromo-2-chloro-4-(methylsulfanyl)pyrimidine (25.1 mmol) suspended in n-BuOH (20 mL), was added 3-(methylsulfonyl)aniline hydrochloride (25.1 mmol, 5.2 g) followed by HCl in dioxane (25 mL) and refluxed at 100 °C for 3 h. The reaction was cooled to room temperature, diluted with diethyl ether and the solid was filtered and dried to give the title compound (3.1 g).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 221	 5-bromo-4-(methylsulfanyl)-*N*-[3-(methylsulfonyl)phenyl]pyrimidin-2-amine	MS(ES): 374 (M) and 376 (M+2) for $C_{12}H_{12}BrN_3O_2S_2$. 400 MHz, DMSO-d_6: δ 2.61 (s, 3H), 3.33 (s, 3H), 7.51-7.53 (m, 1H), 7.57 (t, J = 7.60 Hz, 1H), 7.85 (d, J = 8.00 Hz, 1H), 8.38 (s, 1H), 8.57 (s, 1H), 10.21 (br s, 1H).	3-(methylsulfonyl)aniline hydrochloride and 5-bromo-2-chloro-4-(methylsulfanyl)pyrimidine

Intermediate 222: 5-bromo-4-(methylsulfonyl)-*N*-[3-(methylsulfonyl)phenyl]pyrimidin-2-amine



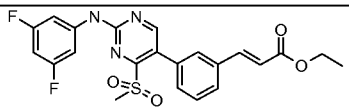
A suspension of 5-bromo-4-(methylsulfanyl)-*N*-[3-(methylsulfonyl) phenyl]pyrimidin-2-amine (**Intermediate 221**, 8.02 mmol, 3 g) in dichloromethane (125 mL) was cooled to 0 °C and 3-chloroperoxybenzoic acid (77 %, 27.72 mmol, 6.22 g) was added portion wise. The suspension became a clear solution after stirring at 0 °C for 30 min. The reaction mixture was then allowed to warm up slowly to room temperature and stirred for 5 h. The pH of the reaction mixture was raised to 8 with the addition of 10 % aq. $NaHCO_3$ solution (50 mL), extracted with dichloromethane (3x10 mL) and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the title compound (1.78 g).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 222	 5-bromo-4-(methylsulfonyl)-*N*-[3-(methylsulfonyl)phenyl]pyrimidin-2-amine	MS(ES): 406 (M) and 408 (M+2) for $C_{12}H_{12}BrN_3O_4S_2$. 400 MHz, DMSO-d_6: δ 3.21 (s, 3H), 3.50 (s, 3H), 7.58-7.63 (m, 2H), 7.83 (d, J = 6.08 Hz, 1H), 8.41 (br s, 1H), 8.97 (s, 1H), 10.75 (br s, 1H).	**Intermediate 221** 5-bromo-4-(methylsulfanyl)-*N*-[3-(methylsulfonyl)phenyl]pyrimidin-2-amine

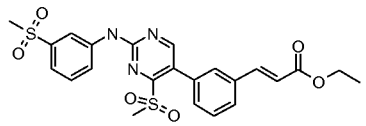
Intermediate 223: ethyl (2*E*)-3-(3-{2-[(3,5-difluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}phenyl)prop-2-enoate

A suspension of 5-bromo-*N*-(3,5-difluorophenyl)-4-(methylsulfonyl)pyrimidin-2-amine **Intermediate 139** (0.85 mmol, 0.3 g), {3-[(1*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]phenyl}boronic acid (0.93 mmol, 0.206 g), bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with CH_2Cl_2 (0.14 mmol, 0.112 g) and sodium carbonate (1.27 mmol, 0.14 g) in acetonitrile/water (5 mL:2 mL) was heated to 90 °C for 30 minutes. The reaction mixture was concentrated *in vacuo* and the residue taken in ethyl acetate (50 mL)

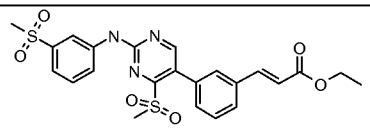
was washed with water and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The crude compound was purified by silica gel column chromatography using 50 % ethyl acetate/hexanes as an eluent to yield the title compound (300 mg).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 223	 ethyl (2*E*)-3-(3-{2-[(3,5-difluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}phenyl)prop-2-enoate	Taken to the next step based on LCMS without further purification. MS(ES): 460 (M+1) for $C_{22}H_{19}F_2N_3O_4S$. (94 % pure by LCMS)	**Intermediate 139** 5-bromo-*N*-(3,5-difluorophenyl)-4-(methylsulfonyl)pyrimidin-2-amine

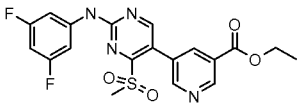
Intermediate 224: ethyl (2*E*)-3-{3-[4-(methylsulfonyl)-2-{[3-(methylsulfonyl)phenyl]amino}pyrimidin-5-yl]phenyl}prop-2-enoate



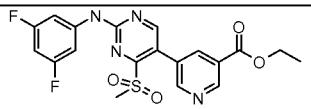
A suspension of 5-bromo-4-(methylsulfonyl)-*N*-[3-(methylsulfonyl)phenyl]pyrimidin-2-amine **Intermediate 222** (3.69 mmol, 1.5 g), {3-[(1*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]phenyl}boronic acid (4.06 mmol, 0.89 g), bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (0.41 mmol, 0.34 g), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (1.11 mmol, 0.53 g) and sodium carbonate (4.43 mmol, 0.47 g) in acetonitrile/water (5:1) was heated to 90 °C for 30 minutes. The reaction mixture was diluted with ethyl acetate (50 mL) and the organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude compound was purified by silica gel column chromatography using EtOAc/hexanes as an eluent to yield the title compound (1.02 g).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 224	 ethyl (2*E*)-3-{3-[4-(methylsulfonyl)-2-{[3-(methylsulfonyl)phenyl]amino}pyrimidin-5-yl]phenyl}prop-2-enoate	MS(ES): 502 (M+1) for $C_{23}H_{23}N_3O_6S_2$. 300 MHz, DMSO-d_6: δ 1.25 (t, J = 7.08 Hz, 3H), 3.21 (s, 3H), 3.41 (s, 3H), 4.19 (q, J = 7.05 Hz, 2H), 6.68 (d, J = 16.02 Hz, 1H), 7.50-7.71 (m, 6H), 7.85-7.92 (m, 2H), 8.50 (br s, 1H), 8.83 (s, 1H), 10.74 (br s, 1H).	**Intermediate 222** 5-bromo-4-(methylsulfonyl)-*N*-[3-(methylsulfonyl)phenyl]pyrimidin-2-amine

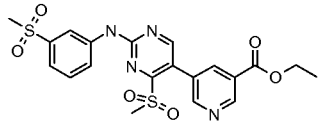
Intermediate 225: ethyl 5-{2-[(3,5-difluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}pyridine-3-carboxylate



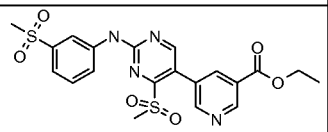
A suspension of 5-bromo-*N*-(3,5-difluorophenyl)-4-(methylsulfonyl)pyrimidin-2-amine **Intermediate 139** (1.38 mmol, 0.5 g), ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (1.65 mmol, 0.46 g), bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (0.14 mmol, 0.112 g) and sodium carbonate (1.37 mmol, 0.146 g) in acetonitrile/water (10 mL:3 mL) was heated to 90 °C for 30 minutes. The reaction mixture was concentrated *in vacuo* and the residue taken in ethyl acetate (50 mL) was washed with water and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The crude compound was purified by silica gel column chromatography using 50 % ethyl acetate/hexanes as an eluent to yield the title compound (400 mg).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 225	 ethyl 5-{2-[(3,5-difluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 435 (M+1) for $C_{19}H_{16}F_2N_4O_4S$. 400 MHz, DMSO-d_6: δ 1.35 (t, J = 7.20 Hz, 3H), 3.40 (s, 3H), 4.39 (q, J = 7.20 Hz, 2H), 6.89-6.93 (m, 1H), 7.52 (dd, J = 2.40, 10.00 Hz, 2H), 8.42 (t, J = 2.00 Hz, 1H), 8.67 (d, J = 2.40 Hz, 1H), 8.67 (s, 1H), 9.13 (s, 1H), 10.81 (s, 1H).	**Intermediate 139** 5-bromo-*N*-(3,5-difluorophenyl)-4-(methylsulfonyl)pyrimidin-2-amine

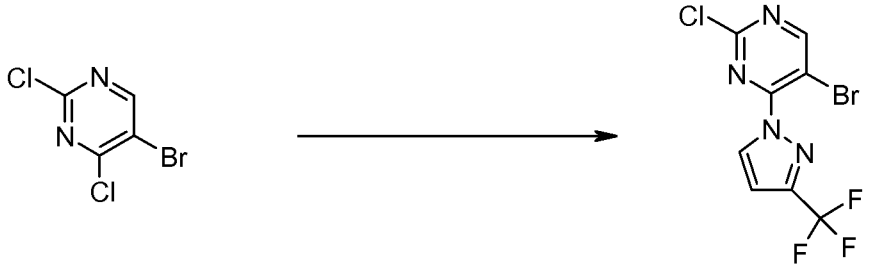
Intermediate 226: ethyl 5-[4-(methylsulfonyl)-2-{[3-(methylsulfonyl)phenyl]amino}pyrimidin-5-yl]pyridine-3-carboxylate



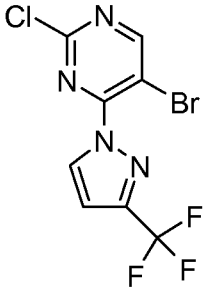
A suspension of 5-bromo-4-(methylsulfonyl)-*N*-[3-(methylsulfonyl)phenyl]pyrimidin-2-amine **Intermediate 224** (3.94 mmol, 1.6 g), ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (4.33 mmol, 1.2 g), bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (0.44 mmol, 0.36 g), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (1.12 mmol, 0.56 g) and sodium carbonate (4.72 mmol, 0.5 g) in acetonitrile/water (5:1) was heated to 90 °C for 30 minutes. The reaction mixture was diluted with ethyl acetate (50 mL) and the organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude compound was purified by silica gel column chromatography using EtOAc/hexanes as an eluent to yield the title compound (1.05 g).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 226	 ethyl 5-[4-(methylsulfonyl)-2-{[3-(methylsulfonyl)phenyl]amino}pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES): 477 (M+1) for $C_{20}H_{20}N_4O_6S_2$.400 MHz, DMSO-d_6: δ 1.34 (t, J = 7.08 Hz, 3H), 3.22 (s, 3H), 3.44 (s, 3H), 4.38 (q, J = 7.12 Hz, 2H), 7.60-7.62 (m, 1H), 7.65 (t, J = 7.84 Hz, 1H), 7.90 (d, J = 7.92 Hz, 1H), 8.42 (t, J = 2.12 Hz, 1H), 8.52 (br s, 1H), 8.87 (s, 1H), 8.89 (d, J = 2.16 Hz, 1H), 9.12 (d, J = 2.00 Hz, 1H), 10.83 (br s, 1H).	**Intermediate 224** 5-bromo-4-(methylsulfonyl)-*N*-[3-(methylsulfonyl)phenyl]pyrimidin-2-amine

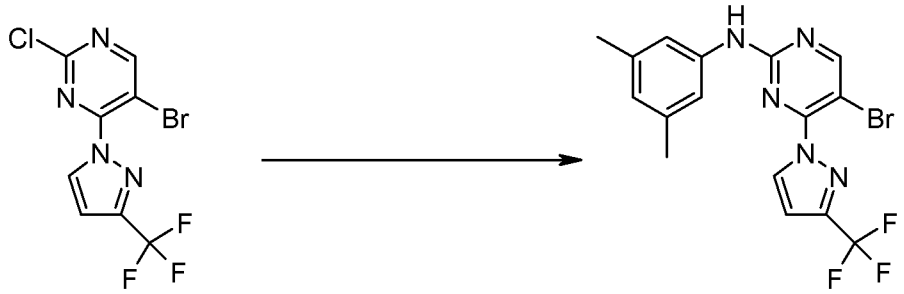
Intermediate 227: 5-bromo-2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine



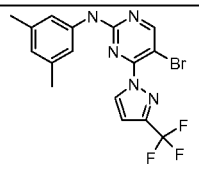
To a suspension of K_2CO_3 (8.8 mmol, 1.2 g) in acetonitrile (25 mL), was added 5-bromo-2,4-dichloropyrimidine (8.8 mmol, 2 g) and the reaction mixture was cooled to -5 to -10 °C. 3-(trifluoromethyl)-1*H*-pyrazole (8.8 mmol, 1.2 g) was dissolved in 25 mL of acetonitrile and added dropwise. After the addition, the reaction mixture was slowly warmed to RT and stirred for 5 h. The reaction mixture was filtered through a celite bed and acetonitrile was removed *in vacuo*. The crude mass was purified by silica gel column chromatography (60-120 mesh; product eluted with 2% EtOAc/hexanes) to yield 1.4 g of the product.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 227		MS(ES): 327 (M) and 329 (M+2) for $C_8H_3BrClF_3N_4$. 300 MHz, $CDCl_3$: δ 6.81 (d, J = 2.73 Hz, 1H), 8.57 (d, J = 1.98 Hz, 1H), 8.91 (s, 1H).	5-bromo-2,4-dichloropyrimidine and 3-(trifluoromethyl)-1*H*-pyrazole

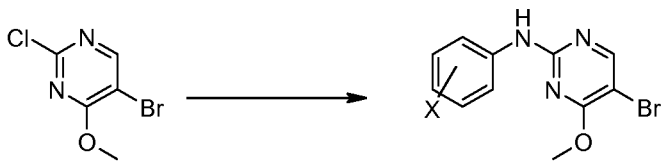
Intermediate 228: 5-bromo-*N*-(3,5-dimethylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine



To a suspension of Cs_2CO_3 (2.4 mmol, 780 mg) in DMF (4 mL), were added 5-bromo-2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine (**Intermediate 227**, 1.2 mmol, 400 mg) and 3,5-dimethylaniline (1.4 mmol, 177 mg) and heated to 100 °C in a sealed tube for 3 h. The reaction mixture was then diluted with EtOAc and passed through a celite bed. The organic layer was washed with brine and dried over sodium suphate. It was further concentrated and the crude mass was purified by silica gel column chromatography (60-120 mesh; product eluted with 5% EtOAc/hexanes) to yield 330 mg of 5-bromo-*N*-(3,5-dimethylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 228	 5-bromo-*N*-(3,5-dimethylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	Taken to the next step based on LCMS without further purification. MS(ES): 412 (M) and 414 (M+2) for $C_{16}H_{13}BrF_3N_5$. (80 % pure by LCMS).	**Intermediate 227** 5-bromo-2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine

General procedures for the synthesis of 5-bromo-*N*-(aryl)-4-methoxypyrimidin-2-amine

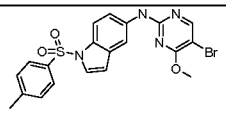
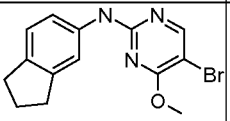
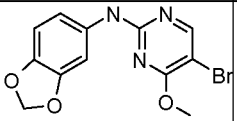


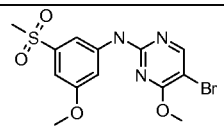
Method A

To a stirred solution of 5-bromo-2-chloro-4-methoxypyrimidine (1 eq) and arylamine (1.02 eq) in n-BuOH (12 v/w) was added dioxane-HCl (1 v/w) slowly. The reaction mixture was heated to 110 °C for 3 h. It was then cooled to room temperature, diethyl ether (150 mL) was added and the resulting solid was filtered to yield the product.

Method B

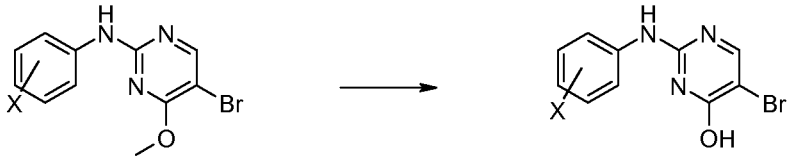
To a stirred solution of 5-bromo-2-chloro-4-methoxypyrimidine (1.3-1.5 eq) and arylamine (1 eq) in 2,2,2-trifluoroethanol (10 v/w), trifluoroacetic acid (2-4 eq) was added and the solution was refluxed at 75 °C for 2-12 h with constant stirring. Water was added to the reaction mixture and extracted with EtOAc (2x50 mL). The organic layer was washed with water, 10% $NaHCO_3$ solution and brine, dried over sodium sulfate and concentrated *in vacuo* to yield the product. The compounds in the below table were prepared using the above methods as indicated and the starting material specified.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 229 [b)]	 *N*-(5-bromo-4-methoxypyrimidin-2-yl)-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-5-amine	MS(ES): 473(M) and and 475 (M+2) for $C_{20}H_{17}BrN_4O_3S$. 300 MHz, DMSO-d_6: δ 2.29 (s, 3H), 3.98 (s, 3H), 6.78 (d, J = 3.60 Hz, 1H), 7.36 (d, J = 8.04 Hz, 2H), 7.58 (d, 1H), 7.71 (d, J = 3.54 Hz, 1H), 7.81-7.84 (m, 3H), 7.99 (s, 1H), 8.33 (d, J = 1.11 Hz, 1H), 9.77 (s, 1H).	5-Amino-1-(4-toluenesulphonyl)-1H-indole hydrochloride
Intermediate 230 [a)]	 5-bromo-*N*-(2,3-dihydro-1*H*-inden-5-yl)-4-methoxypyrimidin-2-amine	MS(ES): 320 (M) and 322 (M+2) for $C_{14}H_{14}BrN_3O$ 400 MHz, DMSO-d_6: δ 1.98-2.02 (m, 2H), 2.78-2.85 (m, 4H), 3.98 (s, 3H), 7.13 (d, J = 8.16 Hz, 1H), 7.41 (dd, J = 1.72, 8.12 Hz, 1H), 7.58 (s, 1H), 8.35 (s, 1H), 9.74 (s, 1H).	5-Aminoindane
Intermediate 231 [b)]	 *N*-(1,3-benzodioxol-5-yl)-5-bromo-4-methoxypyrimidin-2-amine	MS(ES): 324 (M) and 326 (M+2) for $C_{12}H_{10}BrN_3O_3$ 300 MHz, DMSO-d_6: δ 3.95 (s, 3H), 5.95 (s, 2H), 6.85 (d, J = 2.73 Hz, 1H), 7.10 (d, J = 2.85 Hz, 1H), 7.39 (d, J = 1.92 Hz, 1H), 8.31 (s, 1H), 9.60 (s, 1H).	3,4-Methylenedioxyaniline

Intermediate 232 [b]	 5-bromo-4-methoxy-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]pyrimidin-2-amine	Taken to the next step based on LCMS without further purification. MS(ES): 388 (M) and 390 (M+2) for $C_{13}H_{14}BrN_3O_4S$.	3-methoxy-5-(methylsulfonyl)aniline

[a] Method A [b] Method B

General procedures for the Synthesis of 5-bromo-2-[arylamino]pyrimidin-4-ol



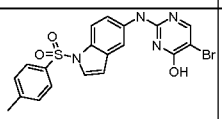
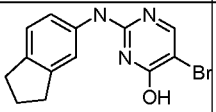
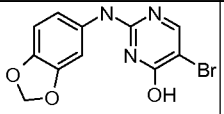
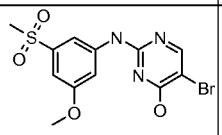
Method C

A mixture of the 4-methoxypyrimidine derivative (1 eq) and aq. sodium thiomethoxide (21% w/v, 4 eq) and DMF (8 ml/g SM) was heated to 60 °C for 2 h; cooled to room temperature, poured into water (150 mL) and acidified with 1.5 N HCl solution. The precipitated solid was filtered to yield the product.

Method D

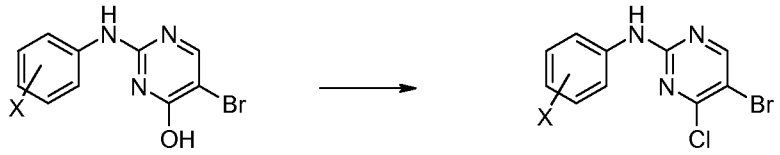
A solution of the 4-methoxypyrimidine derivative (1 g) in n-BuOH (7 ml/g SM) and 4M HCl in dioxane (4 ml/g SM) were heated to 110 °C in a sealed tube and stirred for 18-36 h. The reaction mixture was cooled to room temperature and BuOH was concentrated under vacuum. To the residue obtained, was added water (50 mL) and neutralized using 10% $NaHCO_3$ solution. The resulting solid was filtered and further purified by column chromatography using ethyl acetate/hexanes as eluent to yield the product.

The compounds in the below table were prepared using the above methods as indicated and the starting material specified.

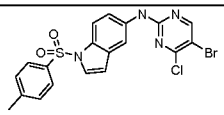
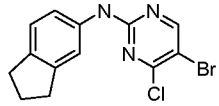
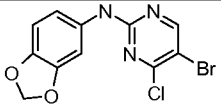
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 233[d]	 5-bromo-2-({1-[(4-methylphenyl)sulfonyl]-1*H*-indol-5-yl}amino)pyrimidin-4-ol	Taken to the next step based on LCMS without further purification. MS(ES): 459 (M) and and 461 (M+2) for $C_{19}H_{15}BrN_4O_3S$. (65% pure by LCMS).	**Intermediate 229** *N*-(5-bromo-4-methoxypyrimidin-2-yl)-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-5-amine
Intermediate 234[c]	 5-bromo-2-(2,3-dihydro-1*H*-inden-5-ylamino)pyrimidin-4-ol	MS(ES): 306 (M) and 308 (M+2) for $C_{13}H_{12}BrN_3O$. 400 MHz, DMSO-d_6: δ 1.97-2.04 (m, 2H), 2.78-2.85 (m, 4H), 7.15 (d, J = 8.08 Hz, 1H), 7.22 (dd, J = 1.40, 8.08 Hz, 1H), 7.44 (s, 1H), 8.01 (s, 1H), 8.87 (s, 1H), 11.21 (br s, 1H).	**Intermediate 230** 5-bromo-*N*-(2,3-dihydro-1*H*-inden-5-yl)-4-methoxypyrimidin-2-amine
Intermediate 235 [c]	 2-(1,3-benzodioxol-5-ylamino)-5-bromopyrimidin-4-ol	Taken to the next step based on LCMS without further purification. MS(ES): 311 (M+1) for $C1_1H_8BrN_3O_3$	**Intermediate 231** *N*-(1,3-benzodioxol-5-yl)-5-bromo-4-methoxypyrimidin-2-amine
Intermediate 236[d]	 5-bromo-2-{[3-methoxy-5-(methylsulfonyl)phenyl]amino}pyrimidin-4-ol	Taken to the next step based on LCMS without further purification. MS(ES): 374 (M) and 376 (M+2) for $C_{12}H_{12}BrN_3O_4S$.	**Intermediate 232** (5-bromo-4-methoxy-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]pyrimidin-2-amine

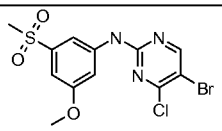
[c] Method C [d] Method D

General procedure for the synthesis of 5-bromo-4-chloro-*N*-(aryl)pyrimidin-2-amine



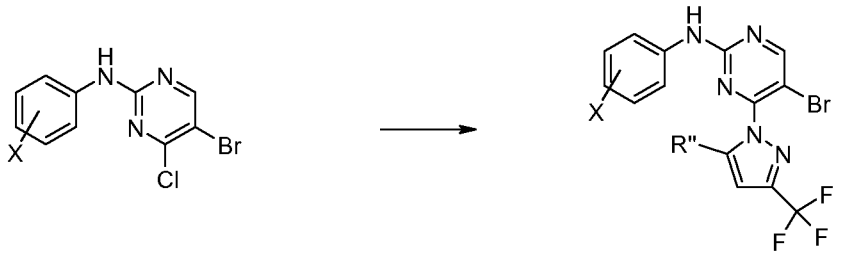
A solution of 5-bromo-2-[arylamino]pyrimidin-4-ol derivative in $POCl_3$ (3- 10 ml/g SM) was heated to reflux for 1 h. It was cooled to RT and $POCl_3$ was removed *in vacuo*. To the residue obtained, was added crushed ice with stirring, and the pH was adjusted 7-8 using 10% sodium bicarbonate solution. The solid obtained was filtered and washed with chilled water to yield the title compound. The compounds in the below table were prepared using the above method and the starting material specified.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 237	 *N*-(5-bromo-4-chloropyrimidin-2-yl)-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-5-amine	MS(ES): 477 (M) and 479 (M+2) for $C_{19}H_{14}BrClN_4O_2S$. 400 MHz, DMSO-d_6: δ 2.31 (s, 3H), 6.82 (d, J = 3.60 Hz, 1H), 7.38 (d, J = 8.28 Hz, 2H), 7.52 (dd, J = 2.00, 9.00 Hz, 1H), 7.76 (d, J = 3.64 Hz, 1H), 7.86 (m, 3H), 7.92 (d, J = 1.88 Hz, 1H), 8.65 (s, 1H), 10.24 (s, 1H).	**Intermediate 233** 5-bromo-2-({1-[(4-methylphenyl)sulfonyl]-1*H*-indol-5-yl}amino)pyrimidin-4-ol
Intermediate 238	 5-bromo-4-chloro-*N*-(2,3-dihydro-1*H*-inden-5-yl)pyrimidin-2-amine	MS(ES): 324 (M) and 326 (M+2) for $C_{13}H_{11}BrClN_3$. 300 MHz, DMSO-d_6: δ 1.96-2.04 (m, 2H), 2.76-2.84 (m, 4H), 7.13 (d, J = 8.13 Hz, 1H), 7.35 (dd, J = 1.44, 6.54 Hz, 1H), 7.51 (s, 1H), 8.61 (s, 1H), 10.06 (s, 1H).	**Intermediate 234** 5-bromo-2-(2,3-dihydro-1*H*-inden-5-ylamino)pyrimidin-4-ol
Intermediate 239	 *N*-(1,3-benzodioxol-5-yl)-5-bromo-4-chloropyrimidin-2-amine	MS(ES): 329 (M+1) and 330 (M+2) for $C_{11}H_7BrClN_3O_2$ 400 MHz, DMSO-d_6: δ 5.98 (s, 2H), 6.87 (d, J = 8.36 Hz, 1H), 7.02 (dd, J = 2.12, 8.44 Hz, 1H), 7.30 (d, J = 2.04 Hz, 1H), 8.62 (s, 1H), 10.06 (s, 1H) .	**Intermediate 235** 2-(1,3-benzodioxol-5-ylamino)-5-bromopyrimidin-4-ol

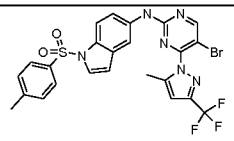
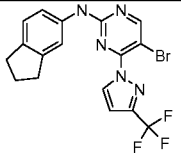
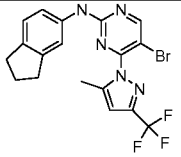
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 240[e)]	 5-bromo-4-chloro-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]pyrimidin-2-amine	Taken to the next step based on LCMS without further purification. MS(ES): 394 (M+2) for $C_{12}H_{11}BrClN_3O_3S$.	**Intermediate 236** 5-bromo-2-{[3-methoxy-5-(methylsulfonyl)phenyl]amino}pyrimidin-4-ol

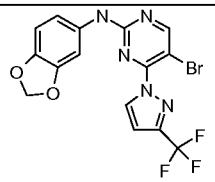
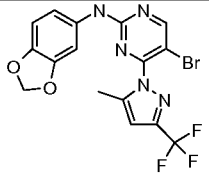
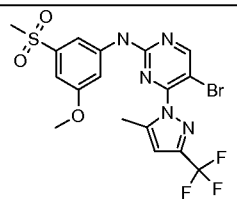
[e)] *N*, *N*-diethylaniline (0.5 eq) was also added

General procedure for the synthesis of 5-bromo-*N*-(aryl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine and 5-bromo-*N*-(aryl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine



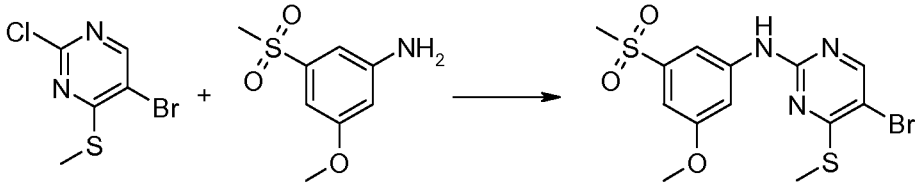
NaH (1.2 eq)was dissolved in 1 mL of NMP and stirred for about 5 min at 0 °C. Then either 3-(trifluoromethyl)-1*H*-pyrazole or 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole (1.1 eq) in NMP was added dropwise at 0 °C for 10 min and stirring continued for 20 min under N_2. Then the 5-bromo-4-chloro-*N*-(aryl)pyrimidin-2-amine derivative (1 eq) in NMP was added dropwise and the reaction was stirred at room temperature overnight. After completion of the reaction, water was added and the solid obtained was filtered, dried and purified by silica gel column chromatography using ethyl acetate/hexanes as eluent to yield the desired product. The compounds in the below table were prepared using the above method and the starting material specified.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 241	 *N*-{5-bromo-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-5-amine	MS(ES): 591 (M) and 593 (M+2) for $C_{24}H_{18}BrF_3N_6O_2S$. 400 MHz, DMSO-d_6: δ 2.31 (s, 3H), 2.38 (s, 3H), 6.81 (d, J = 3.64 Hz, 1H), 6.84 (s, 1H), 7.38 (d, J = 8.20 Hz, 2H), 7.54 (dd, J = 2.12, 8.96 Hz, 1H), 7.76 (d, J = 3.64 Hz, 1H), 7.84-7.89 (m, 4H), 8.89 (s, 1H), 10.30 (s, 1H).	**Intermediate 237** *N*-(5-bromo-4-chloropyrimidin-2-yl)-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-5-amine
Intermediate 242[f]	 5-bromo-*N*-(2,3-dihydro-1*H*-inden-5-yl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 424 (M) and 426 (M+2) for $C_{17}H_{13}BrF_3N_5$ 300 MHz, DMSO-d_6: δ 1.97-2.02 (m, 2H), 2.77-2.85 (m, 4H), 7.11 (d, J = 2.55 Hz, 1H), 7.15 (d, J = 8.07 Hz, 1H), 7.39 (d, J = 7.77 Hz, 1H), 7.56 (s, 1H), 8.59 (s, 1H), 8.83 (s, 1H), 10.11 (s, 1H).	**Intermediate 238** 5-bromo-4-chloro-*N*-(2,3-dihydro-1*H*-inden-5-yl)pyrimidin-2-amine
Intermediate 243[f]	 5-bromo-*N*-(2,3-dihydro-1*H*-inden-5-yl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 438 (M) and 440 (M+2) for $C_{18}H_{15}BrF_3N_5$. 400 MHz, DMSO-d_6: δ 1.97-2.04 (m, 2H), 2.28 (s, 3H), 2.79-2.85 (m, 4H), 6.84 (s, 1H), 7.16 (d, J = 8.16 Hz, 1H), 7.37 (d, J = 8.08 Hz, 1H), 7.52 (s, 1H), 8.88 (s, 1H), 10.15 (s, 1H).	**Intermediate 238** 5-bromo-4-chloro-*N*-(2,3-dihydro-1*H*-inden-5-yl)pyrimidin-2-amine

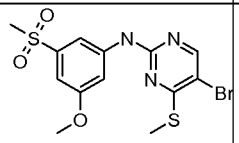
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 244	 *N*-(1,3-benzodioxol-5-yl)-5-bromo-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 429 (M+1) for $C_{15}H_9BrF_3N_5O_2$ 400 MHz, DMSO-d_6: δ 5.99 (s, 2H), 6.88 (d, J = 8.36 Hz, 1H), 7.07 (dd, J = 2.04, 8.42 Hz, 1H), 7.13 (d, J = 2.64 Hz, 1H), 7.37 (d, J = 1.96 Hz, 1H), 8.60 (d, J = 1.60 Hz, 1H), 8.83 (s, 1H), 10.12 (s, 1H).	**Intermediate 239** *N*-(1,3-benzodioxol-5-yl)-5-bromo-4-chloropyrimidin-2-amine
Intermediate 245	 *N*-(1,3-benzodioxol-5-yl)-5-bromo-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 443 (M+1) for $C_{16}H_{11}BrF_3N_5O_2$ 300 MHz, DMSO-d_6: δ 2.36 (s, 3H), 5.97 (s, 2H), 6.81 (s, 1H), 6.86 (d, J = 8.34 Hz, 1H), 7.01 (t, J = 1.98 Hz, 1H), 7.27 (s, 1H), 8.85 (s, 1H), 10.10 (s, 1H) .	**Intermediate 239** *N*-(1,3-benzodioxol-5-yl)-5-bromo-4-chloropyrimidin-2-amine
Intermediate 246[g)]	 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 507 (M+1) and 508 (M+2) for $C_{17}H_{15}BrF_3N_5O_3S$. 400 MHz, DMSO-d_6: δ 2.42 (s, 3H), 3.19 (s, 3H), 3.82 (s, 3H), 6.86 (s, 1H), 7.10 (t, J = 1.72 Hz, 1H), 7.62 (s, 1H), 7.88 (s, 1H), 9.01 (s, 1H), 10.60 (s, 1H), .	**Intermediate 240** 5-bromo-4-chloro-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]pyrimidin-2-amine

[f)] DMSO was used as solvent, 12 h [g)] THF was used as solvent, reflux, 7 h

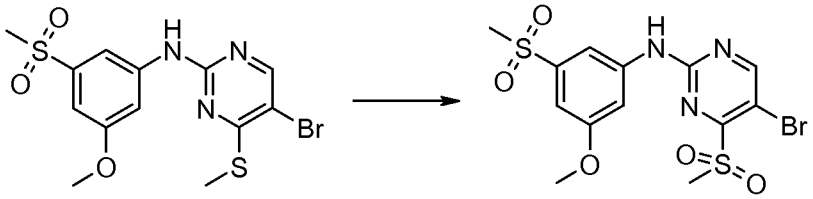
Intermediate 247: 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]-4-(methylsulfanyl)pyrimidin-2-amine.



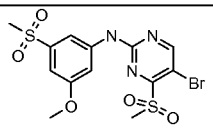
To 6 g of 5-bromo-2-chloro-4-(methylsulfanyl)pyrimidine (1.5 eq) suspended in n-BuOH (30 v/w), was added 3-methoxy-5-(methylsulfonyl)aniline (1 eq followed by. HCl in dioxane (25 mL) and refluxed at 100 °C for 3 h. The reaction was cooled to room temperature, diluted with diethyl ether and the solid was filtered and dried to get.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 247	 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl) phenyl]-4-(methylsulfanyl) pyrimidin-2-amine	MS(ES): 404 (M) and 406 (M+2) for $C_{13}H_{14}BrN_3O_3S_2$. 300 MHz, DMSO-d_6: δ 2.59 (s, 3H), 3.18 (s, 3H), 3.82 (s, 3H), 7.04 (t, J = 2.07 Hz, 1H), 7.52 (s, 1H), 8.12 (s, 1H), 8.37 (s, 1H), 10.13 (s, 1H).	3-methoxy-5-(methylsulfonyl)aniline and 5-bromo-2-chloro-4-(methylsulfanyl)pyrimidine

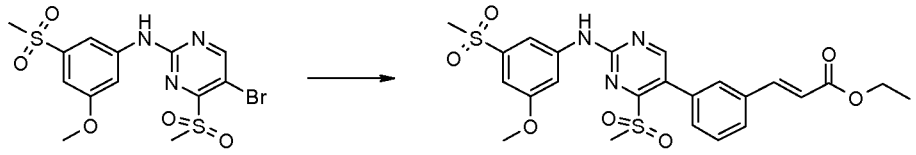
Intermediate 248: 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]-4-(methylsulfonyl)pyrimidin-2-amine (PE-048-017-II)



A suspension of 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]-4-(methylsulfanyl)pyrimidin-2-amine (**Intermediate 247**, 1 eq) in acetone was cooled to 0 °C and 3-chloroperoxybenzoic acid (77 %, 2 eq) was added portion wise. After the completion of the reaction, acetone was removed *in vacuo* and the residue taken in EtOAc was washed with 10 % aq. $NaHCO_3$ solution (50 mL) and water, dried over Na_2SO_4, filtered and concentrated to give the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 248	 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl) phenyl]-4-(methylsulfonyl) pyrimidin-2-amine	Taken to the next step based on LCMS without further purification. MS(ES): 436 (M) and 438 (M+2) for $C_{13}H_{14}BrN_3O_5S_2$.(72 % pure by LCMS)	**Intermediate 247** 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]-4-(methylsulfanyl)pyrimidin-2-amine

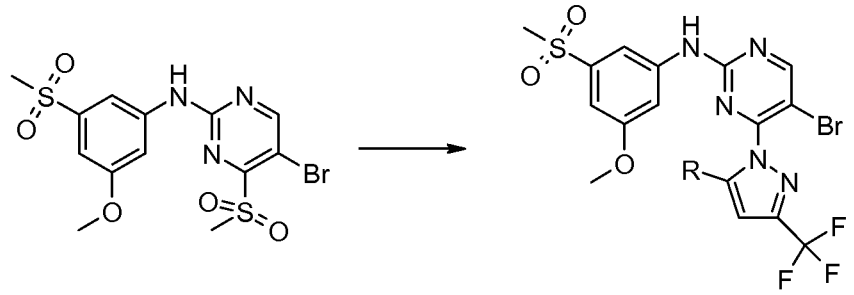
Intermediate 249: ethyl (2*E*)-3-{3-[2-{[3-methoxy-5-(methylsulfonyl)phenyl]amino}-4-(methylsulfonyl)pyrimidin-5-yl]phenyl}prop-2-enoate



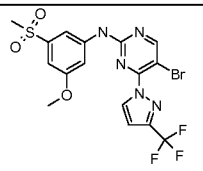
A suspension of 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]-4-(methylsulfonyl)pyrimidin-2-amine **Intermediate 248** (1 eq), {3-[(1*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]phenyl}boronic acid (1.5 eq), bis (diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (10 mol %) and sodium carbonate (1.5 eq) in acetonitrile/water (10 mL:5 mL) was heated to 90 °C for 30 minutes. The reaction mixture was concentrated *in vacuo* and the residue taken in ethyl acetate (50 mL) was washed with water and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The crude compound was purified by silica gel column chromatography using 50 % ethyl acetate/hexanes as an eluent to yield **Intermediate 249.** MS(ES): 532 (M+1) for $C_{24}H_{25}N_3O_7S_2$.

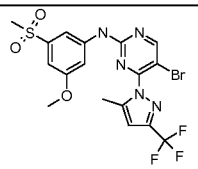
Intermediate 250: 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

Intermediate 251: 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

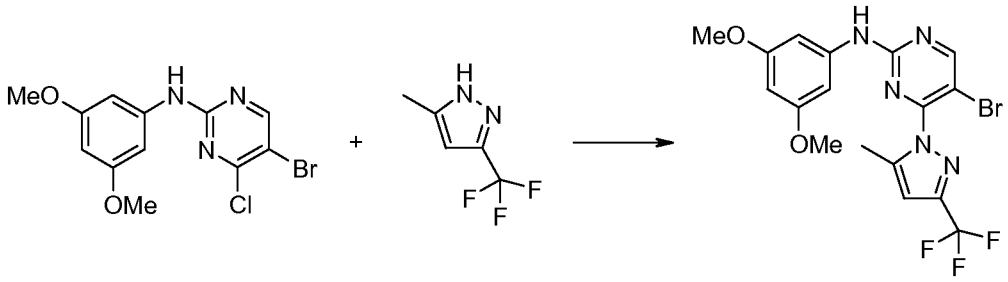


NaH (60 % dispersion in mineral oil, 2 eq) was dissolved in 1 mL of DMF and stirred for about 5 min at 0 °C. Then 3-(trifluoromethyl)-1*H*-pyrazole or 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole (2 eq) in NMP (2 mL) was added dropwise at 0 °C for about 10 min and stirring continued for about 20 min under N_2. Then 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]-4-(methylsulfonyl)pyrimidin-2-amine (**Intermediate 248**, 1 eq) in DMF was added dropwise and the reaction was stirred overnight at room temperature. Water was added and the solid obtained was filtered off, dried and purified by silica gel column chromatography using ethyl acetate/hexanes as eluent to yield the product. The compounds in the below table were prepared following this procedure and using the specified starting material.

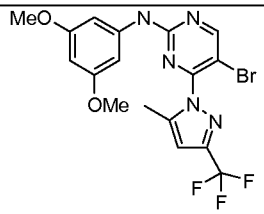
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 250	 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	Taken to the next step based on LCMS without further purification. MS(ES): 492 (M) and 494 (M+2) for $C_{16}H_{13}BrF_3N_5O_3S$. (65 % pure by LCMS)	**Intermediate 248** 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]-4-(methylsulfonyl)pyrimidin-2-amine

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 251	 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl) phenyl]-4-[5-methyl-3-(trifluoromethyl) -1*H*-pyrazol-1-yl]pyrimidin-2-amine	Taken to the next step based on LCMS without further purification. MS(ES): 506 (M) and 508 (M+2) for $C_{17}H_{15}BrF_3N_5O_3S$.	**Intermediate 248** 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl)ph enyl]-4-(methylsulfonyl)py rimidin-2-amine

Intermediate 252: 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

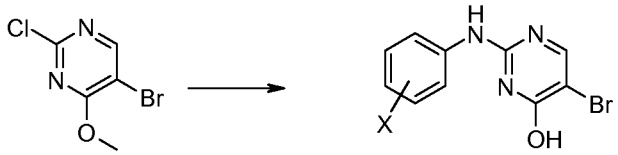


A solution of 3-methyl-5-trifluoromethyl pyrazole (2.87 mmol, 431 mg) in NMP (4 mL) was added slowly to a suspension of sodium hydride (3.13 mmol, 75 mg) in NMP (1 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C. A solution of 5-bromo-4-chloro-N-(3,5-dimethoxyphenyl)pyridine-2-amine (**Intermediate 213,** 2.61 mmol, 900 mg) in NMP (4 mL) was added slowly to the reaction mixture at 0 °C and stirred overnight at RT. The reaction mixture was then quenched with ice cold water at 0-5 °C, and the pH adjusted to 2 with 1.5 N HCl solution. It was then was extracted with ethyl acetate, and the organic layer was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The crude mass was purified by column chromatography using 10-15 % ethyl acetate/hexanes to yield 900 mg of the title compound.

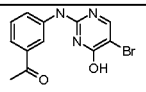
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 252	 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 458 (M) and 460 (M+2) for $C_{17}H_{15}BrF_3N_5O_2$. 400 MHz, DMSO-d_6: δ 2.39 (s, 3H), 3.70 (s, 6H), 6.21 (t, J = 2.20 Hz, 1H), 6.85 (s, 1H), 6.94 (d, J = 2.16 Hz, 2H), 8.93 (s, 1H).	**Intermediate 213** 5-bromo-4-chloro-*N*-(3,5-dimethoxyphenyl)pyrimidin-2-amine

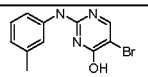
Intermediate 253: 1-{3-[(5-bromo-4-hydroxypyrimidin-2-yl)amino]phenyl}ethanone

Intermediate 254: 5-bromo-2-[(3-methylphenyl)amino]pyrimidin-4-ol



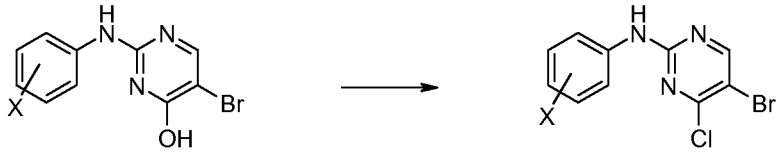
To a stirred solution of 5-bromo-2-chloro-4-methoxypyrimidine (1 eq) and arylamine (1.02 eq) in n-BuOH (12 v/w based on the former), was added dioxane-4M HCl (4 v/w based on the former) and heated to 110 °C in a sealed tube for 18-36 h. The reaction mixture was cooled to room temperature and BuOH was concentrated under vacuum. To the residue obtained, was added water (50 mL) and 10% $NaHCO_3$ solution. The resulting solid was filtered and further purified by column chromatography to yield the product. The compounds in the below table were prepared using this method and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 253	 1-{3-[(5-bromo-4-hydroxypyrimidin-2-yl)amino]phenyl}ethanone	MS(ES): 308 (M) and 310 (M+2) for $C_{12}H_{10}BrN_3O_2$. Purity by LCMS 97%	1-(3-aminophenyl)ethanone

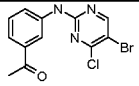
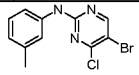
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 254	 5-bromo-2-[(3-methylphenyl)amino]pyrimidin-4-ol	MS(ES): 280 (M) and 282 (M+2) for $C_{11}H_{10}BrN_3O$. 400 MHz, DMSO-d_6: δ 2.29 (s, 3H), 6.89 (d, J = 7.52 Hz, 1H), 7.19-7.20 (m, 1H), 7.35 (s, 2H), 8.05 (s, 1H), 8.82 (s, 1H).	3-methylaniline

Intermediate 255: 1-{3-[(5-bromo-4-chloropyrimidin-2-yl)amino]phenyl}ethanone

Intermediate 256: 5-bromo-4-chloro-*N*-(3-methylphenyl)pyrimidin-2-amine

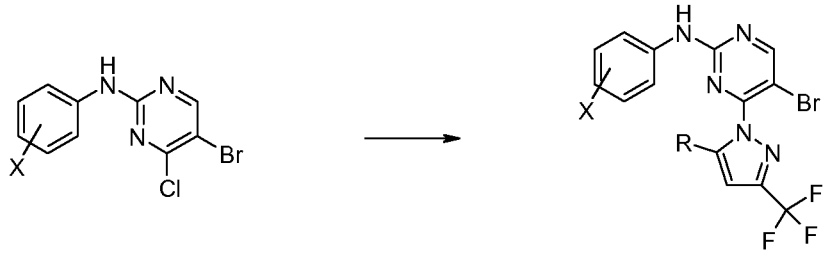


A solution of 5-bromo-2-[arylamino]pyrimidin-4-ol (1 eq) in $POCl_3$ (3- 10 v/w) was heated to reflux for 1 h. It was cooled to RT and $POCl_3$ was removed *in vacuo*. To the residue obtained, was added crushed ice with stirring, and the pH was adjusted to 7-8 using 10% sodium bicarbonate solution. The solid obtained was filtered and washed with chilled water to yield the title compound. The compounds in the below table were prepared using this method and the specified starting material.

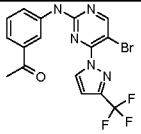
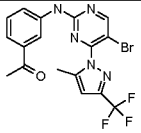
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 255[a)]	 1-{3-[(5-bromo-4-chloropyrimidin-2-yl)amino]phenyl}ethanone	MS(ES): 326 (M) and 328 (M+2) for $C_{12}H_9BrClN_3O$. 400 MHz, DMSO-d_6: δ 2.56 (s, 3H), 7.47 (t, J = 7.88 Hz, 1H), 7.62-7.62 (m, 1H), 7.89-7.90 (m, 1H), 8.26 (t, J = 1.88 Hz, 1H), 8.72 (s, 1H), 10.39 (s, 1H).	**Intermediate 253** 1-{3-[(5-bromo-4-hydroxypyrimidin-2-yl)amino]phenyl}ethanone
Intermediate 256	 5-bromo-4-chloro-*N*-(3-methylphenyl)pyrimidin-2-amine	MS(ES): 298 (M) and 300 (M+2) for $C_{11}H_9BrClN_3$. 300 MHz, DMSO-d_6: δ 2.27 (s, 3H), 6.83 (d, J = 7.47 Hz, 1H), 7.18 (t, J = 7.83 Hz, 1H), 7.44 (d, J = 4.71 Hz, 1H), 7.48 (s, 1H), 8.65 (s, 1H), 10.11 (s, 1H).	**Intermediate 254** 5-bromo-2-[(3-methylphenyl)amino]pyrimidin-4-ol

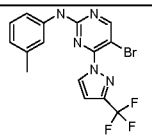
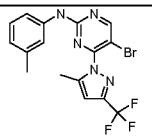
[a)] *N*, *N*-diethylaniline (0.2 eq) and MeCN (10 v/w) were also added

General method for the synthesis of 5-bromo-*N*-(aryl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine and 5-bromo-*N*-(aryl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine



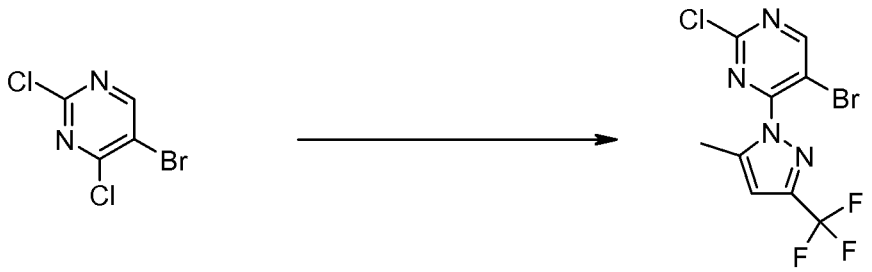
NaH (1.2 eq) was dissolved in 1 mL of NMP and stirred for about 5 min at 0 °C. Then 3-(trifluoromethyl)-1*H*-pyrazole/5-methyl-3-(trifluoromethyl)-1*H*-pyrazole (1.1 eq) in NMP was added dropwise at 0 °C for about 10 min and stirring continued for about 20 min under N_2. Then 5-bromo-4-chloro-*N*-(aryl)pyrimidin-2-amine (1 eq) in NMP was added dropwise and the reaction was stirred overnight at room temperature. Water was added and the solid obtained was filtered, dried and purified by silica gel column chromatography using ethyl acetate/hexanes as eluent to yield the desired product. The compounds in the below table were prepared using this method and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 257	 1-[3-({5-bromo-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)phenyl]ethanone	MS(ES): 426 (M) and 428 (M+2) for $C_{16}H_{11}BrF_3N_5O$. 400 MHz, DMSO-d_6: δ 2.56 (s, 3H), 7.47 (t, *J* = 7.88 Hz, 1H), 7.62-7.65 (m, 1H), 7.89-7.92 (m, 1H), 8.26 (t, *J* = 1.88 Hz, 1H), 8.72 (s, 1H), 10.39 (s, 1H).	**Intermediate 255** (1-{3-[(5-bromo-4-chloropyrimidin-2-yl)amino]phenyl}ethanone)
Intermediate 258	 1-[3-({5-bromo-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)phenyl]ethanone	MS(ES): 440 (M) and 442 (M+2) for $C_{17}H_{13}BrF_3N_5O$. 400 MHz, DMSO-d_6: δ 2.41 (s, 3H), 2.54 (s, 3H), 6.85 (s, 1H), 7.48 (t, *J* = 9.20 Hz, 1H), 7.65 (d, *J* = 7.00 Hz, 1H), 7.87 (d, *J* = 8.20 Hz, 1H), 8.29 (s, 1H), 8.96 (s, 1H), 10.45 (s, 1H).	**Intermediate 255** (1-{3-[(5-bromo-4-chloropyrimidin-2-yl)amino]phenyl}ethanone)

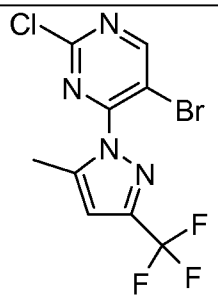
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 259 [b]	 5-bromo-*N*-(3-methylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 398 (M) and 400 (M+2) for $C_{15}H_{11}BrF_3N_5$. 300 MHz, DMSO-d_6: δ 2.28 (s, 3H), 6.84 (d, J = 7.59 Hz, 1H), 7.12 (d, J = 2.43 Hz, 1H), 7.19 (t, J = 7.89 Hz, 1H), 7.51 (d, J = 5.34 Hz, 1H), 7.58 (s, 1H), 8.61 (d, J = 0.96 Hz, 1H), 8.85 (d, J = 1.41 Hz, 1H), 10.15 (s, 1H).	**Intermediate 256** 5-bromo-4-chloro-*N*-(3-methylphenyl)pyrimidin-2-amine
Intermediate 260	 5-bromo-*N*-(3-methylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES):412 (M) and 414 (M+2) for $C_{16}H_{13}BrF_3N_5$ 400 MHz, DMSO-d_6: δ 2.27 (s, 3H), 2.39 (s, 3H), 6.85 (d, J = 9.96 Hz, 2H), 7.19 (t, J = 7.64 Hz, 1H), 7.46 (d, J = 7.80 Hz, 2H), 8.90 (d, J = 1.08 Hz, 1H), 10.19 (s, 1H).	**Intermediate 256** 5-bromo-4-chloro-*N*-(3-methylphenyl)pyrimidin-2-amine

[b] DMF was used as solvent, 12 h

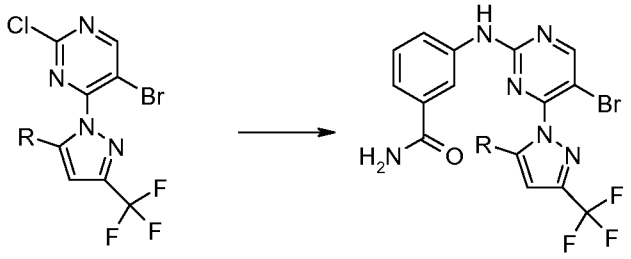
Intermediate 261: 5-bromo-2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine



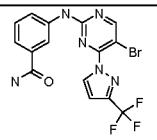
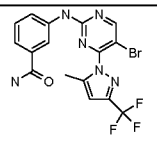
To a suspension of 5-bromo-2,4-dichloropyrimidine (44 mmol, 10 g) in acetonitrile (100 mL), was added K_2CO_3 (44 mmol, 6.1 g) and the reaction mixture was cooled to -5 to -10 °C. 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole (44 mmol, 6.6 g) was dissolved in 100 mL of acetonitrile and added dropwise. After the addition, the reaction mixture was slowly warmed to RT and stirred overnight. The reaction mixture was filtered through a celite bed and acetonitrile was removed *in vacuo*. The crude mass was purified by silica gel column chromatography (60-120 mesh; product eluted with 1% EtOAc/hexanes) to yield 5 g of the product.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 261	 5-bromo-2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine	MS(ES): 341 (M) and 343 (M+2) for $C_9H_5BrClF_3N_4$. 300 MHz, $CDCl_3$: δ 2.52 (s, 3H), 6.53 (s, 1H), 8.94 (s, 1H).	5-bromo-2,4-dichloropyrimidine and 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole

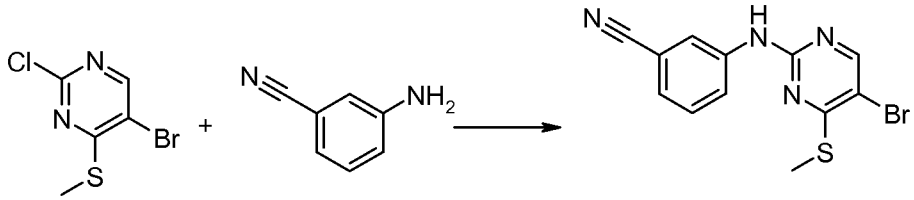
General method for the synthesis of 5-bromo-*N*-(aryl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine and 5-bromo-*N*-(aryl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine



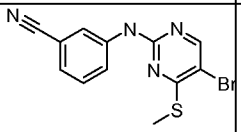
To a suspension of cesium carbonate (2 eq) in dry DMF (4 mL), were added 3-aminobenzamide (1.15 eq) and 5-bromo-2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine (**Intermediate 227**, 1 eq) or 5-bromo-2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine (**Intermediate 261**, 1 eq). The reaction vessel was sealed and heated to 100 °C for 5 h. The reaction mixture was diluted with EtOAc and filtered through a celite bed. The filtrate was washed with water and brine, dried over sodium sulfate and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh). The column was eluted with 3% Methanol/Chloroform to yield the desired product. The compounds in the below table were prepared using this method and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 262	 3-({5-bromo-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)benzamide	MS(ES): 427 (M) and 429 (M+2) for $C_{15}H_{10}BrF_3N_6O$. 300 MHz, DMSO-d_6: δ 7.13 (d, J = 2.73 Hz, 1H), 7.38 (t, J = 7.83 Hz, 2H), 7.52 (d, J = 7.80 Hz, 1H), 7.76 (d, J = 9.90 Hz, 1H), 7.93 (s, 1H), 8.27 (s, 1H), 8.68 (s, 1H), 8.88 (s, 1H), 10.35 (s, 1H).	**Intermediate 227** 5-bromo-2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine
Intermediate 263	 3-({5-bromo-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)benzamide	MS(ES): 441 (M) and 443 (M+2) for $C_{16}H_{12}BrF_3N_6O$. 300 MHz, DMSO-d_6: δ 2.48 (s, 3H), 6.63 (s, 1H), 7.34 (d, J = 7.68 Hz, 2H), 7.39 (d, J = 7.86 Hz, 1H), 7.51 (d, J = 7.80 Hz, 1H), 7.75 (d, J = 8.13 Hz, 1H), 7.89 (s, 1H), 8.14 (s, 1H), 8.92 (s, 1H), 10.34 (s, 1H).	**Intermediate 261** 5-bromo-2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine

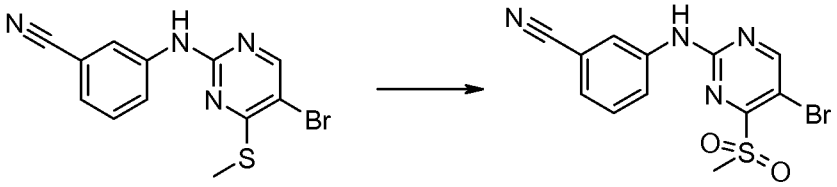
Intermediate 264: 3-{[5-bromo-4-(methylsulfanyl)pyrimidin-2-yl]amino}benzonitrile



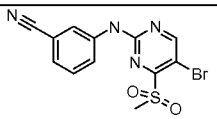
To 6 g of 5-bromo-2-chloro-4-(methylsulfanyl)pyrimidine (1.7 eq) suspended in n-BuOH (20 v/w), was added 3-aminobenzonitrile (1 eq) followed by 4M HCl in dioxane (0.25 eq) and refluxed overnight at 100 °C. The reaction was cooled to room temperature, diluted with diethyl ether and the solid was filtered and dried to give **Intermediate 264**.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 264	 3-{[5-bromo-4-(methylsulfanyl)pyrimidin-2-yl]amino}benzonitrile	Taken to the next step on the basis of LCMS. MS(ES): 321 (M) and 323 (M+2) for $C_{12}H_9BrN_4S$. (94 % pure by LCMS)	3-aminobenzonitrile and (5-bromo-2-chloro-4-(methylsulfanyl)pyrimidine

Intermediate 265: 3-{[5-bromo-4-(methylsulfonyl)pyrimidin-2-yl]amino}benzonitrile

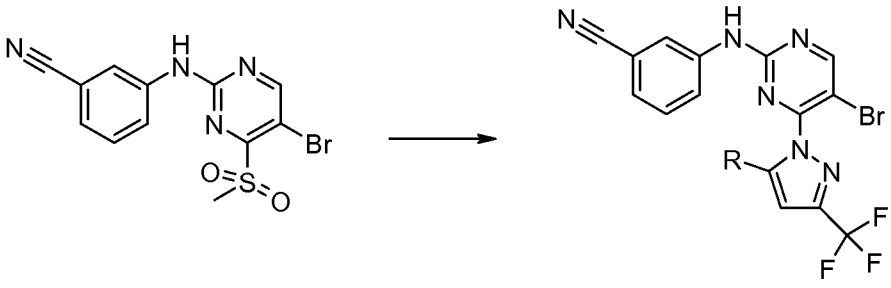


A suspension of 3-{[5-bromo-4-(methylsulfanyl)pyrimidin-2-yl]amino}benzonitrile (**Intermediate 264**, 1 eq) in dichloromethane (50 v/w) was cooled to 0 °C and 3-chloroperoxybenzoic acid (77 %, 4.5 eq) was added portion wise and stirred for 4 h. It was further diluted with dichloromethane and washed with 10 % aq. $NaHCO_3$ solution and water, dried over Na_2SO_4, filtered and concentrated to give **Intermediate 265.**

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 265	 3-{[5-bromo-4-(methylsulfonyl) pyrimidin-2-yl]amino}benzonitrile	MS(ES): 353 (M) and 355 (M+2) for $C_{12}H_9BrN_4O_2S$. 300 MHz, DMSO-d6: δ 3.47 (s, 3H), 7.47-7.57 (m, 2H), 7.90 (d, *J* = 8.13 Hz, 1H), 8.17 (s, 1H), 8.97 (s, 1H), 10.69 (s, 1H).	**Intermediate 264** 3-{[5-bromo-4-(methylsulfanyl)pyrimidin-2-yl]amino}benzonitrile

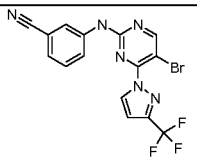
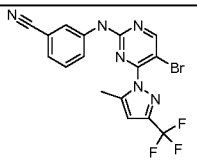
Intermediate 266: 3-({5-bromo-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)benzonitrile

Intermediate 267: 3-({5-bromo-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)benzonitrile



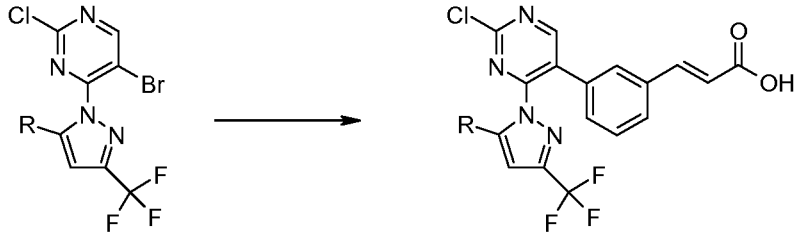
NaH (60 % dispersion in mineral oil, 2 eq) was dissolved in 1 mL of DMF and stirred for about 5 min at 0 °C. Then 3-(trifluoromethyl)-1*H*-pyrazole/5-methyl-3-(trifluoromethyl)-1*H*-pyrazole (2 eq) in DMF (2 mL) was added dropwise at 0 °C for about 10 min and stirring

continued for about 20 min under N_2. Then 3-{[5-bromo-4-(methylsulfonyl)pyrimidin-2-yl]amino}benzonitrile (**Intermediate 265**, 1 eq) in DMF was added dropwise and the reaction was stirred for 2.5 h at room temperature. After completion of the reaction, water was added and the solid obtained was filtered off, dried and purified by silica gel column chromatography using ethyl acetate/hexanes as eluent to yield the title compound. The compounds in the below table were prepared using this method and the specified starting material.

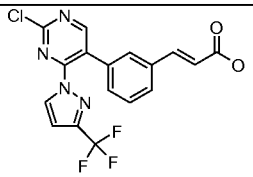
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 266	 3-({5-bromo-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)benzonitrile	MS(ES): 409 (M) and 411 (M+2) for $C_{15}H_8BrF_3N_6$. (83 % pure by LCMS). 300 MHz, DMSO-d_6: δ 7.15 (d, J = 2.64 Hz, 1H), 7.47 (d, J = 7.65 Hz, 1H), 7.53 (d, J = 7.95 Hz, 1H), 7.93 (br s, 1H), 8.20 (br s, 1H), 8.65 (br s, 1H), 8.96 (br s, 1H), 10.58 (br s, 1H).	**Intermediate 265** 3-{[5-bromo-4-(methylsulfonyl)pyrimidin-2-yl]amino}benzonitrile
Intermediate 267	 3-({5-bromo-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)benzonitrile	MS(ES): 423 (M) and 425 (M+2) for $C_{16}H_{10}BrF_3N_6$. 300 MHz, DMSO-d_6: δ 2.39 (s, 3H), 6.86 (s, 1H), 7.47 (d, J = 7.68 Hz, 1H), 7.54 (t, J = 8.01 Hz, 1H), 7.89-7.92 (m, 1H), 8.14 (s, 1H), 9.00 (s, 1H), 10.60 (s, 1H).	**Intermediate 265** 3-{[5-bromo-4-(methylsulfonyl)pyrimidin-2-yl]amino}benzonitrile

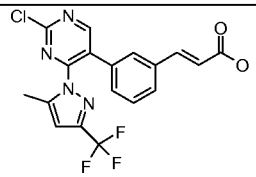
Intermediate 268: (2*E*)-3-(3-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid

Intermediate 269: (2*E*)-3-(3-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid



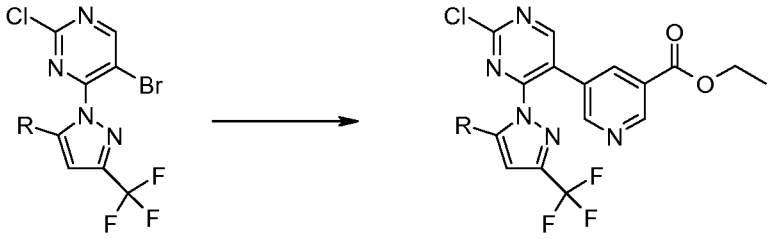
A suspension of 5-bromo-2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine (**Intermediate 227**, 1 eq) or 5-bromo-2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine (**Intermediate 261**, 1 eq), 3-(*trans*-2-carboxyvinyl)phenylboronic acid (1.1 – 1.2 eq), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (10 mol%) and sodium carbonate (2 eq) in acetonitrile/water (4 : 1) was degassed and heated to 90 °C for 15-30 min under inert atmosphere. The solvent was removed *in vacuo* and the crude mixture taken in $CHCl_3$ was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using 3-5% MeOH/$CHCl_3$ as an eluent to give the product. The compounds in the below table were prepared using this method and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 268	 (2*E*)-3-(3-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	Taken to the next step on the basis of LCMS. MS(ES): 395 (M+1) for $C_{17}H_{10}ClF_3N_4O_2$.	**Intermediate 227** 5-bromo-2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine

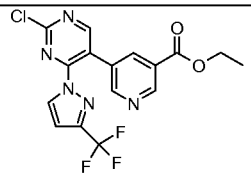
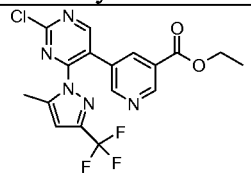
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 269	 (2*E*)-3-(3-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	Taken to the next step on the basis of LCMS. MS(ES): 409 (M+1) for $C_{18}H_{12}ClF_3N_4O_2$. (75 % pure by LCMS)	**Intermediate 261** 5-bromo-2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine

Intermediate 270: ethyl 5-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

Intermediate 271: ethyl 5-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

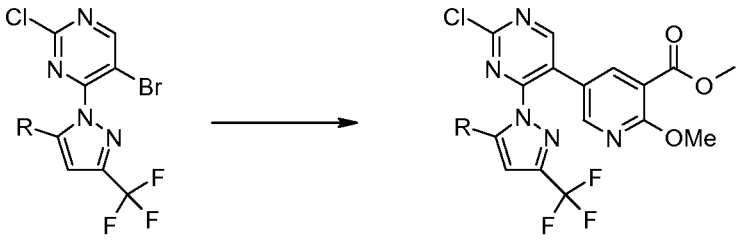


A solution of 5-bromo-2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine (**Intermediate 227**, 1 eq) or 5-bromo-2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine (**Intermediate 261**, 1 eq), ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (1 eq), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (20 mol%) and sodium carbonate (1 eq) in acetonitrile (10 mL)/water (10 mL) was degassed and heated to 90 °C for 20' under nitrogen. The reaction mixture was concentrated *in vacuo*. The residue obtained was taken in ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using 35 % ethyl acetate/hexanes as an eluent. The compounds in the below table were prepared using this method and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 270	 ethyl 5-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 398 (M+1) for $C_{16}H_{11}ClF_3N_5O_2$. 400 MHz, DMSO-d_6: δ 1.31 (t, J = 7.04 Hz, 3H), 4.35 (q, J = 7.08 Hz, 2H), 7.08 (d, J = 2.68 Hz, 1H), 8.26 (t, J = 2.08 Hz, 1H), 8.78 (m, 2H), 9.06 (s, 1H), 9.12 (d, J = 1.96 Hz, 1H).	**Intermediate 227** 5-bromo-2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine
Intermediate 271	 ethyl 5-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 412 (M+1) for $C_{17}H_{13}ClF_3N_5O_2$. 400 MHz, DMSO-d_6: δ 1.31 (t, J = 7.08 Hz, 3H), 2.51 (s, 3H), 4.34 (q, J = 7.04 Hz, 2H), 6.84 (s, 1H), 8.04 (s, 1H), 8.69 (d, J = 1.88 Hz, 1H), 9.08 (d, J = 1.60 Hz, 1H), 9.26 (s, 1H).	**Intermediate 261** 5-bromo-2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine

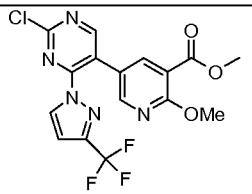
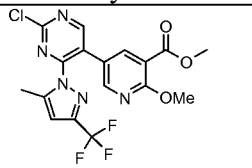
Intermediate 272: methyl 5-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

Intermediate 273: methyl 5-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

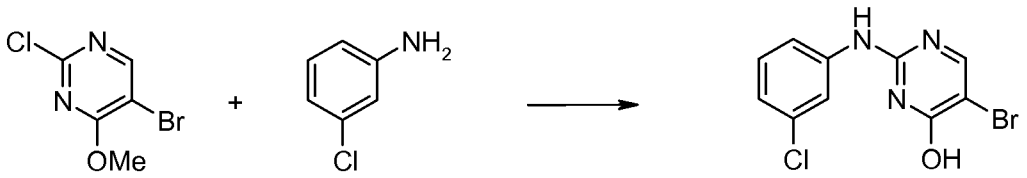


A solution of 5-bromo-2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine (**Intermediate 227**, 1 eq) or 5-bromo-2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine (**Intermediate 261**, 1 eq), methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (1 eq), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (20 mol%) and sodium carbonate (1

eq) in acetonitrile (10 mL)/water (10 mL) was degassed and heated to 90 °C for 20 hours under nitrogen. The reaction mixture was concentrated *in vacuo*. The residue obtained was taken in ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using 30 % ethyl acetate/hexanes as an eluent to give the product. The compounds in the below table were prepared using this method and the specified starting material.

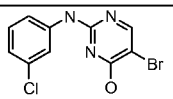
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 272	 methyl 5-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 414 (M+1) for $C_{16}H_{11}ClF_3N_5O_3$. 400 MHz, DMSO-d_6: δ 3.78 (s, 3H), 3.96 (s, 3H), 7.08 (d, J = 2.72 Hz, 1H), 8.05 (d, J = 2.44 Hz, 1H), 8.36 (d, J = 2.48 Hz, 1H), 8.71 (t, J = 0.88 Hz, 1H), 9.04 (s, 1H).	**Intermediate 227** 5-bromo-2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine
Intermediate 273	 methyl 5-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 428 (M+1) for $C_{17}H_{13}ClF_3N_5O_3$. 300 MHz, DMSO-d_6: δ 2.40 (s, 3H), 3.80 (s, 3H), 3.93 (s, 3H), 6.82 (s, 1H), 7.75 (s, 1H), 8.29 (d, J = 2.46 Hz, 1H), 9.21 (s, 1H).	**Intermediate 261** 5-bromo-2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine

Intermediate 274: 5-bromo-2-[(3-chlorophenyl)amino]pyrimidin-4-ol

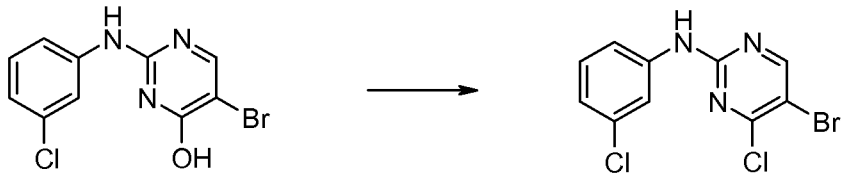


To a stirred solution of 5-bromo-2-chloro-4-methoxypyrimidine (53.8 mmol, 12 g) in n-BuOH (60 mL) was added 3-chloroaniline (59.1 mmol, 7.47 g, 6.2 mL) and 4 N HCl in dioxane (36 mL). The reaction mixture was heated at 80 °C for 20 h. It was then cooled to

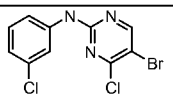
room temperature, acetonitrile (120 mL) was added and the resulting solid was filtered to yield 6 g of 5-bromo-2-[(3-chlorophenyl)amino]pyrimidin-4-ol as white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 274	 5-bromo-2-[(3-chlorophenyl)amino]pyrimidin-4-ol	MS (ES): 300 (M) and 302 (M+2) for $C_{10}H_7BrClN_3O$. 400 MHz, DMSO-d_6: δ 7.09 (d, J = 7.12 Hz, 1H), 7.31-7.34 (m, 1H), 7.38 (s, 1H), 7.83 (s, 1H), 8.11 (s, 1H), 9.10 (br s, 1H), 11.52 (br s, 1H).	5-bromo-2-chloro-4-methoxypyrimidine and 3-chloroaniline

Intermediate 275: 5-bromo-4-chloro-*N*-(3-chlorophenyl)pyrimidin-2-amine

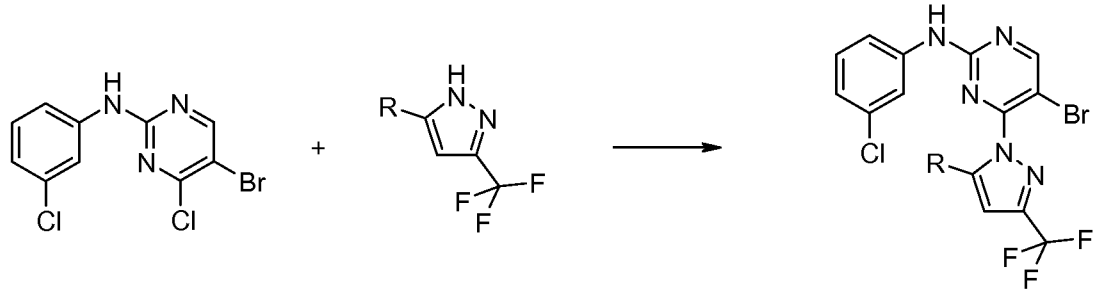


To 6 g of 5-bromo-2-[(3-chlorophenyl)amino]pyrimidin-4-ol (**Intermediate 274**, 20 mmol), was added 30 mL of $POCl_3$ (323 mmol, 49.5 g) and the mixture heated to reflux for 1 h. It was cooled to room temperature and $POCl_3$ was removed *in vacuo*. It was then diluted with water then extracted with ethyl acetate, organic layer washed successively with 10% sodium bicarbonate solution and water, dried over Na_2SO_4, filtered and concentrated to yield 3.0 g of 5-bromo-4-chloro-*N*-(3-chlorophenyl)pyrimidin-2-amine.

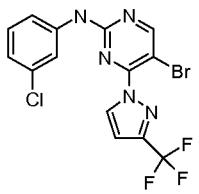
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 275	 5-bromo-4-chloro-*N*-(3-chlorophenyl)pyrimidin-2-amine	MS (ES): 318 (M) and 320 (M+2) for $C_{10}H_6BrCl_2N_3$. 400 MHz, DMSO-d_6: δ 7.05-7.07 (m, 1H), 7.33 (t, J = 8.16 Hz, 1H), 7.56-7.59 (m, 1H), 7.85 (t, J = 2.04 Hz, 1H), 8.74 (s, 1H), 10.40 (s, 1H).	**Intermediate 274** 5-bromo-2-[(3-chlorophenyl)amino]pyrimidin-4-ol

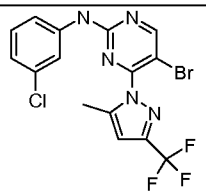
Intermediate 276: 5-bromo-*N*-(3-chlorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

Intermediate 277: 5-bromo-*N*-(3-chlorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

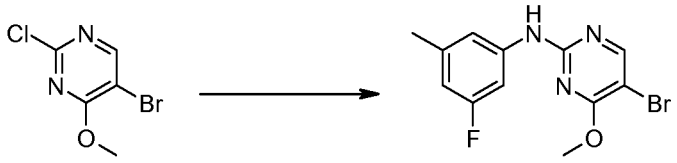


A solution of 3-(trifluoromethyl)-1*H*-pyrazole or 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole (1.2 eq) in DMF (4.0 mL) was added slowly to a suspension of sodium hydride (1.2 eq) in DMF (4.0 mL) at 0 °C. The reaction mixture was stirred for 1 h at room temperature. A solution of 5-bromo-4-chloro-*N*-(3-chlorophenyl)pyrimidin-2-amine (**Intermediate 275,** 1 eq) in DMF (4.0 mL) was added slowly to the reaction mixture at 0 °C and allowed to warm to ambient temperature over 2-3 h. The mixture was quenched with ice cold water at 0-5 °C, pH adjusted to 2 with 1.5 N HCl and then extracted with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated. The crude mass was purified by silica gel column chromatography (product eluted with 10-15 % ethyl acetate/hexanes) to yield the desired product. The compounds in the below table were prepared using this method and the specified starting materials.

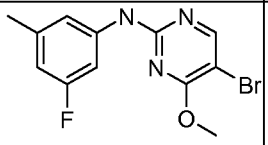
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 276	 5-bromo-*N*-(3-chlorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS (ES): 418 (M) and 420 (M+2) for $C_{14}H_8BrClF_3N_5$. 400 MHz, DMSO-d_6: δ 7.06-7.09 (m, 1H), 7.15 (d, J = 2.72 Hz, 1H), 7.35 (t, J = 8.12 Hz, 1H), 7.61-7.64 (m, 1H), 7.91 (t, J = 2.00 Hz, 1H), 8.64 (t, J = 1.68 Hz, 1H), 8.94 (s, 1H), 10.44 (s, 1H).	**Intermediate 275** 5-bromo-4-chloro-*N*-(3-chlorophenyl)pyrimidin-2-amine and 3-(trifluoromethyl)-1*H*-pyrazole

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 277	 5-bromo-*N*-(3-chlorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS (ES): 432 (M) and 434 (M+2) for $C_{15}H_{10}BrClF_3N_5$. 300 MHz, DMSO-d_6: δ 2.40 (s, 3H), 6.85 (s, 1H), 7.07 (d, J = 7.98 Hz, 1H), 7.34 (t, J = 8.07 Hz, 1H), 7.56 (d, J = 9.33 Hz, 1H), 7.84 (s, 1H), 8.98 (s, 1H), 10.46 (s, 1H).	5-bromo-4-chloro-*N*-(3-chlorophenyl)pyrimidin-2-amine and 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole

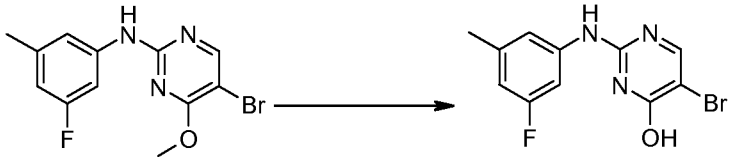
Intermediate 278: 5-bromo-*N*-(3-fluoro-5-methylphenyl)-4-methoxypyrimidin-2-amine



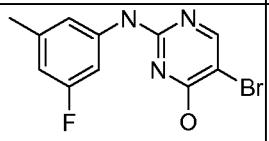
To a stirred solution of 5-bromo-2-chloro-4-methoxypyrimidine (1 eq) and 3-fluoro-5-methylaniline (1.01 eq) in n-BuOH (5 v/w based on the former) was added dioxane-HCl (3 v/w based on the former) and heated to 80 °C in a sealed tube for 3 h. The reaction mixture was cooled to room temperature and BuOH was concentrated under vacuum. To the residue obtained, was added MeCN and stirred at 10-15 °C for 30 minutes. The resulting solid was filtered and washed with MeCN to yield **Intermediate 278**.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 278	 5-bromo-*N*-(3-fluoro-5-methylphenyl)-4-methoxypyrimidin-2-amine	MS(ES): 312 (M) and 314 (M+2) for $C_{12}H_{11}BrFN_3O$. (86 % pure by LCMS)	3-fluoro-5-methylaniline

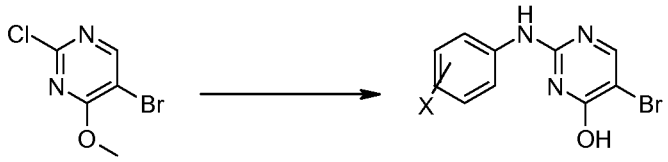
Intermediate 279: 5-bromo-2-[(3-fluoro-5-methylphenyl)amino]pyrimidin-4-ol



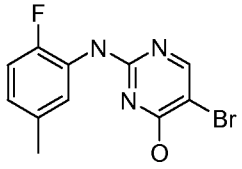
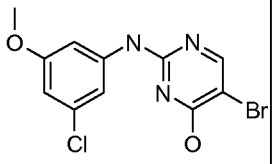
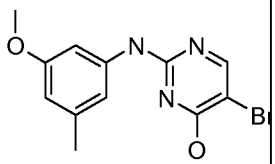
A mixture of 5-bromo-*N*-(3-fluoro-5-methylphenyl)-4-methoxypyrimidin-2-amine **Intermediate 278** (1 eq) and aq. sodium thiomethoxide (21% aq. soln (w/v), 5 v/w based on **Intermediate 278**) and DMF (10 v/w) was heated to 80 °C for 2 h. The reaction mass was cooled to room temperature and quenched with ice-cold water and the pH adjusted to 2 with 1.5 N HCl solution. The precipitated solid was filtered and washed with water to yield **Intermediate 279**.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 279	 5-bromo-2-[(3-fluoro-5-methylphenyl)amino]pyrimidin-4-ol	MS(ES): 298 (M) and 300 (M+2) for $C_{11}H_9BrFN_3O$. 300 MHz, DMSO-d_6: δ 2.27 (s, 3H), 6.70 (d, J = 9.75 Hz, 1H), 7.03 (s, 1H), 7.45 (d, J = 11.58 Hz, 1H), 8.14 (s, 1H), 9.05 (br s, 1H), 11.45 (br s, 1H).	**Intermediate 278** 5-bromo-*N*-(3-fluoro-5-methylphenyl)-4-methoxypyrimidin-2-amine

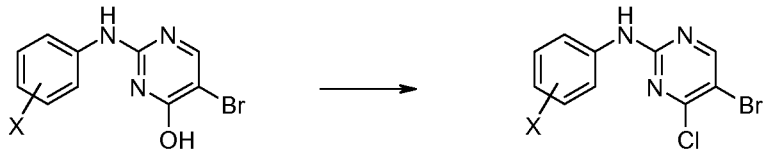
General procedure for the synthesis of 5-bromo-2-[(aryl)amino]pyrimidin-4-ol



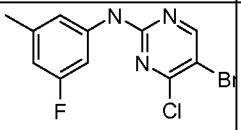
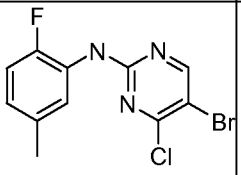
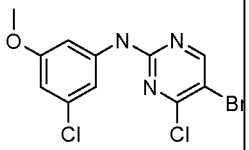
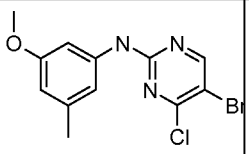
To a stirred solution of 5-bromo-2-chloro-4-methoxypyrimidine (1 eq) and arylamine (1.02 eq) in n-BuOH (12 v/w based on the former) was added 4M HCl in dioxane (4 v/w based on the former) and heated to 110 °C in a sealed tube for 18-36 h. The reaction mixture was cooled to room temperature and BuOH was concentrated under vacuum. To the residue obtained, was added water (50 mL) and 10% $NaHCO_3$ solution. The resulting solid was filtered and further purified by column chromatography to yield the product. The compounds in the below table were prepared using this procedure and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 280	 5-bromo-2-[(2-fluoro-5-methylphenyl)amino]pyrimidin-4-ol	Taken to the next step based on LCMS without further purification. MS(ES): 298 (M) and 300 (M+2) for $C_{11}H_9BrFN_3O$.	2-fluoro-5-methylaniline
Intermediate 281	 5-bromo-2-[(3-chloro-5-methoxyphenyl)amino]pyrimidin-4-ol	MS(ES): 330 (M) and 332 (M+2) for $C_{11}H_9BrClN_3O_2$. 400 MHz, DMSO-d_6: δ 3.76 (s, 3H), 6.72 (t, J = 2.04 Hz, 1H), 7.11 (t, J = 1.88 Hz, 1H), 7.35 (t, J = 1.76 Hz, 1H), 8.12 (s, 1H), 9.45 (s, 1H), 11.53 (s, 1H).	3-chloro-5-methoxyaniline
Intermediate 282	 5-bromo-2-[(3-methoxy-5-methylphenyl)amino]pyrimidin-4-ol	MS(ES): 310 (M) and 312 (M+2) for $C_{12}H_{12}BrN_3O_2$. 400 MHz, DMSO -d_6: δ 2.26 (s, 3H), 3.72 (s, 3H), 6.47 (s, 1H), 6.89 (s, 1H), 7.12 (s, 1H), 7.91 (s, 1H), 9.56 (s, 1H), 11.53 (s, 1H).	3-methoxy-5-methylaniline

General procedure for the synthesis of 5-bromo-4-chloro-*N*-(aryl)pyrimidin-2-amine

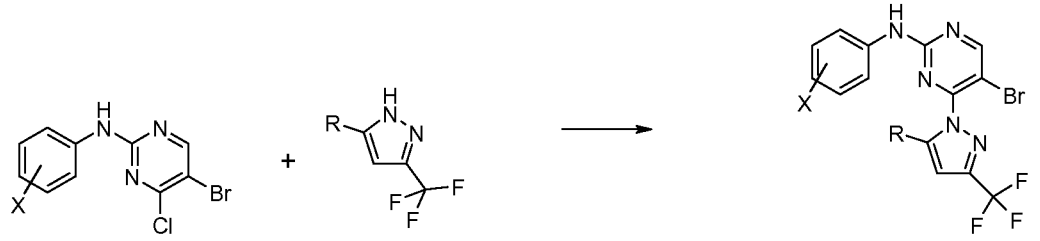


A solution of 5-bromo-2-[arylamino]pyrimidin-4-ol (1 eq) in $POCl_3$ (5 eq) was heated to reflux for 1 h. It was cooled to RT and $POCl_3$ was removed *in vacuo*. To the residue obtained, was added crushed ice with stirring, and the pH was adjusted to 7-8 using 10% $NaHCO_3$ solution. The solid obtained was filtered and washed with chilled water to yield the title compound. The compounds in the below table were prepared using this procedure and the specified starting material.

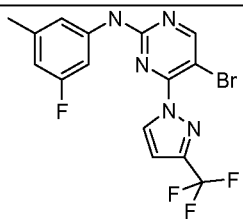
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 283	 5-bromo-4-chloro-*N*-(3-fluoro-5-methylphenyl)pyrimidin-2-amine	MS(ES): 316 (M) and 318 (M+2) for $C_{11}H_8BrClFN_3$. 300 MHz, DMSO- d_6: δ 2.27 (s, 3H), 6.67 (d, J = 9.39 Hz, 1H), 7.21 (s, 1H), 7.48 (d, J = 11.70 Hz, 1H), 8.71 (s, 1H), 10.33 (s, 1H).	**Intermediate 279** 5-bromo-2-[(3-fluoro-5-methyl-phenyl)amino]pyrimidin-4-ol
Intermediate 284[a)]	 5-bromo-4-chloro-*N*-(2-fluoro-5-methylphenyl)pyrimidin-2-amine	MS(ES): 316 (M) and 318 (M+2) for $C_{11}H_8BrClFN_3$. 400 MHz, DMSO- d_6: δ 2.27 (s, 3H), 7.02 (d, J = 5.08 Hz, 1H), 7.12 (t, J = 8.48 Hz, 1H), 7.30 (d, J = 7.76 Hz, 1H), 8.59 (s, 1H), 9.75 (s, 1H).	**Intermediate 280** 5-bromo-2-[(2-fluoro-5-methyl phenyl)amino]pyrimidin-4-ol
Intermediate 285[a)]	 5-bromo-4-chloro-*N*-(3-chloro-5-methoxyphenyl)pyrimidin-2-amine	MS(ES): 348 (M) and 350 (M+2) for $C_{11}H_8BrCl_2N_3O$. 400 MHz, DMSO-d_6: δ 3.76 (s, 3H), 6.69 (t, J = 2.04 Hz, 1H), 7.31 (t, J = 2.08 Hz, 1H), 7.42 (t, J = 1.80 Hz, 1H), 8.75 (s, 1H), 10.37 (s, 1H).	**Intermediate 281** 5-bromo-2-[(3-chloro-5-methoxy phenyl)amino]pyrimidin-4-ol
Intermediate 286	 5-bromo-4-chloro-*N*-(3-methoxy-5-methylphenyl)pyrimidin-2-amine	MS(ES): 328 (M) and 330 (M+2) for $C_{12}H_{11}BrClN_3O$. 400 MHz, DMSO-d_6: δ 2.26 (s, 3H), 3.72 (s, 3H), 6.46 (s, 1H), 7.03 (s, 1H), 7.21 (s, 1H), 8.69 (s, 1H), 10.11 (s, 1H).	**Intermediate 282** 5-bromo-2-[(3-methoxy-5-methylphenyl)amino]pyrimidin-4-ol

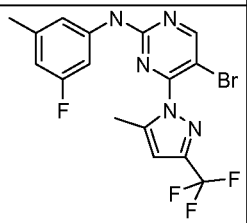
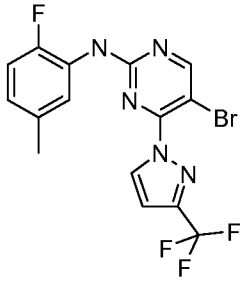
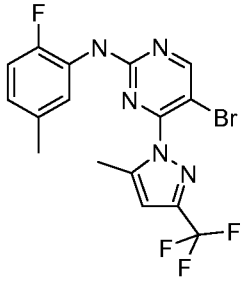
[a)] *N*, *N*-diethylaniline (0.5 eq), $Et_4N^+Cl^-$ (0.5 eq) and MeCN (10 v/w) were also added

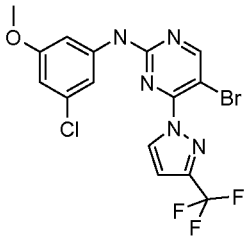
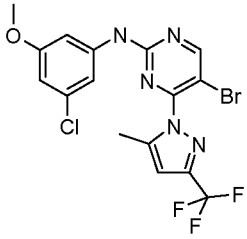
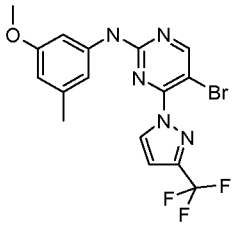
General procedure for the synthesis of 5-bromo-*N*-(aryl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine and 5-bromo-*N*-(aryl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

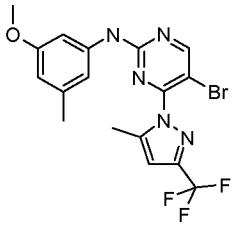


NaH (1.2 eq) was dissolved in 1 mL of DMF and stirred for about 5 min at 0 °C. Then 3-(trifluoromethyl)-1*H*-pyrazole or 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole (1.1 eq) in NMP was added drop-wise at 0°C over about 10 min and stirring continued for about 20 min under N_2. Then 5-bromo-4-chloro-*N*-(aryl)pyrimidin-2-amine (1 eq) in DMF was added dropwise and the reaction was stirred overnight at RT. Water was added and the solid obtained was filtered, dried and purified by silica gel column chromatography using ethyl acetate/hexanes (2:8) as eluent to yield the product. The compounds in the below table were prepared using this procedure and the specified starting material.

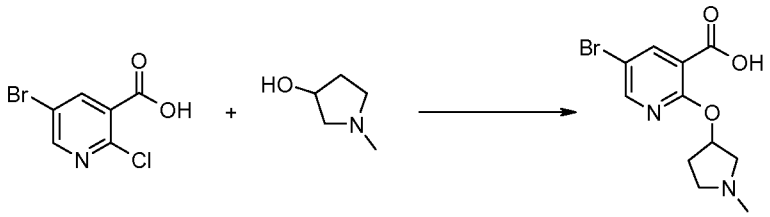
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 287	 5-bromo-*N*-(3-fluoro-5-methylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 416 (M) and 418 (M+2) for $C_{15}H_{10}BrF_4N_5$. 300 MHz, DMSO-d_6: δ 2.28 (s, 3H), 6.68 (d, J = 9.54 Hz, 1H), 7.14 (d, J = 2.58 Hz, 1H), 7.30 (s, 1H), 7.49 (d, J = 11.73 Hz, 1H), 8.63 (d, J = 1.50 Hz, 1H), 8.91 (s, 1H), 10.37 (s, 1H).	**Intermediate 283** 5-bromo-4-chloro-*N*-(3-fluoro-5-methylphenyl)pyrimidin-2-amine

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 288	 5-bromo-*N*-(3-fluoro-5-methylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 430 (M) and 432 (M+2) for $C_{16}H_{12}BrF_4N_5$. 400 MHz, DMSO-d_6: δ 2.27 (s, 3H), 2.39 (s, 3H), 6.69 (d, J = 9.08 Hz, 1H), 6.85 (s, 1H), 7.22 (s, 1H), 7.46 (d, J = 11.48 Hz, 1H), 8.96 (s, 1H).	**Intermediate 283** 5-bromo-4-chloro-*N*-(3-fluoro-5-methylphenyl)pyrimidin-2-amine
Intermediate 289	 5-bromo-*N*-(2-fluoro-5-methylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 416 (M) and 418 (M+2) for $C_{15}H_{10}BrF_4N_5$. 400 MHz, DMSO-d_6: δ 2.28 (s, 3H), 7.01 (s, 1H), 7.09-7.10 (m, 2H), 7.42 (d, J = 6.84 Hz, 1H), 8.50 (s, 1H), 8.80 (s, 1H), 9.81 (s, 1H).	**Intermediate 284** 5-bromo-4-chloro-*N*-(2-fluoro-5-methylphenyl)pyrimidin-2-amine
Intermediate 290	 5-bromo-*N*-(2-fluoro-5-methylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 430 (M) and 432 (M+2) for $C_{16}H_{12}BrF_4N_5$. 400 MHz, DMSO-d_6: δ 2.27 (s, 3H), 2.33 (s, 3H), 6.81 (s, 1H), 7.02-7.03 (m, 1H), 7.15 (dd, J = 8.44, 10.58 Hz, 1H), 7.35 (t, J = 5.88 Hz, 1H), 8.85 (s, 1H), 9.85 (s, 1H).	**Intermediate 284** 5-bromo-4-chloro-*N*-(2-fluoro-5-methylphenyl)pyrimidin-2-amine

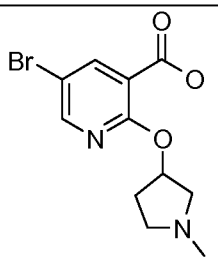
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 291	 5-bromo-*N*-(3-chloro-5-methoxyphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 448 (M) and 450 (M+2) for $C_{15}H_{10}BrClF_3N_5O$. 400 MHz, DMSO-d_6: δ 3.75 (s, 3H), 6.69 (s, 1H), 7.17 (d, J = 2.56 Hz, 1H), 7.42 (m, 2H), 8.65 (s, 1H), 8.95 (s, 1H), 10.42 (s, 1H) .	**Intermediate 285** 5-bromo-4-chloro-*N*-(3-chloro-5-methoxyphenyl)pyrimidin-2-amine
Intermediate 292	 5-bromo-*N*-(3-chloro-5-methoxyphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 462 (M) and 464 (M+2) for $C_{16}H_{12}BrClF_3N_5O$. 400 MHz, DMSO-d_6: δ 2.41 (s, 3H), 3.75 (s, 3H), 6.70 (s, 1H), 6.87 (s, 1H), 7.29 (d, J = 0.76 Hz, 1H), 7.42 (s, 1H), 9.00 (d, J = 1.04 Hz, 1H), 10.43 (s, 1H).	**Intermediate 285** 5-bromo-4-chloro-*N*-(3-chloro-5-methoxyphenyl)pyrimidin-2-amine
Intermediate 293	 5-bromo-*N*-(3-methoxy-5-methylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 428 (M) and 430 (M+2) for $C_{16}H_{13}BrF_3N_5O$. 300 MHz, DMSO- d_6: δ 2.24 (s, 3H), 3.70 (s, 3H), 6.43 (s, 1H), 7.06 (s, 1H), 7.13 (d, J = 2.37 Hz, 1H), 7.26 (s, 1H), 8.62 (s, 1H), 8.86 (s, 1H), 10.15 (s, 1H).	**Intermediate 286** 5-bromo-4-chloro-*N*-(3-methoxy-5-methylphenyl)pyrimidin-2-amine

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 294	 5-bromo-*N*-(3-methoxy-5-methylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine	MS(ES): 442 (M) and 444 (M+2) for $C_{17}H_{15}BrF_3N_5O$. 400 MHz, DMSO-d_6: δ 2.25 (s, 3H), 2.40 (s, 3H), 3.70 (s, 3H), 6.46 (s, 1H), 6.85 (s, 1H), 7.04 (s, 1H), 7.19 (s, 1H), 8.93 (s, 1H), 10.19 (s, 1H).	**Intermediate 286** 5-bromo-4-chloro-*N*-(3-methoxy-5-methylphenyl)pyrimidin-2-amine

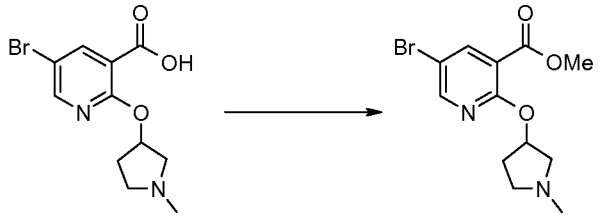
Intermediate 295: 5-bromo-2-[(1-methylpyrrolidin-3-yl)oxy]pyridine-3-carboxylic acid



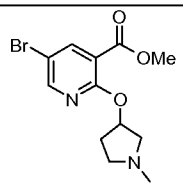
To 5-bromo-2-chloropyridine-3-carboxylic acid (4.21 mmol, 1 g) and 1-methylpyrrolidin-3-ol (17.5 mmol, 1.88 mL, 1.77 g) taken in *tert*-butanol (25 mL), was added sodium *tert*-butoxide (16.9 mmol, 1.64 g) and heated to 85 °C for 2 h. The solvent was removed *in vacuo* and the reaction mixture was diluted with water. The aqueous layer was washed with EtOAc, then carefully acidified with 1 N HCl (pH=5). Water was distilled off and the residue taken in a mixture of MeOH and EtOAc (1:1) was passed through was a celite bed and the resultant crude product (2 g) was used without further purification in the next step.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 295	 5-bromo-2-[(1-methylpyrrolidin-3-yl)oxy]pyridine-3-carboxylic acid	Taken to the next step based on LCMS without further purification. MS(ES): 301 (M) and 303 (M+2) for $C_{11}H_{13}BrN_2O_3$. (92 % pure by LCMS)	1-methylpyrrolidin-3-ol

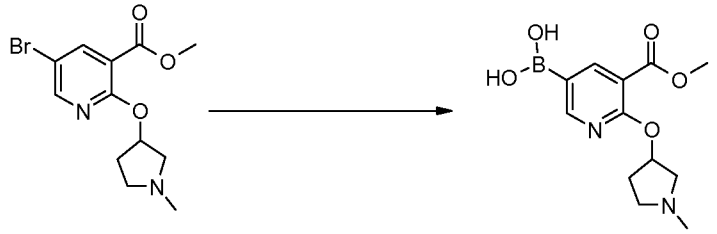
Intermediate 296: methyl 5-bromo-2-[(1-methylpyrrolidin-3-yl)oxy]pyridine-3-carboxylate



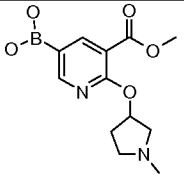
To a suspension of 5-bromo-2-[(1-methylpyrrolidin-3-yl)oxy]pyridine-3-carboxylic acid (**Intermediate 295**, 4.52 mmol, 1.36 g) in MeOH (13 ml) at 0 °C, was slowly added thionyl chloride (8.4 mmol, 0.999 g). After the addition was complete, the reaction mixture was refluxed for 2 h. The solvent was concentrated in *vacuo* and the crude mixture was taken in EtOAc (30 mL), washed with aq. $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated to obtain 1.2 g of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 296	 methyl 5-bromo-2-[(1-methylpyrrolidin-3-yl)oxy]pyridine-3-carboxylate	MS(ES): 315 (M) and 317 (M+2) for $C_{12}H_{15}BrN_2O_3$. 400 MHz, DMSO-d_6: δ 1.18 (t, J = 7.12 Hz, 1H), 1.99 (s, 3H), 2.21-2.37 (m, 2H), 2.57-2.68 (m, 2H), 2.79 (dd, J = 6.24, 10.66 Hz, 1H), 3.82 (s, 3H), 5.33-5.38 (m, 1H), 8.49 (s, 1H), 8.49 (s, 1H).	**Intermediate 295** 5-bromo-2-[(1-methylpyrrolidin-3-yl)oxy] pyridine-3-carboxylic acid

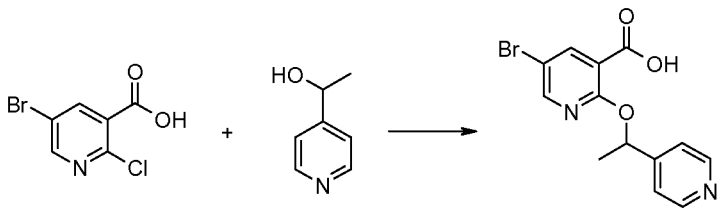
Intermediate 297: {5-(methoxycarbonyl)-6-[(1-methylpyrrolidin-3-yl)oxy]pyridin-3-yl}boronic acid



A suspension of methyl 5-bromo-2-[(1-methylpyrrolidin-3-yl)oxy]pyridine-3-carboxylate (**Intermediate 296**, 1.5 mmol, 0.5 g), bis(pinacolato)diboron (3.1 mmol, 0.804 g), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.3 mmol, 0.219 g) and potassium acetate (4.6 mmol, 0.444 g) was taken in dioxane (5 mL) and it was degassed for 10 min. Then the reaction mixture was heated to 100 °C for 1 h. The reaction mixture was diluted with EtOAc, filtered through a celite bed, washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4 and concentrated in *vacuo* to obtain the title compound as a crude mass (0.7 g) which was taken to the next step without further purification. HPLC-MS analysis indicates the presence of both the boronic acid and boronate pinacol ester.

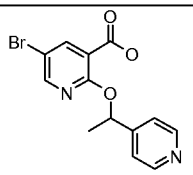
Compound	Structure	Mass spectrum and ^1H NMR	SM
Intermediate 297	 {5-(methoxycarbonyl)-6-[(1-methylpyrrolidin-3-yl)oxy]pyridin-3-yl}boronic acid	Taken to the next step as a mixture based on LCMS without further purification MS(ES): 281 (M+1) for $C_{12}H_{17}BN_2O_5$ (40 % as Boronic acid) and 363 (M+1) for $C_{18}H_{27}BN_2O_5$ (20 % as Boronic ester).	**Intermediate 296** methyl 5-bromo-2-[(1-methyl pyrrolidin-3-yl)oxy] pyridine-3-carboxylate

Intermediate 298: 5-bromo-2-[1-(pyridin-4-yl)ethoxy]pyridine-3-carboxylic acid

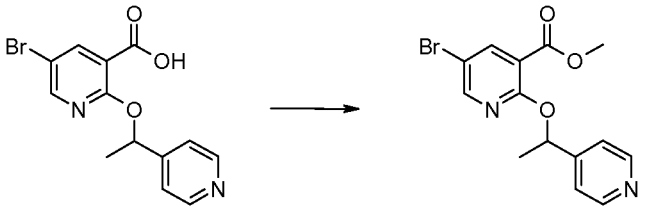


To 5-bromo-2-chloropyridine-3-carboxylic acid (4.2 mmol, 1 g) and 1-(pyridin-4-yl)ethanol (16.9 mmol, 2.08 g) taken in *tert*-butanol (20 mL), was added sodium *tert*-butoxide (16.9 mmol,1.63 g) and the mixture heated to 85 °C for 1 h. The solvent was removed *in*

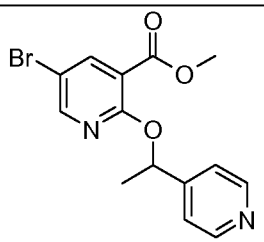
vacuo and the reaction mixture was diluted with water. The aqueous layer was washed with EtOAc, then carefully acidified with 1 N HCl (pH=5). Water was distilled off and the residue taken in a mixture of MeOH and EtOAc (1:1) was passed through was a celite bed. The filtrate was concentrated *in vacuo* and the resultant crude product (2.2 g) was used in the next step without further purification.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 298	 5-bromo-2-[1-(pyridin-4-yl)ethoxy]pyridine-3-carboxylic acid	MS(ES): 323 (M) and 325 (M+2) for $C_{13}H_{11}BrN_2O_3$. The compound was taken to the next step on the basis of LCMS.	1-(pyridin-4-yl)ethanol

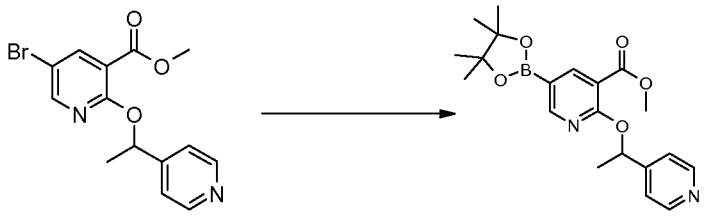
Intermediate 299: methyl 5-bromo-2-[1-(pyridin-4-yl)ethoxy]pyridine-3-carboxylate



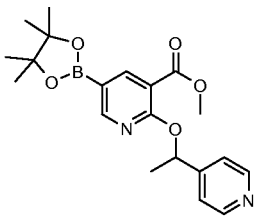
A solution of 5-bromo-2-[1-(pyridin-4-yl)ethoxy]pyridine-3-carboxylic acid (**Intermediate 298**, 6.81 mmol, 2.2 g) taken in MeOH (20 mL) was cooled to 0 °C. Thionyl chloride (0.99 mL, 13.62 mmol, 2 eq) was added slowly to the reaction mixture. After the addition was complete, the reaction mixture was refluxed for 2 h. The solvent was removed *in vacuo* and the crude mixture was taken in EtOAc (30 mL), washed with aq. $NaHCO_3$ solution, water, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using 20 % ethyl acetate/ hexane as the eluent to yield 1 g of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 299	 methyl 5-bromo-2-[1-(pyridin-4-yl)ethoxy] pyridine-3-carboxylate	MS(ES): 337 (M) and 339 (M+2) for $C_{14}H_{13}BrN_2O_3$ 400 MHz, DMSO-d_6: δ 1.56 (d, J = 6.52 Hz, 3H), 3.88 (s, 3H), 6.23 (q, J = 6.52 Hz, 1H), 7.45 (d, J = 6.00 Hz, 2H), 8.30 (d, J = 2.56 Hz, 1H), 8.44 (d, J = 2.56 Hz, 1H), 8.54 (dd, J = 1.52, 4.52 Hz, 2H).	**Intermediate 298** 5-bromo-2-[1-(pyridin-4-yl)ethoxy] pyridine-3-carboxylic acid

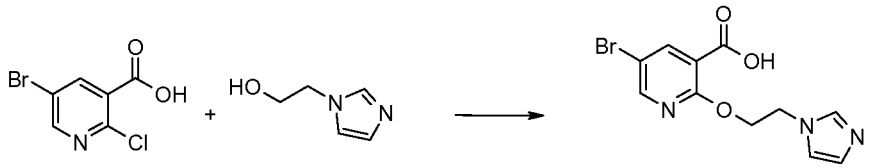
Intermediate 300: methyl 2-[1-(pyridin-4-yl)ethoxy]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate



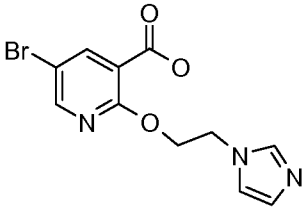
A suspension of methyl 5-bromo-2-[1-(pyridin-4-yl)ethoxy]pyridine-3-carboxylate (**Intermediate 299**, 1.3 mmol, 0.440 g), bis(pinacolato)diboron (2.61 mmol, 0.663 g), [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with CH_2Cl_2 (0.261 mmol, 0.213 g) and potassium acetate (3.91 mmol, 0.384 g) was taken in dioxane (10 mL) and it was degassed for 10 min. Then the reaction mixture was heated to 100 °C for 90 min. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, filtered through a celite bed and concentrated *in vacuo* to yield the product as a crude mass (0.5 g) which was taken to the next step without further purification. LCMS analysis indicated the presence of a mixture of Boronic acid (50 %) and boronate (30 %).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 300	 methyl 2-[1-(pyridin-4-yl)ethoxy]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate	Taken to the next step as a mixture based on LCMS without further purification MS(ES): 303 (M+1) for $C_{14}H_{15}BN_2O_5$ (50 % as Boronic acid) and 385 (M+1) for $C_{20}H_{25}BN_2O_5$ (30 % as Boronic ester).	**Intermediate 299** methyl 5-bromo-2-[1-(pyridin-4-yl)ethoxy]pyridine-3-carboxylate

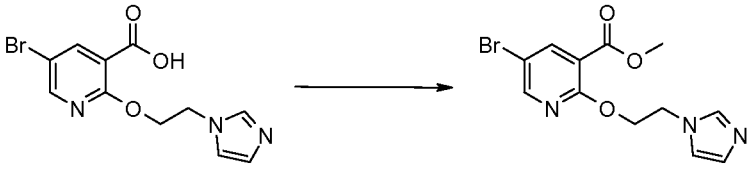
Intermediate 301: 5-bromo-2-[2-(1*H*-imidazol-1-yl)ethoxy]pyridine-3-carboxylic acid



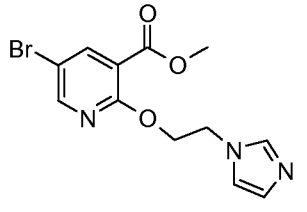
To 5-bromo-2-chloropyridine-3-carboxylic acid (4.2 mmol, 1 g) and 2-(1*H*-imidazol-1-yl)ethanol (12.6 mmol, 1.42 g) taken in *tert*-butanol (25 mL) was added sodium *tert*-butoxide (12.7 mmol, 1.231 g) and the reaction mixture heated to 90 °C for 2 h. The solvent was removed *in vacuo* and the reaction mixture was diluted with water. The aqueous layer was washed with EtOAc, then carefully acidified with 1 N HCl (pH=5). Water was distilled off and the residue taken in a mixture of MeOH and EtOAc (1:1) was passed through was a celite bed. The filtrate was concentrated *in vacuo* and the resultant crude product was taken to the next step without further purification (1.3 g).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 301	 5-bromo-2-[2-(1*H*-imidazol-1-yl)ethoxy]pyridine-3-carboxylic acid	MS(ES): 312 (M) and 314 (M+2) for $C_{11}H_{10}BrN_3O_3$. 400 MHz, DMSO-d_6: δ 4.32 (t, J = 4.52 Hz, 2H), 4.43 (t, J = 4.96 Hz, 2H), 6.88 (s, 1H), 7.15 (s, 1H), 7.60 (s, 1H), 7.89 (d, J = 2.56 Hz, 1H), 8.12 (d, J = 2.52 Hz, 1H), 10.42 (s, 1H).	2-(1*H*-imidazol-1-yl)ethanol

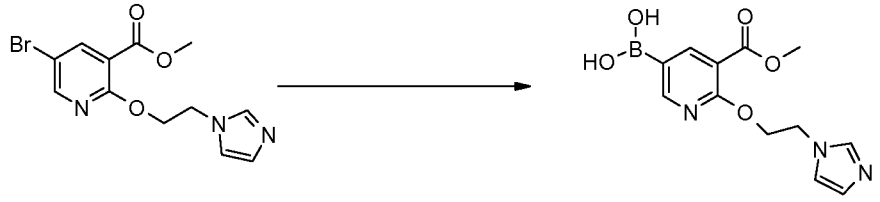
Intermediate 302: methyl 5-bromo-2-[2-(1*H*-imidazol-1-yl)ethoxy]pyridine-3-carboxylate



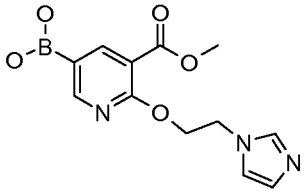
To a suspension of 5-bromo-2-[2-(1*H*-imidazol-1-yl)ethoxy]pyridine-3-carboxylic acid (**Intermediate 301**, 4.16 mmol, 1.3 g) in MeOH (50 mL) at 0 °C, was slowly added thionylchloride (6.4 mmol, 0.74 g). After the addition was complete, the reaction mixture was refluxed at 85 °C for 2 h. The solvent was removed *in vacuo* and the crude mixture taken in EtOAc (30 mL), was washed with aq. $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated to obtain 1.3 g of the title compound which was taken as such to the next step.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 302	 methyl 5-bromo-2-[2-(1*H*-imidazol-1-yl)ethoxy]pyridine-3-carboxylate	MS(ES): 326 (M) and 328 (M+2)for $C_{12}H_{12}BrN_3O_3$. 400 MHz, DMSO-d_6: δ 3.84 (s, 3H), 4.38 (t, J = 4.60 Hz, 2H), 4.54 (t, J = 5.16 Hz, 2H), 6.88 (s, 1H), 7.28 (s, 1H), 7.99 (s, 1H), 8.29 (t, J = 2.56 Hz, 1H), 8.50 (d, J = 2.56 Hz, 1H).	**Intermediate 301** 5-bromo-2-[2-(1*H*-imidazol-1-yl)ethoxy]pyridine-3-carboxylic acid

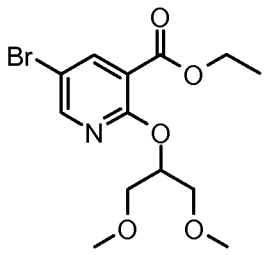
Intermediate 303: {6-[2-(1*H*-imidazol-1-yl)ethoxy]-5-(methoxycarbonyl)pyridin-3-yl}boronic acid



A suspension of **Intermediate 302** (1.53 mmol, 0.5 g), bis(pinacolato)diboron (3.06 mmol, 0.778 g), [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (0.31 mmol, 0.224 g) and potassium acetate (4.6 mmol, 0.452 g) was taken in dioxane (50 mL) and it was degassed for 10 min. Then the reaction mixture was heated to 100 °C for 1 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, filtered through a celite bed and concentrated in *vacuo* to obtain 0.7 g of the crude mass which was taken to the next step without further purification. LCMS analysis indicated the presence of a mixture of boronic acid (42 %) and boronate (17 %).

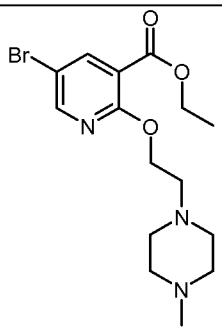
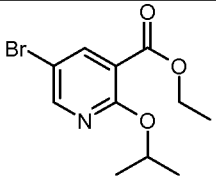
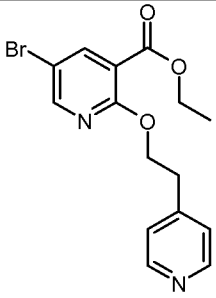
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 303  {6-[2-(1*H*-imidazol-1-yl)ethoxy]-5-(methoxycarbonyl)pyridin-3-yl}boronic acid		Taken to the next step as a mixture based on LCMS without further purification MS(ES): 292 (M+1) for $C_{12}H_{14}BN_3O_3$ (42 % as boronic acid) and 374 (M+1) for $C_{18}H_{24}BN_3O_5$ (17 % as boronic ester) .	**Intermediate 302** methyl 5-bromo-2-[2-(1*H*-imidazol-1-yl)ethoxy]pyridine-3-carboxylate

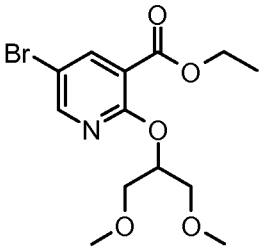
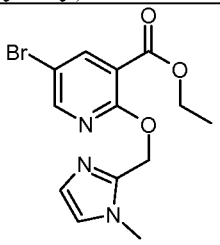
Intermediate 304: ethyl 5-bromo-2-(1,3-dimethoxypropan-2-yloxy)nicotinate



To a suspension of *t*-BuONa (4.36 g, 45 mmol) in THF (100 mL) was added a solution of 1,3-dimethoxypropan-2-ol (4.55 g, 37.8 mmol in 50 mL THF) at 0 °C over a period of 30 min.

The reaction mixture was stirred at 10 °C for 1 h and then cooled to 0 °C. To this reaction mixture was added a solution of ethyl 5-bromo-2-chloronicotinate (10.0 g, 37.8 mmol in 100 mL THF) over a period of 45 min. The reaction mixture was allowed to come to room temperature and stirred for 2 h. The reaction mixture was quenched with cold water (200 mL) and extracted with ethyl acetate (200 mL x 3). The combined organic layer was washed with water (200 mL), brine solution (200 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 100-200 mesh) using 6% ethyl acetate in pet ether as mobile phase to get 6.5 g of the title compound. The compounds in the below table were prepared using this method and the indicated starting material.

Compound	Structure	Mass spectrum	SM
Intermediate 305	 ethyl 5-bromo-2-(2-(4-methylpiperazin-1-yl)ethoxy)nicotinate	MS(ES): 372 (M+1) for $C_{15}H_{22}BrN_3O_3$	2-(4-methylpiperazin-1-yl)ethanol
Intermediate 306	 ethyl 5-bromo-2-isopropoxynicotinate	MS(ES): 288 (M+1) for $C_{11}H_{14}BrNO_3$	iospropanol
Intermediate 307	 ethyl 5-bromo-2-(2-(pyridin-4-yl)ethoxy)nicotinate	MS(ES): 351 (M+1) for $C_{15}H_{15}BrN_2O_3$	2-(pyridin-4-yl)ethanol

Compound	Structure	Mass spectrum	SM
Intermediate 308	 ethyl 5-bromo-2-(1,3-dimethoxypropan-2-yloxy)nicotinate	MS(ES): 349 (M+1) for $C_{13}H_{18}BrNO_5$	1,3-dimethoxypropan-2-ol
Intermediate 309	 ethyl 5-bromo-2-((1-methyl-1H-imidazol-2-yl)methoxy)nicotinate	MS(ES): 340 (M+1) for $C_{13}H_{14}BrN_3O_3$	(1-methyl-1H-imidazol-2-yl)methanol

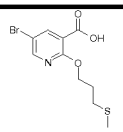
Intermediate 310: 2-(2-acetamidoethoxy)-5-bromonicotinic acid

5-Bromo-2-chloronicotinic acid (1.25 g, 5.27 mmol) was suspended in tert-butanol (35.4 ml) and *N*-(2-hydroxyethyl)acetamide (1.95 ml, 21.08 mmol) was added. Potassium tert-butoxide (2.37 g, 21.08 mmol) was added and the reaction mixture was heated at 90 °C for 1 hour. Tert-butanol was removed *in vacuo* and the resulting material was diluted in ethyl acetate and neutralized with 1N HCl (2 mL). The organic layers were washed with 5 mL of 1N HCl, water, then brine. Combined organic layers were dried over magnesium sulfate, filtered, and concentrated to dryness, then dried under high vacuum to obtain the title compound as an off-white solid (1.44 g).

MS(ES): 304.9 (M+H) for $C_{10}H_{11}BrN_2O_4$

1H NMR (300 MHz, DMSO-d6) δ ppm 1.80 (s, 3 H) 3.40 (q, J=5.97 Hz, 2 H) 4.34 (t, J=5.93 Hz, 2 H) 8.22 (d, J=2.64 Hz, 1 H) 8.46 (d, J=2.64 Hz, 1 H) 13.24 (br. s., 1 H)

The compound in the below table was prepared using the general method described above for **Intermediate 310** and the starting material (SM) indicated.

Ex	Compound	Data	SM
Intermediate 311	 5-bromo-2-(3-(methylthio)propoxy)nicotinic acid	MS(ES): 307.9 (M+H) for $C_{11}H_{14}BrNO_3S$	3-(methylthio) propan-1-ol

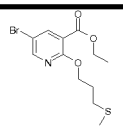
Intermediate 312: ethyl 2-(2-acetamidoethoxy)-5-bromonicotinate

2-(2-acetamidoethoxy)-5-bromonicotinic acid, **Intermediate 310** (1.44 g, 4.74 mmol) was suspended in ethanol (15.5 ml), and concentrated sulfuric acid (0.38 ml, 7.12 mmol) was added. The reaction mixture was heated at 60 °C for 3 h then stirred at rt overnight. The reaction mixture was concentrated, diluted with ethyl acetate, washed with water, brine, and dried over $MgSO_4$. The crude material was purified by flash chromatography (4g, silica column, 0-8% methanol in dichlormethane over 25 min). Fractions were combined to give the title compound as a white solid (1.47 g).

MS(ES): 333.0 (M+H) for $C_{12}H_{15}BrN_2O_4$

1H NMR (300 MHz, DMSO-*d6*) δ ppm 1.25 - 1.33 (m, 3 H) 1.80 (s, 3 H) 3.39 (q, 2 H) 4.24 - 4.31 (m, 2 H) 4.33 (t, *J*=5.37 Hz, 2 H) 7.96 (br. s., 1 H) 8.25 (d, *J*=2.64 Hz, 1 H) 8.49 (d, *J*=2.45 Hz, 1 H)

The compound in the below table was prepared using the general method described above for **Intermediate 312** and the starting material (SM) indicated.

Ex	Compound	Data	SM
Intermediate 313	 ethyl 5-bromo-2-(3-(methylthio)propoxy)nicotinate	MS(ES): 335.9 (M+H) for $C_{12}H_{16}BrNO_3S$	5-bromo-2-(3-(methylthio)propoxy)nicotinic acid **Intermediate 311**

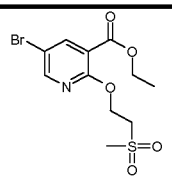
Intermediate 314 ethyl 5-bromo-2-(3-(methylsulfonyl)propoxy)nicotinate

Ethyl 5-bromo-2-(3-(methylthio)propoxy)nicotinate (**Intermediate 313**, 0.4504 g, 1.35 mmol) and mCPBA (0.997 g, 4.04 mmol) were suspended in dichloromethane (5.37 ml) and

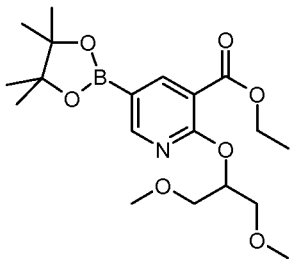
stirred at rt for 3h. Then added 3 mL of dichloromethane and 0.17 g of mCPBA were added and the reaction mixture was stirred overnight. Additional 0.46 g of mCPBA were added and the mixture was stirred at rt 5 hours. The reaction mixture was concentrated *in vacuo*, dissolved in DCM, and filtered. The filtrate was purified by flash chromatography (12 g silica column, 0-10% methanol in dichloromethane over 30 min). Fractions were combined and dried *in vacuo* to obtain the title compound as a white solid (0.45 g). MS(ES): 368.0 (M+H) for $C_{12}H_{16}BrNO_5S$

^{1}H-NMR (300 MHz, DMSO-d6): δ ppm 1.30 (t, *J*=7.16 Hz, 3 H) 2.08 - 2.22 (m, 2 H) 3.00 (s, 3 H) 3.23 - 3.30 (m, 2 H) 4.29 (q, *J*=7.16 Hz, 2 H) 4.42 (t, *J*=6.22 Hz, 2 H) 8.27 (d, *J*=2.45 Hz, 1 H) 8.50 (d, *J*=2.45 Hz, 1 H).

The compound in the table below was prepared using the general sequence described above for the preparation of **Intermediates 313** and **314** and the starting material (SM) indicated.

Ex	Compound	Data	SM
Intermediate 314-B	 ethyl 5-bromo-2-(2-(methylsulfonyl)ethoxy)nicotinate	MS(ES): 352 (M+H) for $C_{11}H_{14}BrNO_5S$	5-Bromo-2-chloronicotinic acid and 2-(methylthio)ethanol (followed by thiol oxidation as for **Intermediate 314)**

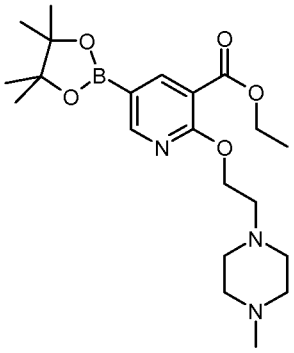
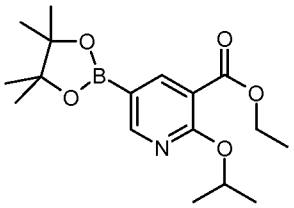
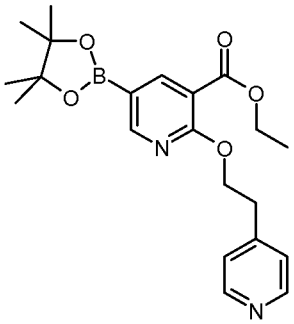
<u>Intermediate 315: ethyl 2-(1,3-dimethoxypropan-2-yloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate</u>

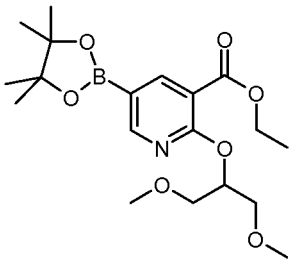
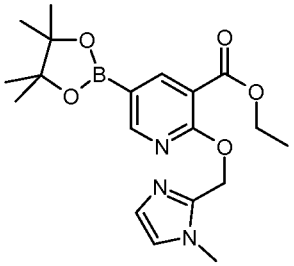
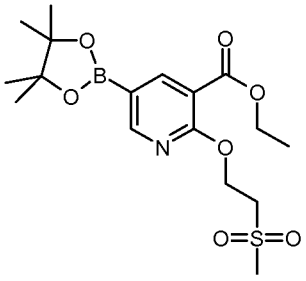


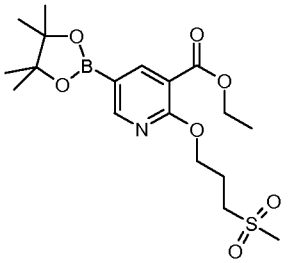
To an argon purged solution of ethyl 5-bromo-2-(1,3-dimethoxypropan-2-yloxy)nicotinate (**Intermediate 308**, 4.5 g, 12.9 mmol) in dioxane (135 mL, 30 vol.) was added bis(pinacolato)diboron (3.93 g, 15.5 mmol) at room temperature. The reaction mixture was degassed for 15 min. (argon) and was added $Pd(dppf)Cl_2$ (1.89 g, 2.5 mmol) followed by

potassium acetate (3.8 g, 38 mmol). The reaction mixture was heated at 90 °C for 2 h. The solvent was evaporated under reduced pressure and the residue was diluted with 30% ethyl acetate in pet-ether (200 mL) and passed through neutral alumina bed. The filtrate was evaporated under reduced pressure to get the crude title compound.

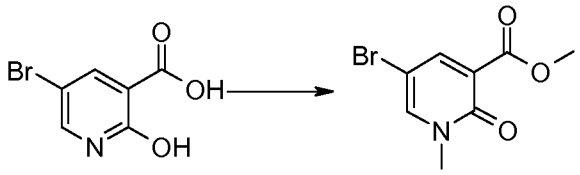
The compounds in the table below were prepared using this method and the indicated starting material.

Compound	Structure	Mass spectrum	SM
Intermediate 316	 ethyl 2-(2-(4-methylpiperazin-1-yl)ethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate	MS(ES): 420 (M+1) for $C_{21}H_{34}BN_3O_5$	**Intermediate 305** ethyl 5-bromo-2-(2-(4-methylpiperazin-1-yl)ethoxy)nicotinate
Intermediate 317	 ethyl 2-isopropoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate	MS(ES): 336 (M+1) for $C_{17}H_{26}BNO_5$	**Intermediate 306** ethyl 5-bromo-2-isopropoxynicotinate
Intermediate 318	 ethyl 2-(2-(pyridin-4-yl)ethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate	MS(ES): 399 (M+1) for $C_{21}H_{27}BN_2O_5$	**Intermediate 307** ethyl 5-bromo-2-(2-(pyridin-4-yl)ethoxy)nicotinate

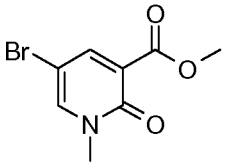
Compound	Structure	Mass spectrum	SM
Intermediate 319	 ethyl 2-(1,3-dimethoxypropan-2-yloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate	MS(ES): 396 (M+1) for $C_{19}H_{30}BNO_7$	**Intermediate 308** ethyl 5-bromo-2-(1,3-dimethoxypropan-2-yloxy)nicotinate
Intermediate 320	 ethyl 2-((1-methyl-1H-imidazol-2-yl)methoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate	MS(ES): 388 (M+1) for $C_{19}H_{26}BN_3O_5$	**Intermediate 309** ethyl 5-bromo-2-((1-methyl-1H-imidazol-2-yl)methoxy)nicotinate
Intermediate 321	 ethyl 2-(2-(methylsulfonyl)ethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate	MS(ES): 400 (M+H) for $C_{17}H_{26}BNO_7S$	**Intermediate 314** ethyl 5-bromo-2-(2-(methylsulfonyl)ethoxy)nicotinate

Compound	Structure	Mass spectrum	SM
Intermediate 321-B	 ethyl 2-(3-(methylsulfonyl)propoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate	MS(ES): 414.0 (M+H) for $C_{18}H_{28}BNO_7S$ 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.27 - 1.35 (m, 15 H) 2.10 - 2.23 (m, 2 H) 3.00 (s, 3 H) 3.34 (br. s., 2 H) 4.29 (q, *J*=7.03 Hz, 2 H) 4.48 (t, *J*=6.12 Hz, 2 H) 8.30 (d, *J*=1.88 Hz, 1 H) 8.54 (d, *J*=1.88 Hz, 1 H)	**Intermediate 314** ethyl 5-bromo-2-(2-(methylsulfonyl)ethoxy)nicotinate

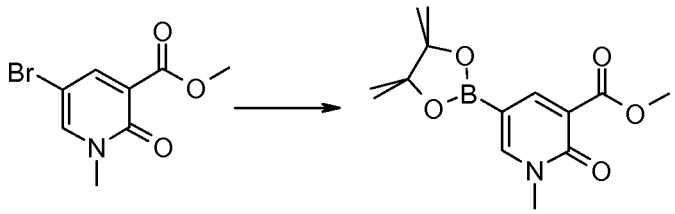
Intermediate 322 : Methyl 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate



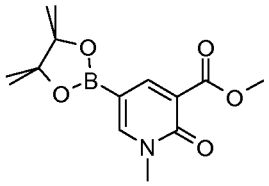
To a suspension of cesium carbonate (18.2 mmol, 5.9 g) in dry methanol (20 mL), 5-bromo-2-hydroxypyridine-3-carboxylic acid (9.2 mmol, 2 g) and iodomethane (27.3 mmol, 3.87 g) were added and heated to 80 °C for 3 h in a sealed tube. The mixture was diluted with methanol and filtered through a celite bed. The filtrate was concentrated and purified by silica gel (60-120 mesh) (product eluted with 2% Methanol in Chloroform) to yield 1.6 g of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 322	 methyl 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 246 (M) and 248 (M+2) for $C_8H_8BrNO_3$. 300 MHz, $CDCl_3$: δ 3.59 (s, 3H), 3.92 (s, 3H), 7.67 (d, *J* = 2.85 Hz, 1H), 8.19 (d, *J* = 2.82 Hz, 1H).	5-bromo-2-hydroxypyridine-3-carboxylic acid

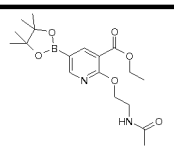
Intermediate 323: methyl 1-methyl-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate



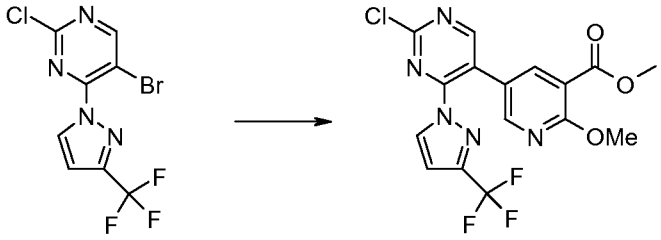
Methyl 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (**Intermediate 322,** 2 mmol, 0.5 g), bis(pinacolato)diboron (2.42 mmol, 0.619 g), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.3 mmol, 0.244 g) and potassium acetate (6 mmol, 0.59 g) were suspended in dry dioxane (10 mL) and degassed with nitrogen for 10 min. The reaction was then heated to 100 °C for 1 h. The reaction mixture was diluted with DCM and filtered through a diatomaceous earth bed and concentrated. Then the crude mass was taken to the next step without purification. HPLC-MS analysis indicated the presence of a mixture of Boronic acid (23 %) and boronate (42 %).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 323	 methyl 1-methyl-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate	Taken to the next step as a mixture based on LCMS without further purification MS(ES): 212 (M+1) for $C_8H_{10}BNO_5$ (23 % as Boronic acid) and 294 (M+1) for $C_{14}H_{20}BNO_5$ (42 % as Boronic ester).	**Intermediate 322** methyl 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate

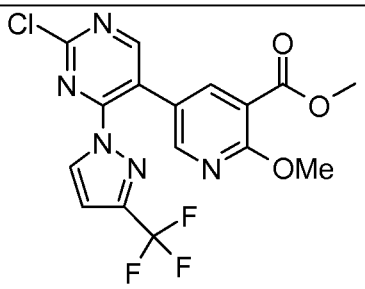
The compound in the below table was prepared using the general method described above for **Intermediate 323** and the starting material (SM) indicated.

Ex	Compound	Data	SM
Intermediate 324	 ethyl 2-(2-acetamidoethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate	MS(ES): 379.2 (M+H) for $C_{18}H_{27}BN_2O_6$ 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.26 - 1.34 (m, 15 H) 1.80 (s, 3 H) 3.37 - 3.45 (m, 2 H) 4.28 (q, *J*=7.16 Hz, 2 H) 4.38 (t, *J*=6.03 Hz, 2 H) 7.93 (s, 1 H) 8.27 (d, *J*=1.88 Hz, 1 H) 8.52 (d, *J*=1.88 Hz, 1 H)	ethyl 2-(2-acetamidoethoxy)-5-bromonicotinate **Intermediate 312**

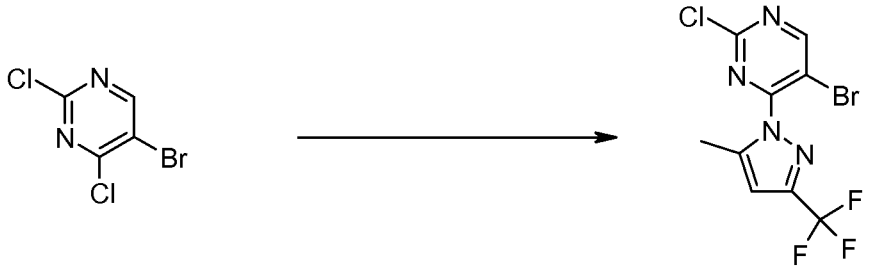
Intermediate 325: methyl 5-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate



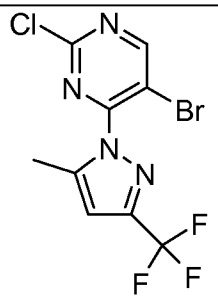
A solution of 5-bromo-2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine (**Intermediate 227**, 2.3 mmol, 750 mg), methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (2.3 mmol, 680 mg), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.46 mmol, 340 mg) and sodium carbonate (2.3 mmol, 250 mg) in acetonitrile (10 mL)/water (10 mL) was degassed and heated to 90 °C for 20 min under nitrogen. The reaction mixture was concentrated *in vacuo*. The residue obtained was taken in ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using 15% ethyl acetate/hexanes to yield 300 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 325	 methyl 5-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	Taken to the next step based on UPLC without further purification. MS(ES): 414 (M+1) for $C_{16}H_{11}ClF_3N_5O_3$. (88 % pure by UPLC).	**Intermediate 227** 5-bromo-2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine

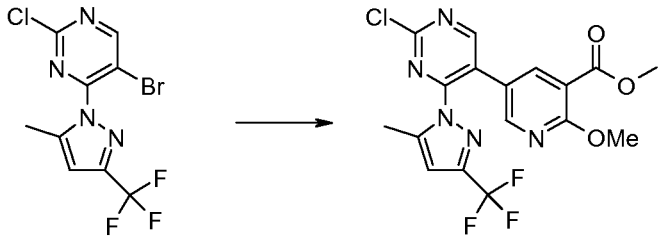
Intermediate 326: 5-bromo-2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine



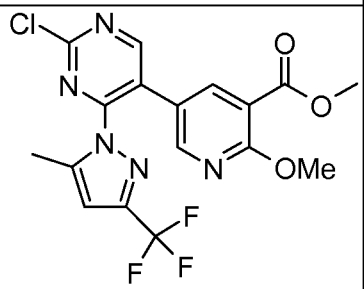
To a suspension of 5-bromo-2,4-dichloropyrimidine (44 mmol, 10 g) in acetonitrile (100 mL), was added K_2CO_3 (44 mmol, 6.1 g) and the reaction mixture was cooled to -5 to -10 °C. 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole (44 mmol, 6.6 g) was dissolved in 100 mL of acetonitrile and added dropwise. After the addition, the reaction mixture was slowly warmed to RT and stirred overnight. The reaction mixture was filtered through a celite bed and acetonitrile was removed *in vacuo*. The crude mass was purified by silica gel column chromatography (60-120 mesh; product eluted with 1% EtOAc/hexanes) to yield 5 g of the product.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 326	 5-bromo-2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine	MS(ES): 341 (M) and 343 (M+2) for $C_9H_5BrClF_3N_4$. 300 MHz, $CDCl_3$: δ 2.52 (s, 3H), 6.53 (s, 1H), 8.94 (s, 1H).	5-bromo-2,4-dichloropyrimidine and 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole

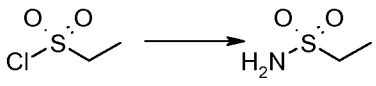
Intermediate 327: methyl 5-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate



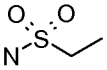
A solution of 5-bromo-2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine (**Intermediate 326**, 2.05 mmol, 700 mg), methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (2.46 mmol, 725 mg), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.4 mmol, 300 mg) and sodium carbonate (2.05 mmol, 210 mg) in acetonitrile (25 mL)/water (5 mL) was degassed and heated to 90 °C for 20 min under nitrogen. The reaction mixture was concentrated *in vacuo*. The residue obtained was taken in ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using 15-20% ethyl acetate/hexanes to yield 280 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 327	 methyl 5-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	Taken to the next step based on UPLC without further purification. MS(ES): 428 (M+1) for $C_{17}H_{13}ClF_3N_5O_3$. (60 % pure by UPLC)	**Intermediate 326** 5-bromo-2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidine

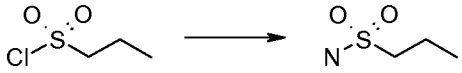
Intermediate 328: Ethanesulfonamide



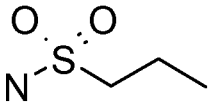
Ammonia gas was passed into a cooled THF solution (25 mL) of ethanesulfonyl chloride (19.4 mmol, 2.5 g) for 1 h. The reaction mixture was sealed and stirred at RT for 2-3 h. After completion of reaction, the reaction mixture was diluted with chloroform (20 mL) and filtered through a bed of diatomaceous earth. The filtrate was concentrated under reduced pressure and dried to get quantitative yield of the title compound as a white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 328	 ethanesulfonamide	400 MHz, DMSO-d_6: δ 1.21 (t, J = 7.40 Hz, 3H), 2.92 (q, J = 7.40 Hz, 2H), 6.70 (s, 2H).	ethanesulfonyl chloride

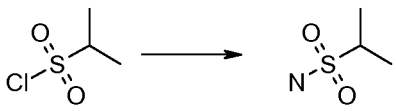
Intermediate 329: propane-1-sulfonamide



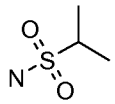
Ammonia gas was passed into a cooled THF solution (25 mL) of propane-1-sulfonyl chloride (17.5 mmol, 2.5 g) for 1 h. The reaction mixture was sealed and stirred at RT for 2-3 h. After completion of reaction, the reaction mixture was diluted with chloroform (20 mL) and filtered through a bed of diatomaceous earth. The filtrate was concentrated under reduced pressure and dried to yield the sulfonamide as a white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 329	 propane-1-sulfonamide	MS(ES): 123 (M) for $C_3H_9NO_2S$. 400 MHz, DMSO-d_6: δ 0.97 (t, J = 7.52 Hz, 3H), 1.67-1.69 (m, 2H), 2.91-2.92 (m, 2H), 6.72 (s, 2H).	propane-1-sulfonyl chloride

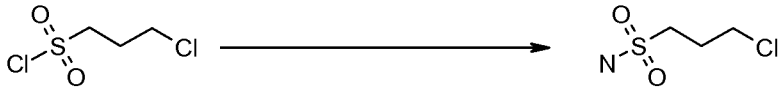
Intermediate 330: propane-2-sulfonamide



Ammonia gas was passed into a cooled THF solution (25 mL) of propane-2-sulfonyl chloride (17.5 mmol, 2.5 g) for 1 h. Then the reaction mixture was sealed and stirred at RT for 2-3 h. After completion of reaction was monitored by TLC, the reaction mixture was diluted with chloroform (20 mL), filtered through a celite bed, concentrated under reduced pressure & dried to get quantitative yield of the sulfonamide as a pale yellow thick mass.

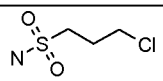
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 330	 propane-2-sulfonamide	MS(ES): 123 (M) for $C_3H_9NO_2S$. 400 MHz, DMSO-d_6: δ 1.23 (d, J = 6.80 Hz, 6H), 2.98-3.00 (m, 1H), 6.66 (s, 2H).	propane-2-sulfonyl chloride

Intermediate 331: 3-chloropropane-1-sulfonamide

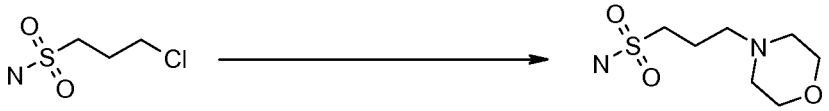


Ammonia gas was passed into a cooled THF solution (25 mL) of 3-chloropropane-1-sulfonyl chloride (14.2 mmol, 2.5 g) for 1 h. Then the reaction mixture was sealed and stirred at RT

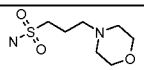
for 2-3 h. After completion of reaction, the reaction mixture was diluted with chloroform (20 mL) and filtered through celite bed, concentrated under reduced pressure and dried to get quantitative yield of the desired sulfonamide as a white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 331	 3-chloropropane-1-sulfonamide	400 MHz, DMSO-d_6: δ 2.09-2.11 (m, 2H), 3.09 (q, J = 5.68 Hz, 2H), 3.76 (t, J = 6.48 Hz, 2H), 6.89 (s, 2H).	3-chloro-propane-1-sulfonyl chloride

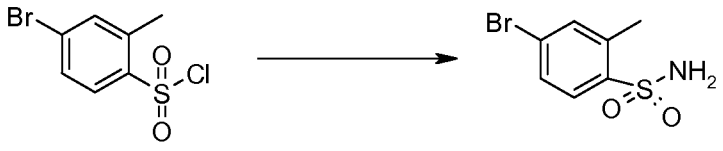
Intermediate 332: 3-(morpholin-4-yl)propane-1-sulfonamide



The solution of 3-chloropropane-1-sulfonamide **Intermediate 331** (1.58 mmol, 0.250 g), Morpholine (1.58 mmol, 0.138 g), Na_2CO_3 (3.16 mmol, 0.335 g) and NaI (0.158 mmol, 24 mg) in dry Dioxane (5 mL) was heated to 75 °C, overnight, in a sealed tube. After completion of reaction, the reaction mixture was diluted with chloroform (20 mL) and filtered through celite bed and the filtrate was concentrated under reduced pressure and dried to get the desired compound as a colorless mass (0.21 g).

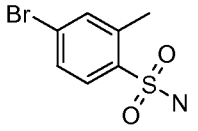
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 332	 3-(morpholin-4-yl)propane-1-sulfonamide	300 MHz, DMSO-d_6: δ 1.77-1.79 (m, 2H), 2.35 (t, J = 6.99 Hz, 5H), 2.95-2.97 (m, 2H), 3.55 (t, J = 5.64 Hz, 5H), 6.75 (s, 2H).	**Intermediate 331** 3-chloro propane-1-sulfonamide

Intermediate 333: 4-bromo-2-methylbenzenesulfonamide

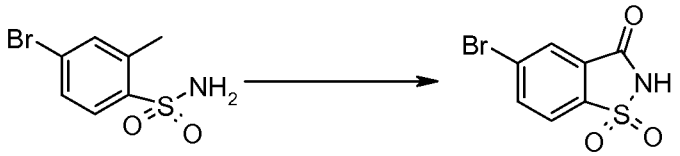


Ammonia gas was passed into a cooled THF solution (25 mL) of 4-bromo-2-methylbenzenesulfonyl chloride (9.27 mmol, 2.5 g) for 1 h. Then the reaction mixture was sealed and stirred overnight at rt. After completion of reaction, as monitored by TLC, the reaction mixture was diluted with chloroform (20 mL) and filtered through celite bed and the

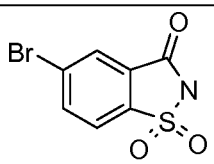
filtrate was concentrated under reduced pressure and dried to get quantitative yield of the desired sulfonamide as a white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 333	 4-bromo-2-methylbenzenesulfonamide	MS(ES): 249 (M-1) for $C_7H_8BrNO_2S$ 400 MHz, DMSO-d_6: δ 2.58 (s, 3H), 7.50 (s, 2H), 7.60 (dd, J = 1.64, 8.40 Hz, 1H), 7.65 (s, 1H), 7.76 (d, J = 8.40 Hz, 1H).	4-bromo-2-methylbenzenesulfonyl chloride

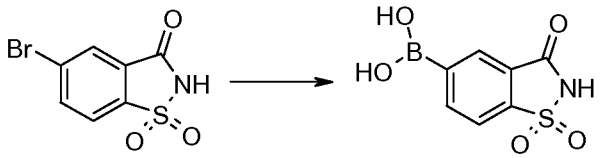
Intermediate 334: 5-bromo-1,2-benzothiazol-3(2*H*)-one 1,1-dioxide



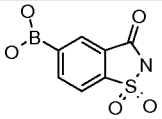
A suspension of 4-bromo-2-methylbenzenesulfonamide (**Intermediate 333**, 9.6 mmol, 2.4 g), periodic acid (76.8 mmol, 17.5 g), Chromium oxide (4.8 mmol, 0.047 g) in dry acetonitrile (25 mL) was heated to reflux for 3 h. Isopropyl alcohol (5 mL) was added slowly and the reaction mixture was heated to reflux for another 10 min. Then the reaction mixture was cooled to rt and it was filtered and washed with acetone (10 mL × 3). The filtrate was concentrated and triturated with 10 mL of 2 N H_2SO_4 and filtered to get 1.5 g of the title compound as an off-white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 334	 5-bromo-1,2-benzothiazol-3(2*H*)-one 1,1-dioxide	MS(ES): 262 (M) and 264 (M+2) for $C_7H_4BrNO_3S$ 400 MHz, DMSO-d_6: δ 8.06 (d, J = 1.52 Hz, 1H), 8.08 (d, J = 1.44 Hz, 1H), 8.11-8.15 (m, 1H).	**Intermediate 333** 4-bromo-2-methylbenzenesulfonamide

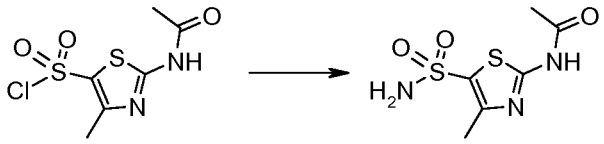
Intermediate 335: (1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzothiazol-5-yl)boronic acid



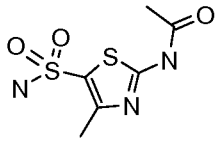
5-bromo-1,2-benzothiazol-3(2*H*)-one 1,1-dioxide (**Intermediate 334**, 0.954 mmol, 0.25 g), bis(pinacolato)diboron (2.862 mmol, 0.726 g), [1,1′-bis(diphenylphosphino) ferrocene]dichloropalladium(II) (0.0954 mmol, 0.077 g) and potassium acetate (2.862 mmol, 0.28 g) were suspended in dry DMSO (5 mL) and degassed with nitrogen for 10 min. The reaction was then subjected to microwave condition at 100 °C for 30 min. The reaction mixture was concentrated under vacuum. The residue obtained was washed with hexane (5 mL), decanted and dried to give the product. Taken to the next step without purification.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 335	 (1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzothiazol-5-yl)boronic acid	Taken to the next step based on LCMS without further purification MS(ES): 226 (M-1) for $C_7H_6BNO_5S$. (78 % pure by LCMS)	**Intermediate 334** 5-bromo-1,2-benzo thiazol-3(2*H*)-one 1,1-dioxide

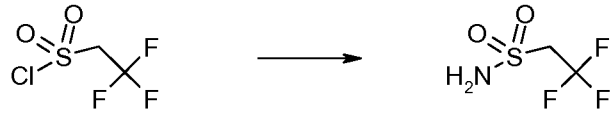
Intermediate 336: *N*-(4-methyl-5-sulfamoyl-1,3-thiazol-2-yl)acetamide



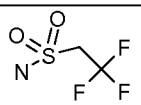
Ammonia gas was passed into a cooled THF solution (2 mL) of 2-(acetylamino)-4-methyl-1,3-thiazole-5-sulfonyl chloride (0.39 mmol, 0.1 g) for 1 h. Then the reaction mixture was sealed and stirred at RT for 2-3 h. After completion of reaction, the reaction mixture was diluted with chloroform (20 mL) and filtered through a celite bed. The filtrate was concentrated under reduced pressure and dried to get quantitative yield of an off-white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 336	 *N*-(4-methyl-5-sulfamoyl-1,3-thiazol-2-yl)acetamide	MS(ES): 236 (M+1) for $C_6H_9N_3O_3S_2$. 300 MHz, DMSO-d_6: δ 2.15 (d, J = 5.07 Hz, 3H), 2.36 (s, 3H), 7.61 (s, 2H), 12.40 (s, 1H).	2-(acetylamino)-4-methyl-1,3-thiazole-5-sulfonyl chloride

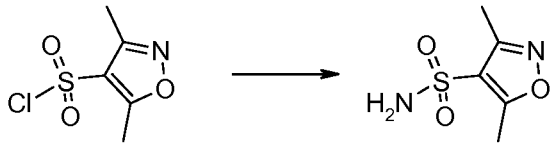
Intermediate 337: 2,2,2-trifluoroethanesulfonamide



Ammonia gas was passed into a cooled THF solution (2 mL) of 2,2,2-trifluoroethanesulfonyl chloride (5.48 mmol, 1 g) for 1 h. Then the reaction mixture was sealed and stirred at RT for 2 h. Completion of reaction was monitored by TLC. The reaction mixture was diluted with dichloromethane (50 mL) and filtered through celite bed and the filtrate was concentrated under reduced pressure and dried to get 800 mg of the title compound as a white solid.

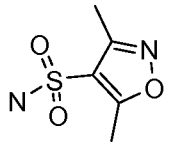
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 337	 2,2,2-trifluoroethanesulfonamide	400 MHz, DMSO-d_6: δ 4.21-4.29 (m, 2H), 7.49 (s, 2H).	2,2,2-trifluoroethanesulfonyl chloride

Intermediate 338: 3,5-dimethyl-1,2-oxazole-4-sulfonamide

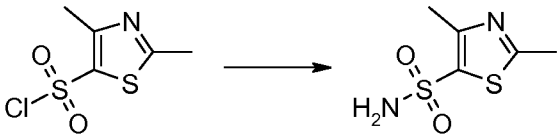


Ammonia gas was passed into a cooled THF solution (2 mL) of 3,5-dimethyl-1,2-oxazole-4-sulfonyl chloride (0.76 mmol, 150 mg) for 1 h. Then the reaction mixture was sealed and

stirred at RT for 2-3 h. The reaction mixture was diluted with chloroform (20 mL) and filtered through celite bed and the filtrate was concentrated under reduced pressure and dried to get 120 mg of the title compound as a white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 338	 3,5-dimethyl-1,2-oxazole-4-sulfonamide	MS(ES): 177 (M+1) for $C_5H_8N_2O_3S$.	3,5-dimethyl-1,2-oxazole-4-sulfonyl chloride

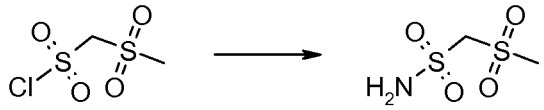
Intermediate 339: 2,4-dimethyl-1,3-thiazole-5-sulfonamide



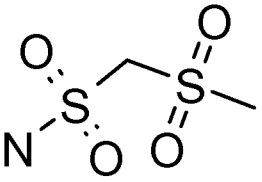
Ammonia gas was passed into a cooled THF solution (25 mL) of 2,4-dimethyl-1,3-thiazole-5-sulfonyl chloride (0.47 mmol, 100 mg) for 1 h. Then the reaction mixture was sealed and stirred at RT for 2 h. The reaction mixture was diluted with chloroform (20 mL) and filtered through celite bed and the filtrate was concentrated under reduced pressure and dried to get 90 mg of the desired sulfonamide as a white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 339	 2,4-dimethyl-1,3-thiazole-5-sulfonamide	MS(ES): 193 (M+2) for $C_5H_8N_2O_2S_2$. (91% pure by UPLC)	2,4-dimethyl-1,3-thiazole-5-sulfonyl chloride

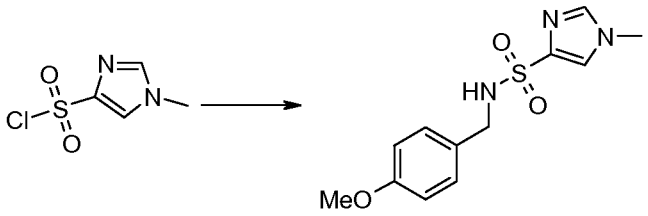
Intermediate 340: 1-(methylsulfonyl)methanesulfonamide



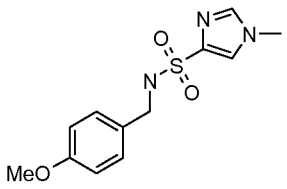
Ammonia gas was passed into a cooled THF solution (2 mL) of (methylsulfonyl)methanesulfonyl chloride (1.1 mmol, 200 mg) for 1 h. Then the reaction mixture was sealed and stirred at RT for 2 h. After completion of reaction, as monitored by TLC, the reaction mixture was diluted with chloroform (20 mL) and filtered through celite bed and the filtrate was concentrated under reduced pressure and dried to get 65 mg of white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 340	 1-(methylsulfonyl)methanesulfonamide	MS(ES): 174 (M+1) for $C_2H_7NO_4S_2$. 300 MHz, DMSO-d_6: δ 3.16 (s, 3H), 4.96 (s, 1H), 7.38 (s, 1H).	(methylsulfonyl)methanesulfonyl chloride

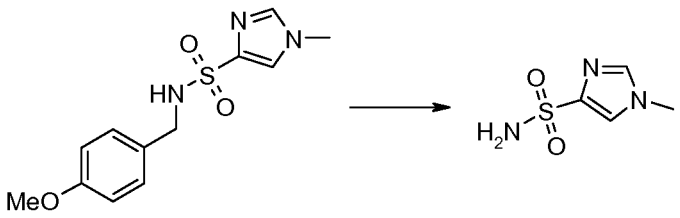
Intermediate 341: *N*-(4-methoxybenzyl)-1-methyl-1*H*-imidazole-4-sulfonamide



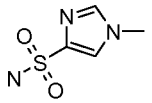
To a solution of 1-methyl-1*H*-imidazole-4-sulfonyl chloride (4.4 mmol, 0.8 g) in dry CH_2Cl_2 (10 mL), was added 4-methoxybenzylamine (3.5 mmol, 0.49 g) and Et_3N (1.33 mmol, 1.34 g) and left to stir overnight at RT. The reaction mixture was diluted with dichloromethane (20 mL) and water. The organic layer was separated, dried over Na_2SO_4 and concentrated. The solid that was obtained was further recrystallised from $CHCl_3$ and petroleum ether to get 500 mg of the desired protected sulfonamide.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 341	 *N*-(4-methoxybenzyl)-1-methyl-1*H*-imidazole-4-sulfonamide	MS(ES): 282 (M+1) for $C_{12}H_{15}N_3O_3S$. 400 MHz, DMSO-d_6: δ 3.67 (s, 3H), 3.71 (s, 3H), 3.94 (d, J = 6.28 Hz, 2H), 6.82-6.85 (m, 2H), 7.16 (d, J = 8.60 Hz, 2H), 7.67 (d, J = 1.20 Hz, 1H), 7.76 (s, 1H), 7.87 (t, J = 6.28 Hz, 1H).	1-methyl-1*H*-imidazole-4-sulfonyl chloride

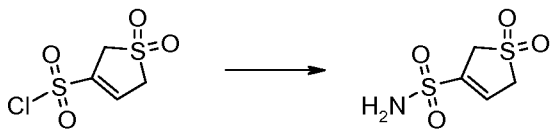
Intermediate 342: 1-methyl-1*H*-imidazole-4-sulfonamide



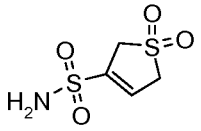
To a cooled solution of *N*-(4-methoxybenzyl)-1-methyl-1*H*-imidazole-4-sulfonamide (**Intermediate 341**, 1.06 mmol, 0.3 g), was added TFA (15 mL) and the reaction mixture was stirred at 0 °C for 1 hour. The mixture was concentrated and methanol was added to the residue and further concentrated to get 150 mg of the desired sulfonamide.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 342	 1-methyl-1*H*-imidazole-4-sulfonamide	MS(ES): 162 (M+1) for $C_4H_7N_3O_2S$. 400 MHz, DMSO-d_6: δ 3.69 (s, 3H), 7.13 (s, 2H), 7.61 (d, J = 0.88 Hz, 1H), 7.74 (s, 1H).	**Intermediate 341** *N*-(4-methoxybenzyl)-1-methyl-1*H*-imidazole-4-sulfonamide

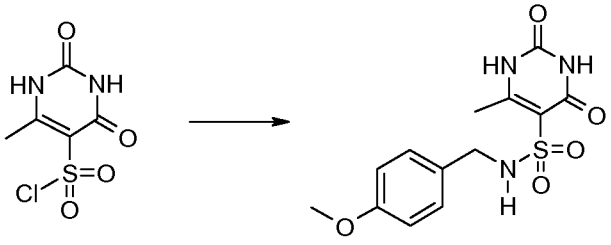
Intermediate 343: 2,5-dihydrothiophene-3-sulfonamide 1,1-dioxide



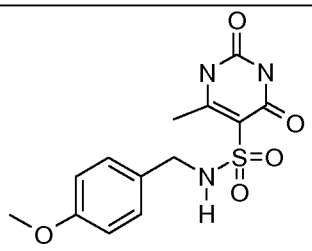
Ammonia gas was passed into a cooled THF solution (25 mL) of 2,5-dihydrothiophene-3-sulfonyl chloride 1,1-dioxide (0.93 mmol, 200 mg) for around 20 min. Then the reaction mixture was sealed and stirred at RT for 2-3 h. The reaction mixture was diluted with ethyl acetate (20 mL) and filtered. The filtrate was concentrated under reduced pressure and dried to get quantitative yield of the desired sulfonamide as a white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 343	 2,5-dihydrothiophene-3-sulfonamide 1,1-dioxide	400 MHz, DMSO-d_6: δ 4.11 (s, 2H), 4.21 (d, J = 1.60 Hz, 2H), 6.74 (s, 1H), 7.44-7.48 (m, 2H).	2,5-dihydrothiophene-3-sulfonyl chloride 1,1-dioxide

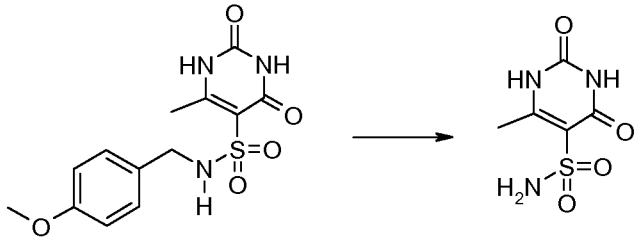
Intermediate 344: *N*-(4-methoxybenzyl)-6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonamide



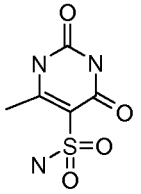
To a solution of 6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonyl chloride (2.23 mmol, 500 mg) in dry CH_2Cl_2 (10 mL), was added 4-methoxybenzylamine (1.78 mmol, 244 mg) and Et_3N (11.6 mmol, 1.13 g) and left to stir overnight at RT. The reaction mixture was diluted with dichloromethane (20 mL) and water. The organic layer was separated and the precipitate formed in aqueous layer was filtered and dried to get 350 mg of the product.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 344	 *N*-(4-methoxybenzyl)-6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonamide	MS(ES): 326 (M+1) for $C_{13}H_{15}N_3O_5S$. 400 MHz, DMSO-d_6: δ 2.31 (s, 3H), 3.70 (s, 3H), 3.99 (d, J = 6.48 Hz, 2H), 6.79 (d, J = 8.64 Hz, 2H), 7.17 (d, J = 8.60 Hz, 2H), 7.23 (t, J = 6.56 Hz, 1H), 11.32 (br s, 2H).	6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonyl chloride

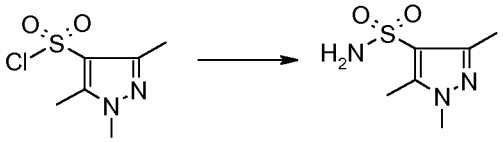
Intermediate 345: 6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonamide



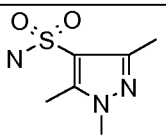
To a cooled solution of *N*-(4-methoxybenzyl)-6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonamide (**Intermediate 344**, 1.07 mmol, 350 mg), was added TFA (10 mL) and the reaction mixture was stirred at rt for 6 h. The mixture was concentrated and methanol was added to the residue and further concentrated to get 200 mg of the desired sulfonamide.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 345	 6-methyl-2,4-dioxo-1,2,3,4-tetrahydro pyrimidine-5-sulfonamide	MS(ES): 206 (M+1) for $C_5H_7N_3O_4S$. 300 MHz, DMSO-d_6: δ 2.40 (s, 3H), 6.81 (d, J = 12.72 Hz, 2H), 11.42 (br s, 1H), 11.60 (br s, 1H).	**Intermediate 344** *N*-(4-methoxy-benzyl)-6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonamide

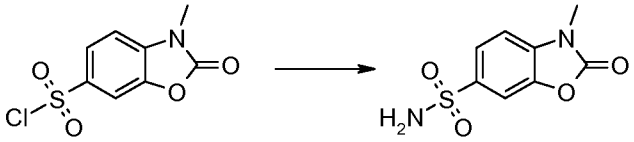
Intermediate 346: 1,3,5-trimethyl-1*H*-pyrazole-4-sulfonamide



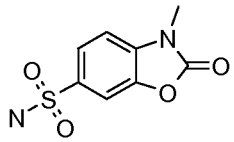
Ammonia gas was passed into a cooled THF solution (25 mL) of 1,3,5-trimethyl-1H pyrazole-4-sulfonyl chloride (0.96 mmol, 0.2 g) for around 1 h. Then the reaction mixture was sealed and stirred at RT for 2-3 h. After completion of reaction, the reaction mixture was diluted with chloroform (15 mL) and filtered through celite bed. The filtrate was concentrated under reduced pressure and dried to get the title compound as a white solid (149 mg).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 346	 1,3,5-trimethyl-1*H*-pyrazole-4-sulfonamide	MS (ES): 190 (M+1) for $C_6H_{11}N_3O_2S$. 400 MHz, DMSO-d_6: δ 2.23 (s, 3H), 2.36 (s, 3H), 3.65 (s, 3H), 7.03 (s, 2H).	1,3,5-trimethyl-1*H*-pyrazole-4-sulfonyl chloride

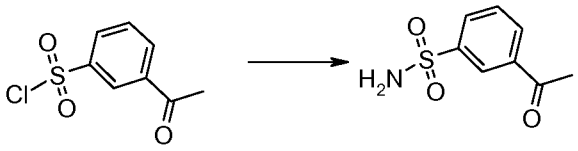
Intermediate 347: 3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-sulfonamide



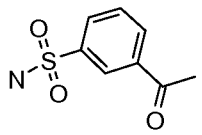
Ammonia gas was passed into a cooled THF solution (25 mL) of 3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-sulfonyl chloride (0.5 mmol, 0.125 g) for 1 h and sealed. Then the reaction mixture was stirred at RT for 2-3 h. The reaction mixture was diluted with chloroform (20 mL) and filtered through celite bed. The filtrate was concentrated under reduced pressure and dried to get quantitative yield of the title compound as an off-white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 347	 3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-sulfonamide	MS(ES): 227 (M-1) for $C_8H_8N_2O_4S$. 400 MHz, DMSO-d_6: δ 3.36 (s, 3H), 7.37 (s, 2H), 7.39-7.42 (m, 1H), 7.70-7.73 (m, 2H).	3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-sulfonyl chloride

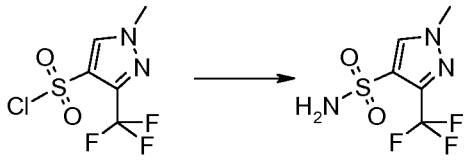
Intermediate 348: 3-acetylbenzenesulfonamide



Ammonia gas was passed into a cooled solution (25 mL) of 3-acetylbenzenesulfonyl chloride (2.2 mmol, 500 mg) in dry 1,4-dioxane(15 mL) for 20 min and sealed. Then the reaction mixture was stirred at RT for 2 h. It was then diluted with ethyl acetate (20 mL) and filtered. The filtrate was concentrated under reduced pressure and dried to get the desired sulfonamide as a white solid in quantitative yield.

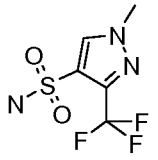
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 348	 3-acetylbenzene-sulfonamide	MS(ES): 200 (M+1) for $C_8H_9NO_3S$.	3-acetylbenzenesulfonyl chloride

Intermediate 349: 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-4-sulfonamide

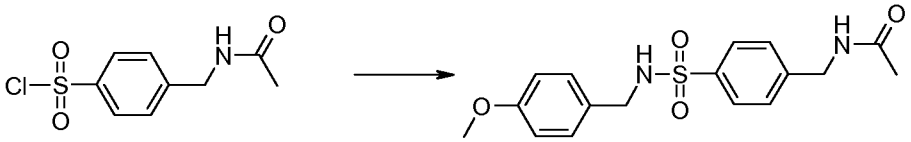


Ammonia gas was passed into a cooled THF solution (25 mL) of 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-4-sulfonyl chloride (0.5 mmol, 0.125 g) for 1 h. Then the

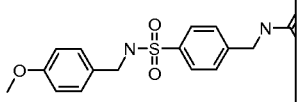
reaction mixture was sealed and stirred at RT for 2-3 h. After completion of reaction, the reaction mixture was diluted with chloroform (20 mL) and filtered through celite bed. The filtrate was concentrated under reduced pressure and dried to get quantitative yield of the title compound as a white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 349	 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-4-sulfonamide	MS(ES): 228 (M-1) for $C_5H_6F_3N_3O_2S$. 400 MHz, DMSO-d_6: δ 3.95 (s, 3H), 7.62 (s, 2H), 8.36 (s, 1H).	1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-4-sulfonyl chloride

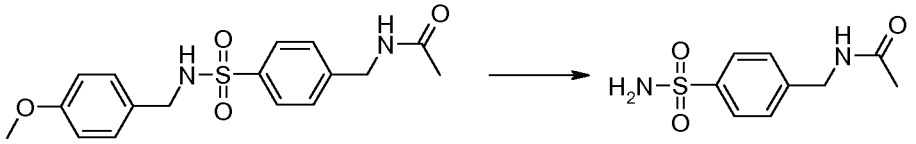
Intermediate 350: *N*-{4-[(4-methoxybenzyl)sulfamoyl] benzyl}acetamide



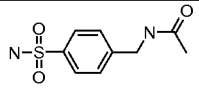
To a cooled solution of 4-methoxybenzylamine (4.24 mmol, 0.581 g) and Et_3N (0.99 mL, 7.07 mmol) in dry dichloromethane, was added 4-[(acetylamino)methyl]benzenesulfonyl chloride (2.83 mmol, 0.7 g) and the reaction mixture was stirred overnight at RT. The reaction mixture was diluted with chloroform (20 mL) and the organic layer was washed with 10 % citric acid solution (50 mL), 10 % sodium bicarbonate solution (50 mL) and brine (25 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure and dried to get 0.2 g of the protected sulfonamide as an off-white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 350	 *N*-{4-[(4-methoxybenzyl)sulfamoyl]benzyl}acetamide	MS(ES): 349 (M+1) for $C_{17}H_{20}N_2O_4S$. 400 MHz, DMSO-d_6: δ 1.91 (s, 3H), 3.72 (s, 3H), 3.88 (d, *J* = 6.08 Hz, 2H), 4.33 (d, *J* = 5.84 Hz, 2H), 6.85 (d, *J* = 8.56 Hz, 2H), 7.14 (d, *J* = 8.52 Hz, 2H), 7.44 (d, *J* = 8.12 Hz, 2H), 7.75 (d, *J* = 8.20 Hz, 2H), 8.02 (t, *J* = 6.12 Hz, 1H), 8.46 (t, *J* = 9.32 Hz, 1H).	4-[(acetylamino)methyl]benzenesulfonyl chloride

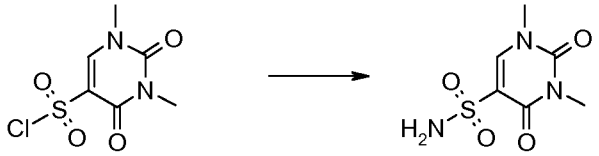
Intermediate 351: *N*-(4-sulfamoylbenzyl)acetamide



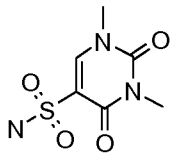
To a cooled solution of *N*-{4-[(4-methoxybenzyl)sulfamoyl]benzyl}acetamide (**PE-66-14-I**, 0.56 mmol, 195 mg), was added TFA (10 mL) and the reaction mixture was stirred overnight at rt. The mixture was concentrated and methanol was added to the residue and further concentrated to get 200 mg of the desired sulfonamide as a pale brown solid which was taken to the next step without further purification.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 351	 *N*-(4-Sulfamoylbenzyl) acetamide	MS(ES): 229 (M+1) for $C_9H_{12}N_2O_3S$. 300 MHz, DMSO-d_6: δ 1.87 (s, 3H), 4.29 (d, *J* = 5.79 Hz, 2H), 7.30 (s, 2H), 7.40 (d, *J* = 7.92 Hz, 2H), 7.75 (d, *J* = 7.53 Hz, 2H).	**Intermediate 350** *N*-{4-[(4-methoxybenzyl)sulfamoyl]benzyl}acetamide

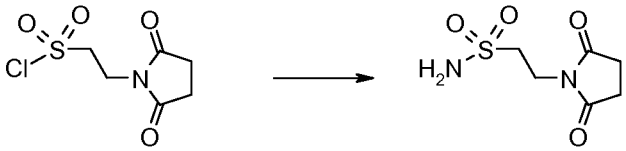
Intermediate 352: 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonamide



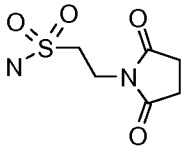
Ammonia gas was passed into a cooled THF solution (25 mL) of 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonyl chloride (0.53 mmol, 0.125 g) for 1 h and sealed. Then the reaction mixture was stirred at RT for 2-3 h. After completion of reaction, the reaction mixture was diluted with chloroform (20 mL) and filtered through celite bed. The filtrate was concentrated under reduced pressure and dried to get quantitative yield of the title compound as a white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 352	 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonamide	MS(ES): 220 (M+1) for $C_6H_9N_3O_4S$. 300 MHz, DMSO-d_6: δ 3.19 (s, 3H), 3.39 (s, 3H), 7.07 (s, 2H), 8.40 (s, 1H).	1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonyl chloride

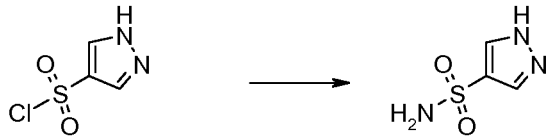
Intermediate 353: 2-(2,5-dioxopyrrolidin-1-yl)ethanesulfonamide



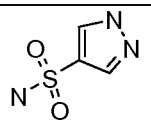
Ammonia gas was passed into a cooled solution (25 mL) of 2-(2,5-dioxopyrrolidin-1-yl)ethanesulfonyl chloride (1.77 mmol, 400 mg) in dry 1,4-dioxane (10 mL) for 20 min and sealed. Then the reaction mixture was stirred at RT for 2 h. It was then diluted with ethyl acetate (20 mL) and filtered. The filtrate was concentrated under reduced pressure and dried to get 150 mg of the desired sulfonamide as a white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 353	 2-(2,5-dioxopyrrolidin-1-yl)ethanesulfonamide	300 MHz, DMSO-d_6: δ 2.57 (d, J = 11.43 Hz, 4H), 3.13-3.18 (m, 2H), 3.69-3.74 (m, 2H), 7.00 (s, 2H).	2-(2,5-dioxopyrrolidin-1-yl)ethanesulfonyl chloride

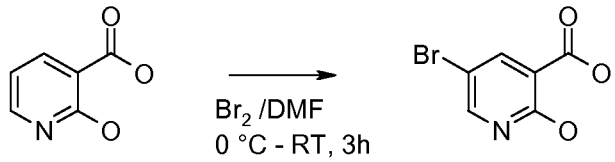
Intermediate 354: 1*H*-pyrazole-4-sulfonamide



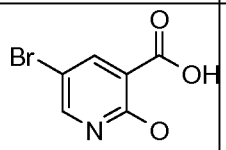
Ammonia gas was passed into a cooled THF solution (25 mL) of 1*H*-pyrazole-4-sulfonyl chloride (0.75 mmol, 0.125 g) for 1 h and sealed. Then the reaction mixture was stirred at RT for 2-3 h. After completion of reaction, the reaction mixture was diluted with chloroform (20 mL) and filtered through celite bed. The filtrate was concentrated under reduced pressure and dried to get quantitative yield of the title compound as a white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 354	 1*H*-pyrazole-4-sulfonamide	MS(ES): 148 (M+1) for $C_3H_5N_3O_2S$.	1*H*-pyrazole-4-sulfonyl chloride

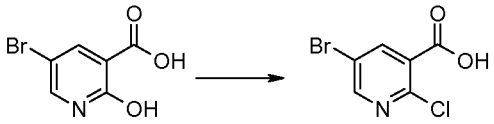
Intermediate 355: 5-Bromo-2-hydroxypyridine-3-carboxylic acid



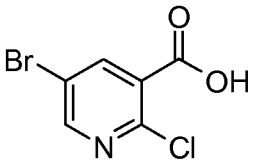
To a solution of 2-hydroxypyridine-3-carboxylic acid (35.94 mmol, 5 g) in dry DMF cooled with an ice-water bath, a solution of bromine (57.51 mmol, 3 mL, 9.19 g in cooled DMF) was added dropwise at 0 °C over 1 h. The reaction mixture was stirred at rt for 3 h and then quenched with ice-water. The resulting yellow solid was filtered, washed with water and dried under vacuum to get 6 g of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 355	 5-Bromo-2-hydroxypyridine-3-carboxylic acid	MS (ES): 218 (M) and 220(M+2) for $C_6H_4BrNO_3$. 400 MHz, DMSO-d_6: δ 8.26 (d, J = 3.56 Hz, 1H), 8.34 (d, J = 3.68 Hz, 1H), 13.70 (s, 2H).	2-Hydroxy pyridine-3-carboxylic acid

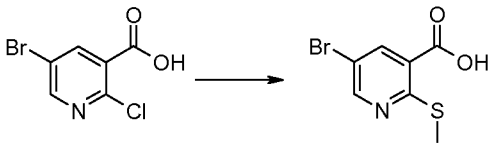
Intermediate 356: 5-bromo-2-chloropyridine-3-carboxylic acid



A solution of 5-bromo-2-hydroxypyridine-3-carboxylic acid (**Intermediate 355**, 26.83 mmol, 5.85 g) in $POCl_3$ (14.63 mL, 2.5 v/w) was heated to reflux for 12 h. It was cooled to RT and $POCl_3$ was removed *in vacuo*. Then ice water was added to the reaction mixture and extracted with EtOAc. The EtOAc layer was concentrated to get a yellow solid. The solid obtained was washed with chilled $CHCl_3$ to yield the title compound (2.86 g).

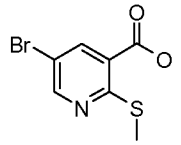
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 356	 5-Bromo-2-chloropyridine-3-carboxylic acid	MS(ES): 237 (M+1) for $C_6H_3BrClNO_2$. 400 MHz, DMSO-d_6: δ 8.44 (d, J = 2.52 Hz, 1H), 8.72 (d, J = 2.48 Hz, 1H), 13.91 (s, 1H).	**Intermediate 355** 5-Bromo-2-hydroxypyridine-3-carboxylic acid

Intermediate 357: 5-bromo-2-(methylsulfanyl)pyridine-3-carboxylic acid

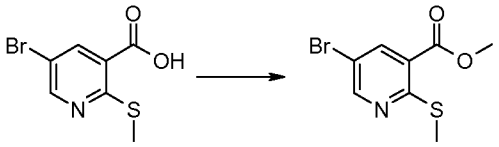


To a solution of 5-bromo-2-chloropyridine-3-carboxylic acid (**Intermediate 356,** 10.57 mmol, 2.5 g) in dioxane was added 21% aqueous solution of NaSMe (8.8 mL, 26.43 mmol, 1.85 g) and the mixture was heated in a sealed tube at 110 °C for 2 h. After completion of the

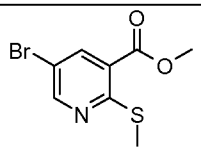
reaction, the crude mass was dissolved in water and acidified with 10% citric acid solution and the solid obtained was filtered and dried to yield the product (2 g).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 357	 5-Bromo-2-(methylsulfanyl)pyridine-3-carboxylic acid	MS(ES): 248 (M) and 250 (M+2) for $C_7H_6BrNO_2S$. 400 MHz, DMSO-d_6: δ 2.41 (s, 3H), 8.29 (d, J = 3.16 Hz, 1H), 8.77 (d, J = 3.16 Hz, 1H), 13.70 (s, 1H).	**Intermediate 356** 5-Bromo-2-chloropyridine-3-carboxylic acid

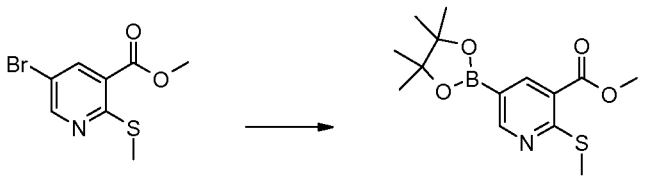
Intermediate 358: Methyl 5-bromo-2-(methylsulfanyl)pyridine-3-carboxylate



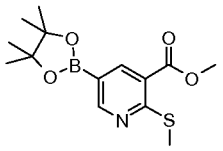
To a suspension of 5-bromo-2-(methylsulfanyl)pyridine-3-carboxylic acid (**Intermediate 357,** 7.66 mmol, 1.9 g) in MeOH (20 ml) at 0 °C, was slowly added thionyl chloride (15.32 mmol, 1.82 g). After the addition was complete, the reaction mixture was refluxed for 3 h. The solvent was concentrated in *vacuo* and the crude mixture was taken in EtOAc (30 mL), washed with aq. $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated to obtain 1.6 g of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 358	 Methyl 5-bromo-2-(methylsulfanyl)pyridine-3-carboxylate	MS(ES): 262 (M) and 262 (M+2) for $C_8H_8BrNO_2S$. 400 MHz, DMSO-d_6: δ 2.44 (s, 3H), 3.85 (s, 3H), 8.33 (d, J = 3.20 Hz, 1H), 8.81 (d, J = 3.20 Hz, 1H).	**Intermediate 357** 5-Bromo-2-(methylsulfanyl)pyridine-3-carboxylic acid

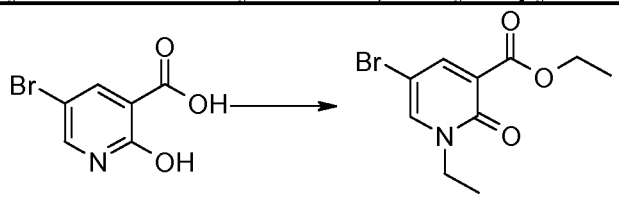
Intermediate 359: methyl 2-(methylsulfanyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate



A suspension of methyl 5-bromo-2-(methylsulfanyl)pyridine-3-carboxylate (**Intermediate 358,** 5.7 mmol, 1.5 g), bis(pinacolato)diboron (6.2 mmol, 1.59 g), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (0.57 mmol, 0.467 g) and potassium acetate (17.17 mmol, 1.685 g) was taken in dioxane (5 mL) and degassed for 10 min. Then the reaction mixture was heated to 100 °C for 1 h. The reaction mixture was passed through a column and the product was eluted at 5% EtOAc in hexanes. The residue obtained upon evaporation of the product containing fractions was then triturated with petroleum ether to get 1.3 g of the title compound. LCMS analysis indicated the presence of a mixture of boronic acid (86%) and boronate (12%).

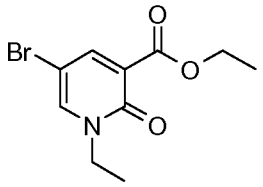
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 359	 Methyl 2-(methylsulfanyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate	MS(ES): 310 (M+1) for $C_{14}H_{20}BNO_4S$ (12 % as Boronic ester) and 228 (M+1) for $C_8H_{10}BNO_4S$ (86 % as Boronic acid). 400 MHz, DMSO-d_6: δ 1.31 (s, 12H), 2.47 (s, 3H), 3.86 (s, 3H), 8.37 (s, 1H), 8.77 (s, 1H).	**Intermediate 358** Methyl 5-bromo-2-(methylthio) nicotinate

Intermediate 360: ethyl 5-bromo-1-ethyl-2-oxo-1,2-dihydropyridine-3-carboxylate

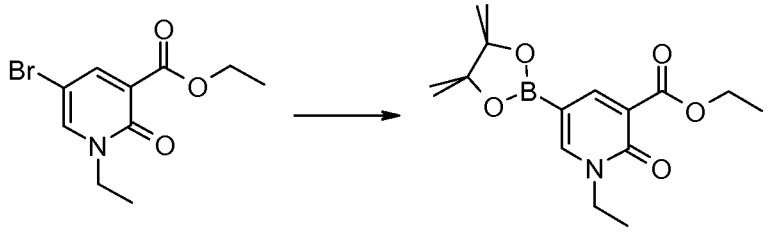


To a suspension of cesium carbonate (12.3 mmol, 4 g) in dry ethanol (20 mL), 5-bromo-2-hydroxypyridine-3-carboxylic acid (9.2 mmol, 2 g) and iodoethane (24.3 mmol, 3.8 g) were added and heated to 80 °C for 3 h in a sealed tube. The mixture was diluted with methanol

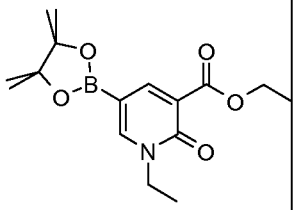
and filtered through a celite bed. The filtrate was concentrated to yield 2.2 g of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 360	 ethyl 5-bromo-1-ethyl-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 274 (M) and 276 (M+2) for $C_{10}H_{12}BrNO_3$. 300 MHz, $CDCl_3$: δ 1.32-1.40 (m, 6H), 4.02 (q, *J* = 7.17 Hz, 2H), 4.36 (q, *J* = 7.14 Hz, 2H), 7.64 (d, *J* = 2.88 Hz, 1H), 8.12 (d, *J* = 2.91 Hz, 1H) .	5-bromo-2-hydroxypyridine-3-carboxylic acid

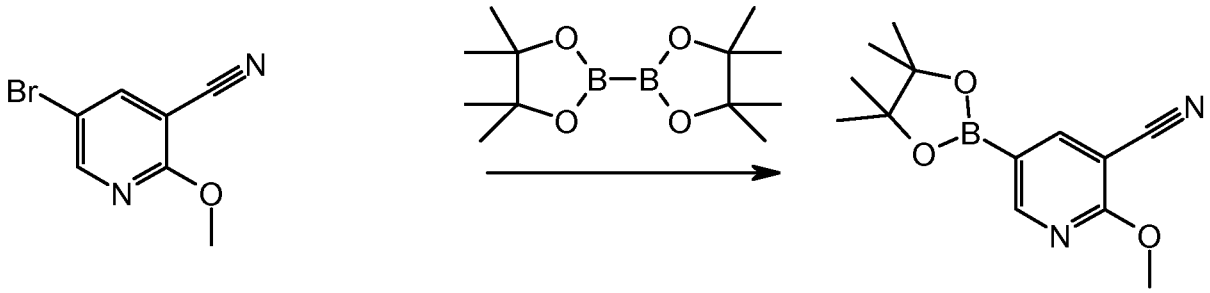
Intermediate 361: ethyl 1-ethyl-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate



Ethyl 5-bromo-1-ethyl-2-oxo-1,2-dihydropyridine-3-carboxylate (**Intermediate 360,** 1.82 mmol, 0.5 g), bis(pinacolato)diboron (2.1 mmol, 0.56 g), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)complex with CH_2Cl_2 (0.27 mmol, 0.22 g) and potassium acetate (5.4 mmol, 0.53 g) were suspended in dry dioxane (10 mL) and degassed with nitrogen for 10 min. The reaction was then heated to 100 °C for 1 h. The reaction mixture was diluted with DCM and filtered through a celite bed and concentrated to give the crude title compound which was used in the next step without further purification. HPLC-MS analysis indicated the presence of a mixture of boronic acid (39 %) and boronate (35 %).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 361	 Ethyl 1-ethyl-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate	Taken to the next step as a mixture based on LCMS without further purification MS(ES): 240 (M+1) for $C_{10}H_{14}BNO_5$ (39 % as Boronic acid) and MS(ES): 322 (M+1) for $C_{16}H_{24}BNO_5$ (35 % as Boronic ester).	**Intermediate 360** ethyl 5-bromo-1-ethyl-2-oxo-1,2-dihydro pyridine-3-carboxylate

Intermediate

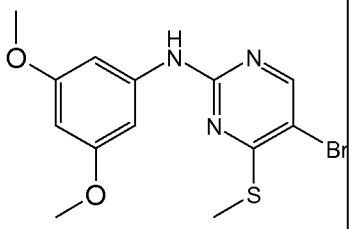


362: 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile

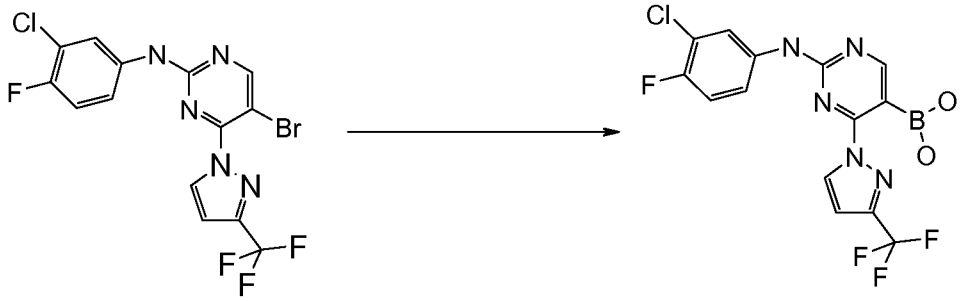
5-Bromo-2-methoxynicotinonitrile (0.5 g, 2.35 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.834 g, 3.29 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride-dichloromethane adduct (0.575 g, 0.70 mmol), and potassium acetate (0.691 g, 7.04 mmol) were suspended in 1,4-dioxane (20 ml) and degassed with nitrogen for 10 min. The reaction was then heated at 90 °C for 2 h, diluted with dichloromethane and purified by flash chromatography (25g silica column, 0-8% methanol in dichloromethane). Fractions were combined to obtain reddish-brown solid corresponding to title compound.
MS(ES): 260.99 (M+H) for $C_{13}H_{17}BN_2O_3$
^{1}H-NMR (400 MHz, DMSO-d6): δ ppm 1.30 (s, 12H) 4.03 (s, 3 H) 8.30 (d, *J*=1.70 Hz, 1 H) 8.62 (d, *J*=1.70 Hz, 1 H).

Intermediate 363: 5-bromo-*N*-(3,5-dimethoxy)phenyl]-4-(methylthio)pyrimidin-2-amine

The title compound was prepared using the general method described above for **Intermediate 65** using 5-bromo-2-chloro-4-(methylthio)pyrimidine and 3,5-dimethoxy-aniline.

Int	Compound	Data	SM
Intermediate 363	 5-bromo-*N*-(3,5-dimethoxy)phenyl]-4-(methylthio)pyrimidin-2-amine	MS: ES+ 356 for $C_{13}H_{14}BrN_3O_2S$ 1H NMR (300 MHz, DMSO-D6) δ ppm 2.58 (s, 3 H) 3.72 (s, 6 H) 6.16 (t, J=2.26 Hz, 1 H) 7.00 (d, J=2.26 Hz, 2 H) 8.31 (s, 1 H) 9.69 (s, 1 H)	3,5-dimethoxy-aniline

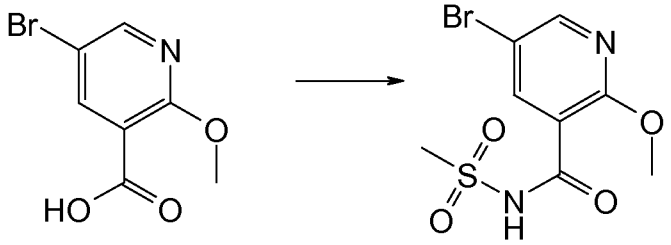
Intermediate 364: 2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-ylboronic acid



5-bromo-N-(3-chloro-4-fluorophenyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine **Intermediate 115** (300 mg, 0.69 mmol) and triisopropyl borate (0.319 mL, 1.37 mmol) were combined in anhydrous THF (3.00 mL) and anhydrous toluene (12 mL) to give a colorless solution under argon. The mixture was cooled to -78 °C, then 2.5M BuLi in Hexanes (0.550 mL, 1.37 mmol) was added dropwise over 1 hour. After 30 minutes, 1 M HCl (20 ml) was added at -78 °C, then the the ice bath was removed and the mixture was allowed to warm to RT. The mixture was concentrated followed by addition of water and ethyl acetate. The water layer was extracted with ethyl acetate. The combined organic layers were washed with brine (1 x 50 mL) then dried over $MgSO_4$. The residue after filtration and evaporation was purified by silica gel chromatography using 0-10% MeOH in methylene chloride. The title compound was isolated as a white solid. (80mg).

MS (Electrospray): 402 (MH^+) $C_{14}H_9BClF_4N_5O_2$

Intermediate 365: 5-Bromo-2-methoxy-N-(methylsulfonyl)nicotinamide



To a stirred suspension of 5-bromo-2-methoxynicotinic acid (1.15 g, 4.96 mmol) and oxalyl chloride (0.649 ml, 7.43 mmol) in methylene chloride (10 mL), under an atmosphere of nitrogen at ambient temperature, were added two drops of DMF. This mixture was allowed to stir for 2 hours. The solution was concentrated under vacuum; the residue was redissolved in methylene chloride (5 mL) and added dropwise to a stirred suspension of methanesulfonamide (0.471 g, 4.96 mmol) and pyridine (0.802 ml, 9.91 mmol) in methylene chloride (5 mL), under an atmosphere of nitrogen at ambient temperature. This mixture was stirred overnight, concentrated and purified by flash chromatography (silica gel, 0-6% methanol in methylene chloride) to yield the title compound (1.1 g). MS: ES+ 310 for $C_8H_9BrN_2O_4S$.

1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 3.41 (s, 3 H) 4.16 (s, 3 H) 8.43 (d, *J*=2.64 Hz, 1 H) 8.58 (d, *J*=2.64 Hz, 1 H) 10.05 (br. s., 1 H)

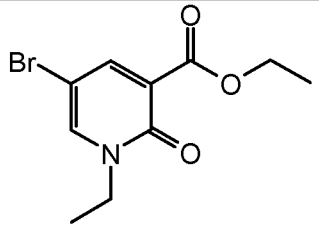
Intermediate 366: Methyl 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate



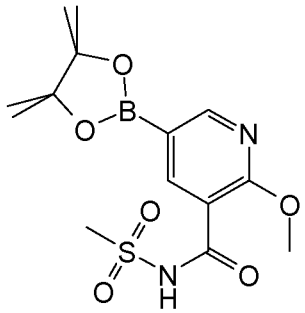
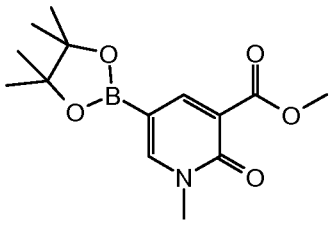
Methyl 5-bromo-2-hydroxynicotinate (0.9 g, 3.88 mmol), dimethyl sulfate (1.186 mL, 12.41 mmol), and triethylamine (1.730 mL, 12.41 mmol) were dissolved in MeOH (10.5 mL) and heated in a microwave reactor at 100 °C for 30 min. The reaction was diluted with DCM, washed with water, and the organic layer was evaporated and purified by flash chromatography (silica gel, 0-12% MeOH in DCM) to afford the desired product (847 mg). MS: ES+ 247 for $C_8H_8BrNO_3$

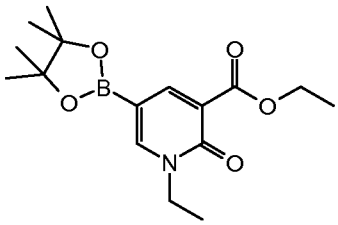
1H NMR (300 MHz, DMSO-d_6) d ppm 3.45 (s, 3 H) 3.75 (s, 3 H) 8.04 (d, *J*=3.01 Hz, 1 H) 8.36 (d, *J*=2.83 Hz, 1 H)

The compound in the table below was prepared using the procedure described above for **Intermediate 366** using iodoethane as the alkylating agent, potassium carbonate as the base and ethanol as solvent.

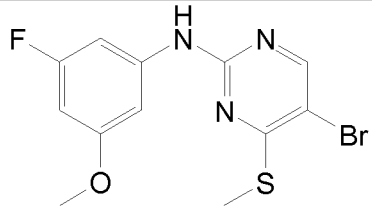
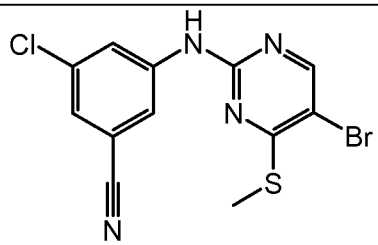
Intermediate	Compound	Mass and NMR	SM
Intermediate 367	 ethyl 5-bromo-1-ethyl-2-oxo-1,2-dihydropyridine-3-carboxylate	MS: ES+ 275 for $C_{10}H_{12}BrNO_3$ 1H NMR (300 MHz, DMSO-d_6) d ppm 1.24 (dt, *J*=10.78, 7.13 Hz, 6 H) 3.94 (q, *J*=7.16 Hz, 2 H) 4.21 (q, *J*=7.10 Hz, 2 H) 8.01 (d, *J*=2.83 Hz, 1 H) 8.35 (d, *J*=2.83 Hz, 1 H)	methyl 5-bromo-2-hydroxy nicotinate

The intermediates in the table below were prepared using the procedure for **Intermediate 134** and the specified starting material.

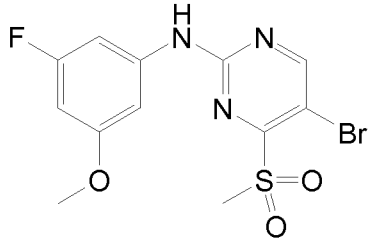
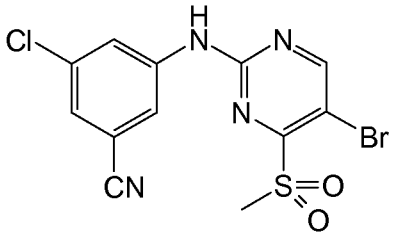
Intermediate	Compound	Mass and NMR	SM
Intermediate 368	 2-Methoxy-N-(methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinamide	MS: ES+ 357 for $C_{14}H_{21}BN_2O_6S$ 1H NMR (300 MHz, CHLOROFORM-*d*) d ppm 1.35 (s, 12 H) 3.41 (s, 3 H) 4.19 (s, 3 H) 8.71 (d, *J*=2.07 Hz, 1 H) 8.85 (d, *J*=1.88 Hz, 1 H) 10.06 (s, 1 H)	**Intermediate 365**
Intermediate 369	 methyl 1-methyl-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate	MS: ES+ 294 for $C_{14}H_{20}BNO_5$ 1H NMR (300 MHz, DMSO-d_6) d ppm 1.28 (s, 12 H) 3.50 (s, 3 H) 3.74 (s, 3 H) 8.12 (d, *J*=2.26 Hz, 1 H) 8.29 (d, *J*=2.26 Hz, 1 H)	**Intermediate 366**

Intermediate	Compound	Mass and NMR	SM
Intermediate 370	 ethyl 1-ethyl-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate	MS: ES+ 322 for $C_{16}H_{24}BNO_5$ 1H NMR (300 MHz, DMSO-d_6) d ppm 1.16 - 1.34 (m, 18 H) 4.01 (q, *J*=6.91 Hz, 2 H) 4.21 (q, *J*=7.03 Hz, 2 H) 8.07 (d, *J*=2.07 Hz, 1 H) 8.26 (d, *J*=2.26 Hz, 1 H)	**Intermediate 367**

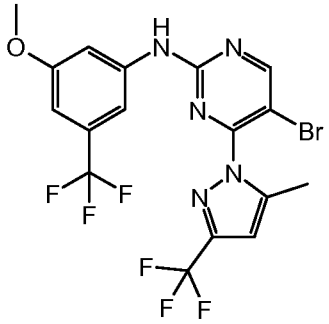
The compounds in the table below were prepared using the procedure for **Intermediate 65** and the specified starting materials.

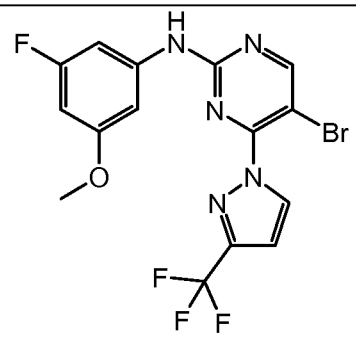
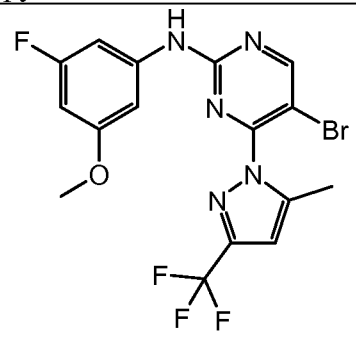
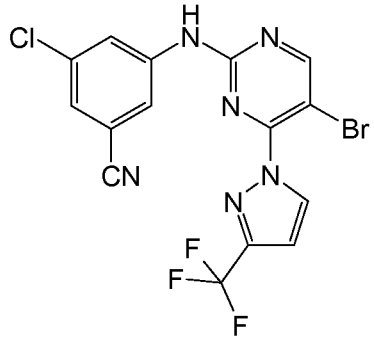
Intermediate	Compound	Mass and NMR	S.M.
Intermediate 371	 5-Bromo-N-(3-fluoro-5-methoxyphenyl)-4-(methylthio)pyrimidin-2-amine	MS: ES+ 345 for $C_{12}H_{11}BrFN_3OS$ 1H NMR (300 MHz, DMSO-D6) δ ppm 2.59 (s, 3 H) 3.75 (s, 3 H) 6.31 - 6.58 (m, 1 H) 7.18 (s, 1 H) 7.23 - 7.38 (m, 1 H) 8.36 (s, 1 H) 9.92 (s, 1 H).	3-Fluoro-5-methoxyaniline and 5-bromo-2-chloro-4-(methylthio)pyrimidine
Intermediate 372	 3-(5-bromo-4-(methylthio)pyrimidin-2-ylamino)-5-chlorobenzonitrile	MS: ES+ 356 for $C_{12}H_8BrClN_4S$ 1H NMR (300 MHz, DMSO-D6) δ ppm 2.60 (s, 3 H) 7.48 - 7.68 (m, 1 H) 8.08 - 8.14 (m, 1 H) 8.19 (t, *J*=1.98 Hz, 1 H) 8.43 (s, 1 H) 10.29 (s, 1 H).	5-bromo-2-chloro-4-(methylthio)pyrimidine and 3-amino-5-chlorobenzonitrile

The compounds in the table below were prepared using the procedure for **Intermediate 69** and the specified starting material.

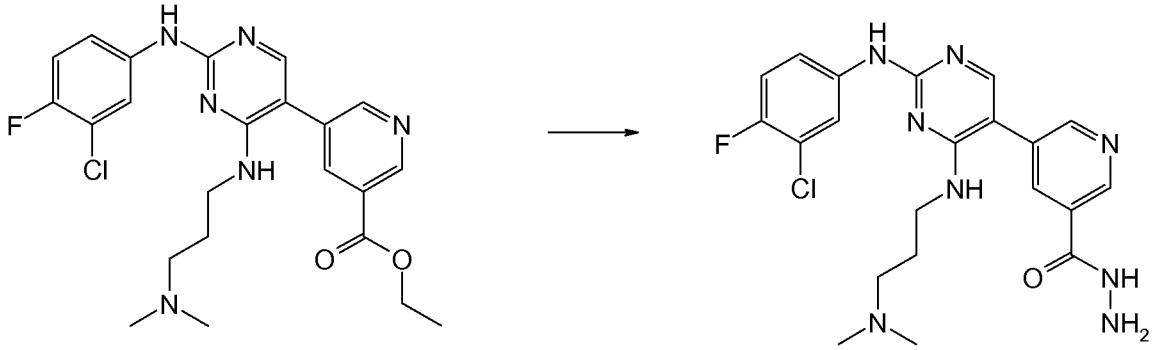
Intermediate	Compound	Mass and NMR	S.M.
Intermediate 373	 5-bromo-N-(3-fluoro-5-methoxyphenyl)-4-(methylsulfonyl)pyrimidin-2-amine	MS: ES+ 377 for $C_{12}H_{11}BrFN_3O_3S$ 1H NMR (300 MHz, DMSO-D6) δ ppm 3.47 (s, 3 H) 3.76 (s, 3 H) 6.39 - 6.70 (m, 1 H) 7.08 - 7.36 (m, 2 H) 8.95 (s, 1 H) 10.48 (s, 1 H)	**Intermediate 371**
Intermediate 374	 3-(5-bromo-4-(methylsulfonyl)pyrimidin-2-ylamino)-5-chlorobenzonitrile	MS: ES+ 388 for $C_{12}H_8BrClN_4O_2S$ 1H NMR (300 MHz, DMSO-d_6) d ppm 3.36 (s, 3 H) 7.52 - 7.55 (m, 1 H) 7.97 (ddd, *J*=7.77, 2.07, 1.84 Hz, 2 H) 8.90 (s, 1 H) 10.68 (s, 1 H)	**Intermediate 372**

The compounds in the table below were prepared using the procedure for **Intermediate 112** and the specified starting materials.

Intermediate	Compound	Mass and NMR	S.M.
Intermediate 375	 5-bromo-N-(3-methoxy-5-(trifluoromethyl)phenyl)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine	MS: ES+ 497 for $C_{17}H_{12}BrF_6N_5O$ 1H NMR (300 MHz, DMSO-D6) d ppm 2.41 (s, 3 H) 3.81 (s, 3 H) 6.76 - 7.05 (m, 2 H) 7.60 (s, 1 H) 7.69 (s, 1 H) 9.01 (s, 1 H) 10.54 (s, 1 H)	**Intermediate 70** and 3-trifluoromethyl-5-methylpyrazole

Intermediate	Compound	Mass and NMR	S.M.
Intermediate 376	 5-bromo-N-(3-fluoro-5-methoxyphenyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine	MS: ES+ 433 for $C_{15}H_{10}BrF_4N_5O$ 1H NMR (300 MHz, DMSO-D6) δ ppm 3.76 (s, 3 H) 6.41 - 6.69 (m, 1 H) 7.15 (d, *J*=2.83 Hz, 1 H) 7.18 - 7.46 (m, 2 H) 8.64 (d, *J*=1.51 Hz, 1 H) 8.94 (s, 1 H) 10.40 (s, 1 H)	**Intermediate 373** and 3-trifluoromethyl pyrazole
Intermediate 377	 5-bromo-N-(3-fluoro-5-methoxyphenyl)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine	MS: ES+ 447 for $C_{16}H_{12}BrF_4N_5O$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.40 (s, 3 H) 3.74 (s, 3 H) 6.50 (dt, *J*=10.97, 2.33 Hz, 1 H) 6.85 (s, 1 H) 7.12 - 7.16 (m, 1 H) 7.20 (dt, *J*=11.49, 1.98 Hz, 1 H) 8.98 (s, 1 H) 10.42 (s, 1 H)	**Intermediate 373** and 3-trifluoromethyl-5-methylpyrazole
Intermediate 378	 3-(5-bromo-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-5-chlorobenzonitrile	MS: ES+ 444 for $C_{15}H_7BrClF_3N_6$ 1H NMR (300 MHz, DMSO-d_6) d ppm 7.17 (d, 1 H) 7.62 - 7.65 (m, 1 H) 8.13 (ddd, *J*=8.90, 2.07, 1.84 Hz, 2 H) 8.66 (dd, *J*=2.73, 1.04 Hz, 1 H) 9.01 (s, 1 H) 10.73 (s, 1 H)	**Intermediate 374** and 3-trifluoromethyl pyrazole

Intermediate 379: 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino)propylamino)pyrimidin-5-yl)nicotinohydrazide

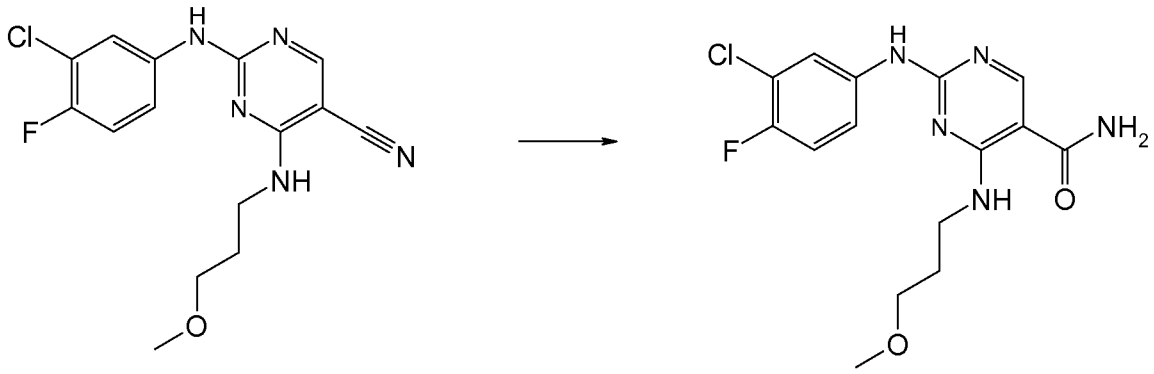


A solution of **Example 5** (100 mg, 0.21 mmol) and hydrazine hydrate (0.015 mL, 0.32 mmol) in 1,4-dioxane (1 mL) was stirred and heated to 115 degrees for 60 minutes. Solvent was removed under reduced pressure, affording the title compound (83 mg).

MS: ES+ 459 for $C_{21}H_{24}ClFN_8O$.

1H NMR (300 MHz, DMSO-d_6) d ppm 1.70 (quin, *J*=6.59 Hz, 2 H) 2.02 (s, 6 H) 2.33 (t, *J*=6.50 Hz, 2 H) 3.38 - 3.50 (m, 2 H) 7.30 (t, *J*=9.14 Hz, 1 H) 7.41 (t, *J*=4.99 Hz, 1 H) 7.63 (ddd, *J*=9.14, 4.24, 2.64 Hz, 1 H) 7.86 (s, 1 H) 8.13 (t, *J*=2.07 Hz, 1 H) 8.26 (dd, *J*=6.97, 2.64 Hz, 1 H) 8.68 (d, *J*=2.07 Hz, 1 H) 8.93 (d, *J*=1.88 Hz, 1 H) 9.48 (s, 1 H) 9.99 (br. s., 1 H)

Intermediate 380: 2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidine-5-carboxamide

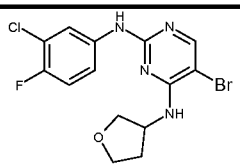
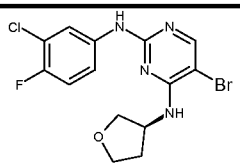


Intermediate 127 (120 mg, 0.35 mmol) was suspended in methanol (0.5 mL) and water (0.5 mL) and stirred under ambient conditions. To this mixture was added aqueous sodium hydroxide (50 wt %, 84 mg, 1.05 mmol). Upon warming to 50 degrees a small amount of dioxane was added to aid in solubility. After 90 minutes the mixture was removed from

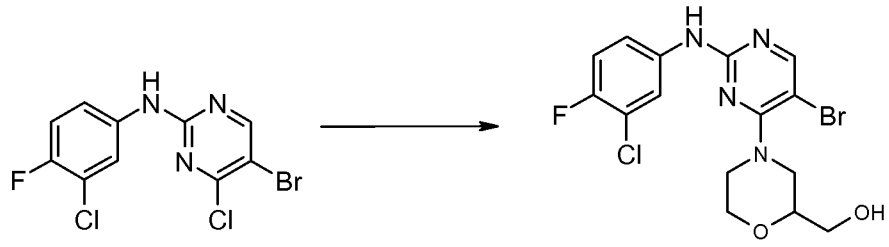
heating then water was added to precipitate a solid; this was collected and washed with water to give the title compound (87 mg). MS: ES+ 354 for $C_{15}H_{17}ClFN_5O_2$.

1H NMR (300 MHz, DMSO-d_6) δ ppm 1.81 (quin, J=6.50 Hz, 2 H) 3.22 (s, 3 H) 7.18 (br. s., 1 H) 7.30 (t, J=9.14 Hz, 1 H) 7.54 - 7.66 (m, 1 H) 7.80 (br. s., 1 H) 8.20 (dd, J=6.78, 2.45 Hz, 1 H) 8.52 (s, 1 H) 9.20 (t, J=5.37 Hz, 1 H) 9.69 (s, 1 H).

The following intermediates were prepared using the general method described above for **Intermediate 72** using 5- bromo-2-[N-(3-chloro-4-fluorophenyl)]-4-(methyl sulfonyl)pyrimidin-2-amine (**Intermediate 69**) and the starting material (SM) indicated.

Int	Compound	Data	SM
Intermediate 381	 5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(tetrahydrofuran-3-yl)pyrimidine-2,4-diamine	MS(ES): 387(M) 389 (M+3) for $C_{14}H_{13}BrClFN_4O$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 1.90 - 2.13 (m, 1 H) 2.13 - 2.33 (m, 1 H) 3.57 - 3.81 (m, 2 H) 3.81 - 4.05 (m, 2 H) 4.42 - 4.72 (m, 1 H) 6.86 (d, J=6.22 Hz, 1 H) 7.31 (t, J=9.14 Hz, 1 H) 7.52 (ddd, J=9.14, 4.24, 2.64 Hz, 1 H) 8.03 - 8.21 (m, 2 H) 9.51 (s, 1 H)	3-Aminotetra-hydrofuran
Intermediate 382	 (S)-5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(tetrahydrofuran-3-yl)pyrimidine-2,4-diamine	MS(ES): 387(M) 389 (M+3) for $C_{14}H_{13}BrClFN_4O$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 1.90 - 2.13 (m, 1 H) 2.13 - 2.33 (m, 1 H) 3.57 - 3.81 (m, 2 H) 3.81 - 4.05 (m, 2 H) 4.42 - 4.72 (m, 1 H) 6.86 (d, J=6.22 Hz, 1 H) 7.31 (t, J=9.14 Hz, 1 H) 7.52 (ddd, J=9.14, 4.24, 2.64 Hz, 1 H) 8.03 - 8.21 (m, 2 H) 9.51 (s, 1 H)	S(-)-3-Aminotetra-hydrofuran

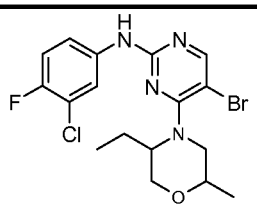
Intermediate 383: (4-(5-bromo-2-(3-chloro-4-fluorophenylamino)pyrimidin-4-yl)morpholin-2-yl)methanol



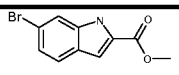
To 600 mg of 5-bromo-4-chloro-*N*-(3-chloro-4-fluorophenyl)pyrimidin-2-amine (**Intermediate 63,** 1.78 mmol) in 1,4-Dioxane (8 mL), was added triethylamine (0.27 mL, 1.96 mmol) and 2-hydroxymethylmorpholine (1.78 mmol, 209 mg) under inert atmosphere. The reaction mixture was stirred at room temperature for 2 days. The reaction mixture was diluted with ethyl acetate and MeOH and adsorbed on silica gel. The mixture was purified by column chromatography using 0-10 % MeOH in DCM to obtain (4-(5-bromo-2-(3-chloro-4-fluorophenylamino)pyrimidin-4-yl)morpholin-2-yl)methanol (473 mg). MS(ES): 417 (M) and 419 (M+2) for $C_{15}H_{15}BrClFN_4O_2$.

^{1}H NMR (300 MHz, DMSO-D6) δ ppm 2.71 - 2.94 (m, 1 H) 2.94 - 3.14 (m, 1 H) 3.33 - 3.76 (m, 4 H) 3.92 (d, *J*=11.11 Hz, 1 H) 4.09 (d, *J*=12.81 Hz, 1 H) 4.22 (d, *J*=13.00 Hz, 1 H) 4.82 (t, *J*=5.27 Hz, 1 H) 7.30 (t, *J*=9.14 Hz, 1 H) 7.43 - 7.70 (m, 1 H) 7.89 - 8.14 (m, 1 H) 8.26 (s, 1 H) 9.70 (s, 1 H).

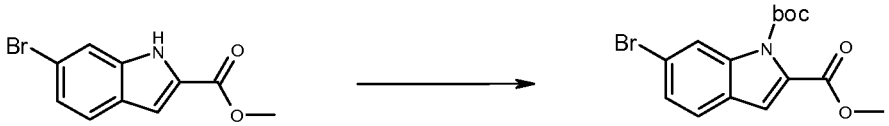
The following compound was prepared using the general method described for **Intermediate 383** and the starting materials (SM) indicated.

Int	Compound	Data	SM
Intermediate 384	 5-bromo-N-(3-chloro-4-fluorophenyl)-4-(5-ethyl-2-methylmorpholino)pyrimidin-2-amine	MS(ES): 429 (M) and 431(M+2) for $C_{17}H_{19}BrClFN_4O$	5-bromo-4-chloro-*N*-(3-chloro-4-fluorophenyl) pyrimidin-2-amine **Intermediate 63** and 5-ethyl-2-methylmorpholine

The following compound was prepared using the general method described for **Intermediate 131** and the starting material (SM) indicated.

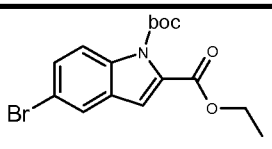
Int	Compound	Data	SM
Intermediate 385	 Methyl 6-bromo-1H-indole-2-carboxylate	^{1}H NMR (300 MHz, DMSO-D6) δ ppm 3.87 (s, 3 H) 7.09 - 7.28 (m, 2 H) 7.49 - 7.80 (m, 2 H) 12.07 (s, 1 H)	6-Bromoindole-2-carboxylic acid

Intermediate 386: 1-tert-butyl 2-methyl 6-bromo-1H-indole-1,2-dicarboxylate

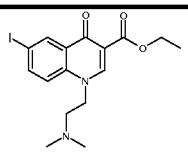
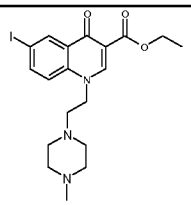


To 1 g of methyl 6-bromo-1H-indole-2-carboxylate (**Intermediate 385**, 3.94 mmol) in THF (20 mL) was added di-t-Butyl dicarbonate (1.074 g, 4.92 mmol) and treated with 4-dimethylaminopyridine (48 mg, 0.39 mmol). The mixture was stirred at room temperature under nitrogen for 4 days. The mixture was concentrated at reduced pressure and the residue was adsorbed on silica gel and purified by column chromatography with 0-25% EtOAc in hexanes to afford 1-tert-butyl 2-methyl 6-bromo-1H-indole-1,2-dicarboxylate (1.33 g). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.55 (s, 9 H) 3.86 (s, 3 H) 7.29 (s, 1 H) 7.49 (dd, *J*=8.48, 1.70 Hz, 1 H) 7.69 (d, *J*=8.48 Hz, 1 H) 8.13 (s, 1 H).

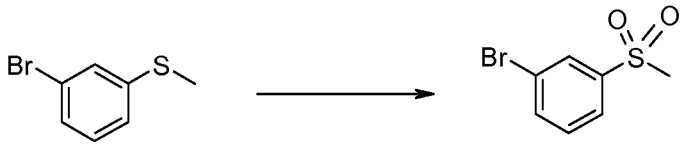
The following compound was prepared using the general method described above for **Intermediate 386** using the starting material (SM) indicated.

Int	Compound	Data	SM
Intermediate 387	 1-tert-butyl 2-ethyl 5-bromo-1H-indole-1,2-dicarboxylate	^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.31 (t, *J*=7.06 Hz, 3 H) 1.56 (s, 9 H) 4.32 (q, *J*=7.16 Hz, 2 H) 7.23 (s, 1 H) 7.60 (dd, *J*=8.85, 2.07 Hz, 1 H) 7.82 - 8.06 (m, 2 H)	Ethyl 5-bromo-1H-indole-2-carboxylate

The following compounds were prepared using the general method described above for **Intermediate 133** using **Intermediate 132** and the starting material (SM) indicated.

Int	Compound	Data	SM
Intermediate 388	 ethyl 1-(2-(dimethylamino)ethyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate	MS(ES): 415 (M+1) for $C_{16}H_{19}IN_2O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.28 (t, 3 H) 2.17 (s, 6 H) 2.57 (t, *J*=5.84 Hz, 2 H) 4.22 (q, *J*=7.16 Hz, 2 H) 4.44 (t, *J*=5.93 Hz, 2 H) 7.65 (d, *J*=9.04 Hz, 1 H) 8.06 (dd, *J*=8.85, 2.26 Hz, 1 H) 8.50 (d, *J*=2.07 Hz, 1 H) 8.63 (s, 1 H)	N1,N1-dimethylethane-1,2-diamine
Intermediate 389	 Ethyl 6-iodo-1-(2-(4-methylpiperazin-1-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate	MS(ES): 470 (M+1) for $C_{19}H_{24}IN_3O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.29 (t, 3 H) 2.11 (s, 3 H) 2.14 - 2.49 (m, 8 H) 2.59 (t, *J*=5.56 Hz, 2 H) 4.23 (q, *J*=7.03 Hz, 2 H) 4.43 (t, *J*=5.65 Hz, 2 H) 7.67 (d, *J*=8.85 Hz, 1 H) 8.05 (dd, *J*=8.95, 2.17 Hz, 1 H) 8.50 (d, *J*=2.26 Hz, 1 H) 8.59 (s, 1 H)	2-(4-Methylpiperazin-1-yl)ethanamine

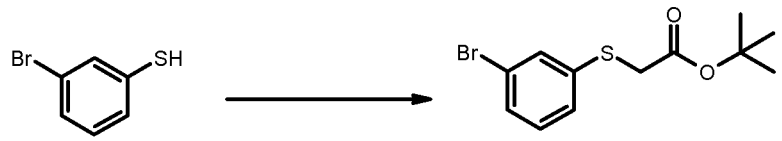
Intermediate 390: 3-bromo-5-(methylsulfonyl)pyridine



A solution of 3-bromo-5-(methylthio)pyridine (2.17 g, 10.63 mmol) in DCM (40 mL) was cooled to 0 °C. The reaction was then treated with m-Chloroperbenzoic acid (4.89 g, 21.27 mmol) and allowed to stir at 0 °C for 30 min (reaction became a suspension after mcpba addition) before it was allowed to warm up to room temperature for 1 hr. The reaction mixture was diluted with EtOAc, basified with sodium carbonate, and the layers were separated. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed at reduced pressure and the residue was adsorbed on silica and purified by column chromatography with 50-100% EtOAc in hexanes to afford 3-bromo-5-(methylsulfonyl)pyridine (1.97 g). MS(ES): 236 (M) and 238 (M+2) for $C_6H_6BrNO_2S$.

^{1}H NMR (300 MHz, DMSO-D6) δ ppm 3.39 (s, 3 H) 8.57 (t, *J*=2.07 Hz, 1 H) 9.04 (d, *J*=1.88 Hz, 1 H) 9.07 (d, *J*=2.07 Hz, 1 H).

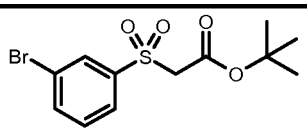
Intermediate 391: tert-butyl 2-(3-bromophenylthio)acetate



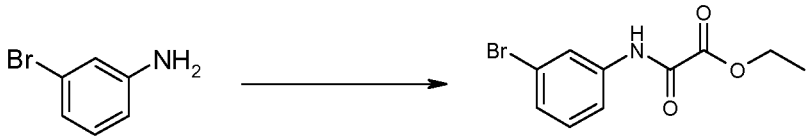
A solution of 3-bromobenzenethiol (0.788 mL, 6.66 mmol) in DMF (12 mL) was treated with tert-butyl 2-bromoacetate (1.034 mL, 7.00 mmol) and potassium carbonate (1.842 g, 13.33 mmol). The reaction was stirred at room temperature under nitrogen overnight. The reaction was diluted with EtOAc/H_2O and the layers were separated. The organic phase was washed with brine and dried over sodium sulfate. The solvent was removed at reduced pressure and the residue was adsorbed on silica and purified by column chromatography with 0-20% EtOAc in hexanes to afford tert-butyl 2-(3-bromophenylthio)acetate (1.6 g).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.35 (s, 9 H) 3.82 (s, 2 H) 7.15 - 7.47 (m, 3 H) 7.54 (t, *J*=1.79 Hz, 1 H).

The following compound was prepared using the general method described above for **Intermediate 390** using mcpba and the starting material (SM) indicated.

Int	Compound	Data	SM
Intermediate 392	 tert-butyl 2-(3-bromophenylsulfonyl)acetate	^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.40 (s, 9 H) 4.05 (s, 2 H) 7.47 (t, *J*=8.01 Hz, 1 H) 7.74 - 7.97 (m, 2 H) 8.10 (t, *J*=1.79 Hz, 1 H)	tert-butyl 2-(3-bromophenylthio)acetate **Intermediate 391**

Intermediate 393: Ethyl 2-(3-bromophenylamino)-2-oxoacetate



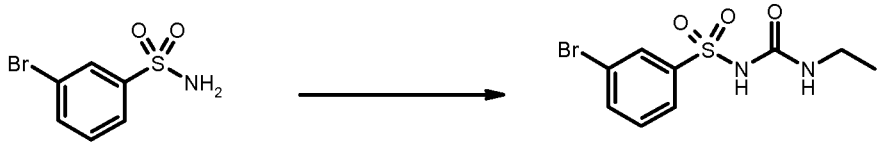
3-Bromoaniline (0.759 mL, 6.98 mmol) was dissolved in THF (20 mL), treated with triethylamine (0.972 mL, 6.98 mmol), and cooled to 0 °C. The solution was then treated with ethyl 2-chloro-2-oxoacetate (0.779 mL, 6.98 mmol) and allowed to slowly warm up to room

temperature and stir overnight under nitrogen. The reaction was diluted with EtOAc/H_2O and the layers were separated. The organic phase was washed with brine and dried over sodium sulfate. The solvent was removed at reduced pressure, the residue was adsorbed on silica, and purified by column chromatography with 0-60% EtOAc in hexanes to afford Ethyl 2-(3-bromophenylamino)-2-oxoacetate (1.78 g).

MS(ES): 272 (M) and 274 (M+2) for $C_{10}H_{10}BrNO_3$.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.32 (t, *J*=7.06 Hz, 3 H) 4.31 (q, *J*=7.16 Hz, 2 H) 7.19 - 7.44 (m, 2 H) 7.74 (dt, *J*=6.45, 2.33 Hz, 1 H) 7.90 - 8.17 (m, 1 H) 10.92 (s, 1 H)

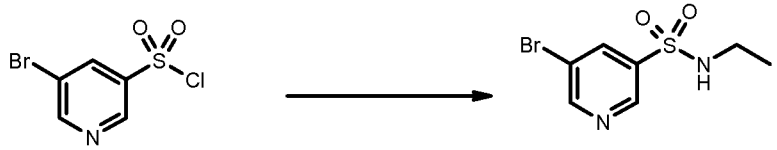
Intermediate 394: 3-Bromo-N-(ethylcarbamoyl)benzenesulfonamide



A solution of 3-bromobenzenesulfonamide (400 mg, 1.69 mmol) in acetone (4.20 mL) was treated with a solution of potassium hydroxide (95 mg, 1.69 mmol) in water (0.6 mL). The reaction was stirred at room temperature for 15 min at which time the solvent was removed at reduced pressure. The residue was re-dissolved in DMF (4.20 mL), treated with ethyl isocyanate (0.266 mL, 3.39 mmol), and stirred overnight. The solvent was removed at reduced pressure and the residue was basified with 2 mL of 1 N NaOH, diluted with water, and then acidified with concentrated HCl. The solid formed was then filtered and dried to afford the desired product (350 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.95 (t, 3 H) 2.81 - 3.13 (m, 2 H) 6.61 (t, *J*=5.37 Hz, 1 H) 7.58 (t, *J*=7.91 Hz, 1 H) 7.90 (dt, *J*=8.15, 1.77 Hz, 2 H) 8.03 (t, *J*=1.79 Hz, 1 H) 10.73 (s, 1 H)

Intermediate 395: 5-bromo-N-ethylpyridine-3-sulfonamide



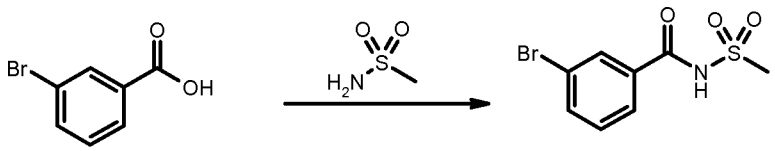
5-bromopyridine-3-sulfonyl chloride hydrochloride (1 g, 3.41 mmol) and ethanamine hydrochloride (0.306 g, 3.75 mmol) were treated with pyridine (2.76 ml, 34.13 mmol) and

stirred at room temperature under nitrogen for 2 hrs. The reaction mixture was then diluted with EtOAc, washed with water, and dried over sodium sulfate. The solvent was removed at reduced pressure, the residue was adsorbed on silica, and purified on column chromatography with 10-80% EtOAc in hexanes to afford 5-bromo-N-ethylpyridine-3-sulfonamide (466 mg).

MS(ES): 265 (M) and 267 (M+2) for $C_7H_9BrN_2O_2S$.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.99 (t, J=7.16 Hz, 3 H) 2.78 - 2.96 (m, 2 H) 7.93 (br. s., 1 H) 8.37 (t, J=2.07 Hz, 1 H) 8.92 (d, J=1.88 Hz, 1 H) 9.00 (d, J=2.07 Hz, 1 H).

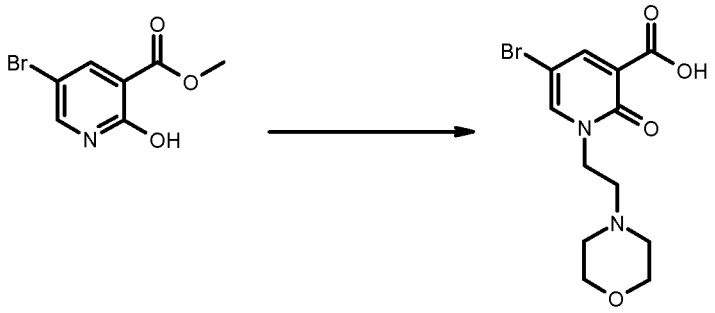
Intermediate 396: 3-Bromo-N-(methylsulfonyl)benzamide



3-Bromobenzoic acid (1 g, 4.97 mmol), methanesulfonamide (0.521 g, 5.47 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.144 g, 5.97 mmol), and 4-dimethylaminopyridine (0.304 g, 2.49 mmol) were dissolved in THF (10 mL) and stirred at room temperature overnight. The residue was diluted with EtOAc, washed with water and brine, and dried over sodium sulfate. The solvent was removed at reduced pressure, the residue was adsorbed on silica, and purified by column chromatography with 20-100% EtOAc in hexanes to afford 3-bromo-N-(methylsulfonyl)benzamide (350 mg).

^{1}H NMR (300 MHz, CHLOROFORM-d) δ ppm 3.46 (s, 3 H) 7.40 (t, J=7.91 Hz, 1 H) 7.68 - 7.86 (m, 2 H) 8.03 (t, J=1.70 Hz, 1 H) 8.67 (br. s., 1 H).

Intermediate 397: 5-bromo-1-(2-morpholinoethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid

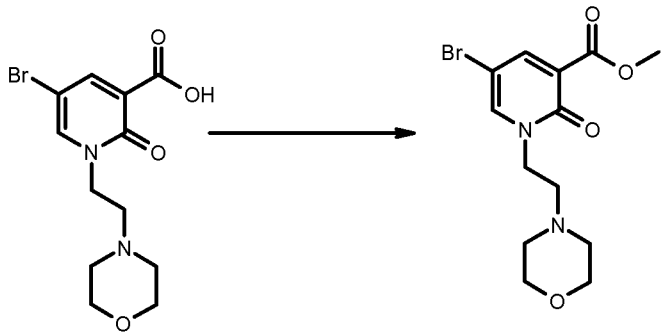


A suspension of methyl 5-bromo-2-hydroxynicotinate (1 g, 4.31 mmol), 4-(2-chloroethyl)morpholine hydrochloride (0.802 g, 4.31 mmol), and potassium carbonate (1.787

g, 12.93 mmol) in MeOH (20 mL) was refluxed overnight. The solvent was removed at reduced pressure and the residue was dissolved in H_2O and neutralized with 1N HCl. The solid formed was filtered (unreacted starting hydroxynicotinate) and the desired product remained in the aqueous layer, which was then concentrated. The residue was re-dissolved in DCM/MeOH, adsorbed on silica, and purified by column chromatography with 0-20% MeOH in DCM to afford bromo-1-(2-morpholinoethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (750 mg)

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.31 - 2.47 (m, 4 H) 2.64 (t, *J*=6.12 Hz, 2 H) 3.43 - 3.69 (m, 4 H) 4.18 (t, *J*=6.03 Hz, 2 H) 8.36 (d, *J*=2.83 Hz, 1 H) 8.50 (d, *J*=2.83 Hz, 1 H) 14.30 (br. s., 1 H)

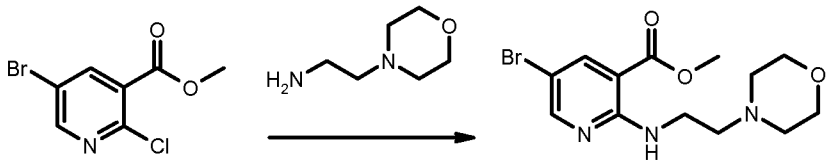
Intermediate 398: methyl 5-bromo-1-(2-morpholinoethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate



A suspension of 5-bromo-1-(2-morpholinoethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (**Intermediate 397**, 750 mg, 2.26 mmol) in methanol (9162 µl, 226.47 mmol) was treated with sulfuric acid (483 µl, 9.06 mmol). The reaction was refluxed for 4 hrs at which time the solvent was removed at reduced pressure. The residue was diluted with EtOAc and carefully neutralized with a solution of sodium carbonate. The layers were then separated and the organic was washed with brine and dried over sodium sulfate. The solvent was removed at reduced pressure and the residue was adsorbed on silica and purified by column chromatography with 0-15% MeOH in DCM toyield methyl 5-bromo-1-(2-morpholinoethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (664 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.33 - 2.46 (m, 4 H) 2.54 (t, *J*=6.22 Hz, 2 H) 3.39 - 3.60 (m, 4 H) 3.74 (s, 3 H) 4.02 (t, *J*=6.22 Hz, 2 H) 8.05 (d, *J*=3.01 Hz, 1 H) 8.26 (d, *J*=3.01 Hz, 1 H)

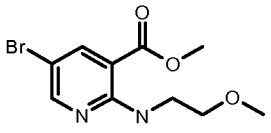
Intermediate 399: Methyl 5-bromo-2-(2-morpholinoethylamino)nicotinate



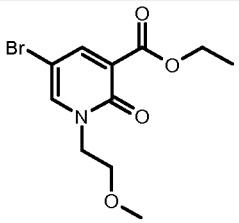
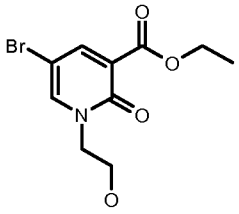
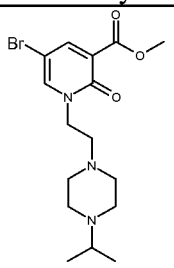
A suspension of methyl 5-bromo-2-chloronicotinate (0.5 g, 2.00 mmol) and 2-morpholinoethanamine (0.390 mL, 2.99 mmol) in EtOH (3 mL) was heated in a microwave reactor at 140 °C for 45 min. The mixture was concentrated at reduced pressure. The residue was then diluted with water, treated with sodium bicarbonate, and extracted with EtOAc. The organic layer was washed with brine and dried over sodium sulfate. The solvent was removed at reduced pressure and the residue was adsorbed on silica and purified by column chromatography with 0-16% MeOH in DCM to afford methyl 5-bromo-2-(2-morpholinoethylamino)nicotinate (582 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.29 - 2.46 (m, 4 H) 2.51 - 2.60 (m, 2 H) 3.43 - 3.67 (m, 6 H) 3.84 (s, 3 H) 8.05 - 8.26 (m, 2 H) 8.37 (d, *J*=2.45 Hz, 1 H)

The following compound was prepared using the general method described above for **Intermediate 399** using methyl 5-bromo-2-chloronicotinate and the starting material (SM) indicated.

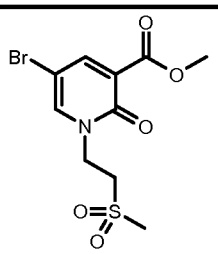
Int	Compound	Data	SM
Intermediate 400	 Methyl 5-bromo-2-(2-methoxyethylamino)nicotinate	MS(ES): 289 (M) and 291 (M+2) for $C_{10}H_{13}BrN_2O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.29 (s, 3 H) 3.43 - 3.55 (m, 2 H) 3.60 (q, *J*=5.15 Hz, 2 H) 3.83 (s, 3 H) 8.07 (t, *J*=4.90 Hz, 1 H) 8.15 (d, *J*=2.64 Hz, 1 H) 8.38 (d, *J*=2.45 Hz, 1 H)	2-methoxyethanamine

The following compounds were prepared using the general method described above for **Intermediate 367** using methyl 5-bromo-2-hydroxynicotinate and the starting material (SM) indicated.

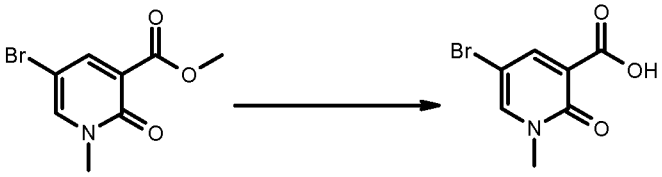
Int	Compound	Data	SM
Intermediate 401	 Ethyl 5-bromo-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 304 (M) and 306 (M+2) for $C_{11}H_{14}BrNO_4$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.26 (t, 3 H) 3.25 (s, 3 H) 3.57 (t, *J*=5.27 Hz, 2 H) 4.10 (t, *J*=5.37 Hz, 2 H) 4.21 (q, *J*=7.03 Hz, 2 H) 8.03 (d, *J*=3.01 Hz, 1 H) 8.21 (d, *J*=3.01 Hz, 1 H)	2-Bromoethyl methylether
Intermediate 402	 Ethyl 5-bromo-1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 290 (M) and 292 (M+2) for $C_{10}H_{12}BrNO_4$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.26 (t, 3 H) 3.62 (q, *J*=5.46 Hz, 2 H) 3.98 (t, *J*=5.27 Hz, 2 H) 4.21 (q, *J*=7.10 Hz, 2 H) 4.91 (t, *J*=5.46 Hz, 1 H) 8.03 (d, *J*=3.01 Hz, 1 H) 8.16 (d, *J*=2.83 Hz, 1 H)	2-Bromoethanol
Intermediate 403	 Methyl 5-bromo-1-(2-(4-isopropylpiperazin-1-yl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 386 (M) and 388 (M+2) for $C_{16}H_{24}BrN_3O_3$ ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.07 (br. s., 6 H) 2.35 - 2.89 (m, 11 H) 3.92 (s, 3 H) 4.05 (t, *J*=5.93 Hz, 2 H) 7.69 (br. s., 1 H) 8.19 (d, *J*=2.83 Hz, 1 H)	1-(2-Chloroethyl)-4-isopropylpiperazine dihydrochloride

The following compound was prepared using the general method described above for **Intermediate 366** using methyl 5-bromo-2-hydroxynicotinate and the starting material (SM) indicated.

5

Int	Compound	Data	SM
Intermediate 404	 Methyl 5-bromo-1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 338 (M) and 340 (M+2) for $C_{10}H_{12}BrNO_5S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.07 (s, 3 H) 3.57 (t, J=6.88 Hz, 2 H) 3.76 (s, 3 H) 4.33 (t, J=6.88 Hz, 2 H) 8.08 (d, J=3.01 Hz, 1 H) 8.36 (d, J=3.01 Hz, 1 H)	1-Bromo-2-(methylsulfonyl) ethane

Intermediate 405: 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

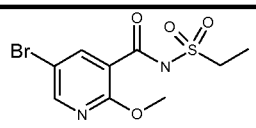
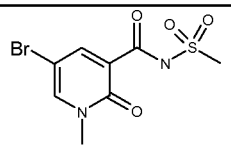


Methyl 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (**Intermediate 366**, 2.00 g, 8.13 mmol) was dissolved in MeOH (40 mL) and treated with sodium hydroxide (16.26 mL, 16.26 mmol). The reaction was stirred at room temperature for 2 hrs. The reaction was neutralized with 1 N HCl and the solvent was removed at reduced pressure. The residue was suspended in water and filtered to afford 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (1.77 g).

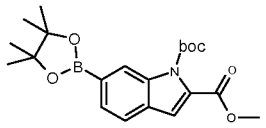
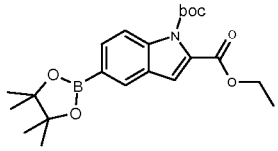
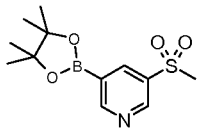
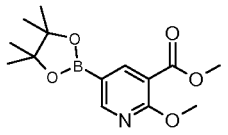
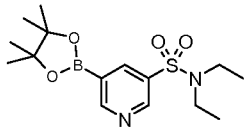
MS (ES): (M) 232 and 234 (M+2) for $C_7H_6BrNO_3$.

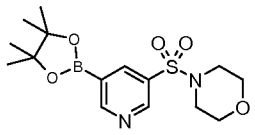
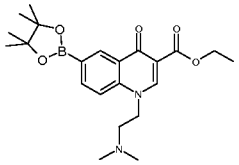
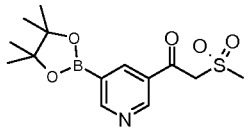
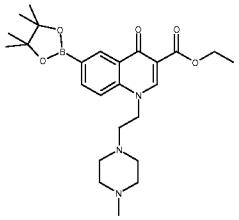
^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.62 (s, 3 H) 8.35 (d, J=2.83 Hz, 1 H) 8.61 (d, J=2.83 Hz, 1 H) 14.38 (s, 1 H)

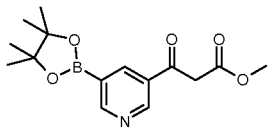
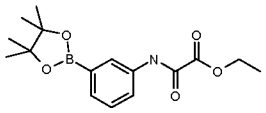
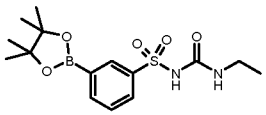
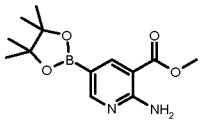
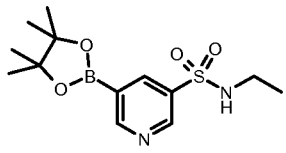
The following compounds were prepared using the general method described for **Intermediate 365** using the starting materials (SM) indicated.

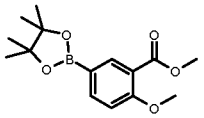
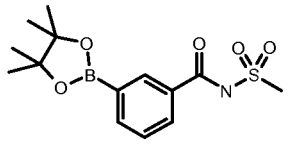
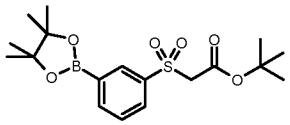
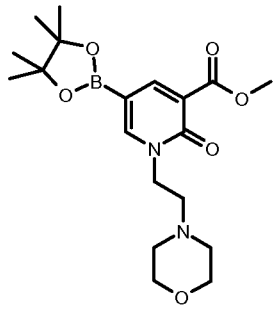
Int	Compound	Data	SM
Intermediate 406	 5-Bromo-N-(ethylsulfonyl)-2-methoxynicotinamide	MS(ES): 323 (M) and 325 (M+2) for $C_9H_{11}BrN_2O_4S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.28 (t, 3 H) 3.47 (q, *J*=7.35 Hz, 2 H) 3.93 (s, 3 H) 8.15 (d, *J*=2.45 Hz, 1 H) 8.47 (d, *J*=2.45 Hz, 1 H) 11.88 (br. s., 1 H)	Ethanesulfonamide and 5-bromo-2-methoxynicotinic acid
Intermediate 407	 5-Bromo-1-methyl-N-(methylsulfonyl)-2-oxo-1,2-dihydropyridine-3-carboxamide	MS(ES): 309 (M) and 311 (M+2) for $C_8H_9BrN_2O_4S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.38 (s, 3 H) 3.60 (s, 3 H) 8.39 (d, *J*=2.83 Hz, 1 H) 8.63 (d, *J*=2.83 Hz, 1 H) 12.65 (s, 1 H)	Methanesulfonamide and 5-bromo-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid **Intermediate 405**

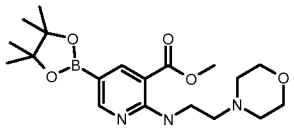
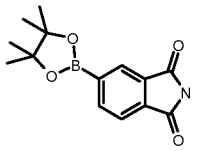
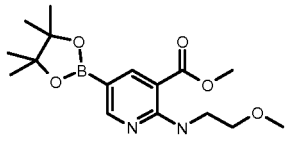
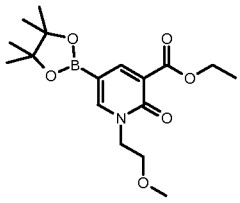
The following compounds were prepared using the general method described above for **Intermediate 134** using bis(pinacolato)diboron, 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride, potassium acetate and the starting material (SM) indicated.

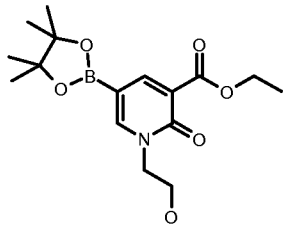
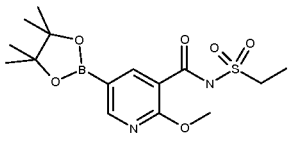
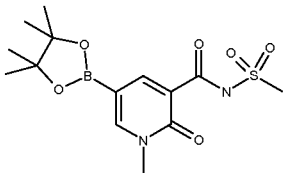
Int	Compound	Data	SM
Intermediate 408	 1-tert-butyl 2-methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-1,2-dicarboxylate	^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.31 (s, 12 H) 1.55 (s, 9 H) 3.87 (s, 3 H) 7.29 (s, 1 H) 7.58 (d, *J*=7.91 Hz, 1 H) 7.71 (d, *J*=7.91 Hz, 1 H) 8.38 (s, 1 H)	1-tert-butyl 2-methyl 6-bromo-1H-indole-1,2-dicarboxylate **Intermediate 386**
Intermediate 409	 1-tert-butyl 2-ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-1,2-dicarboxylate	^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.23 - 1.42 (m, 15 H) 1.56 (s, 9 H) 4.32 (q, *J*=7.16 Hz, 2 H) 7.32 (s, 1 H) 7.74 (dd, *J*=8.38, 1.04 Hz, 1 H) 7.96 (d, *J*=8.48 Hz, 1 H) 8.07 (s, 1 H)	1-tert-butyl 2-ethyl 5-bromo-1H-indole-1,2-dicarboxylate **Intermediate 387**
Intermediate 410	 3-(Methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine	^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.32 (s, 12 H) 3.34 (s, 3 H) 8.30 - 8.50 (m, 1 H) 9.01 (d, *J*=1.51 Hz, 1 H) 9.15 (d, *J*=2.45 Hz, 1 H)	3-Bromo-5-(methylsulfonyl) pyridine **Intermediate 390**
Intermediate 411	 Methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate	^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.29 (s, 12 H) 3.80 (s, 3 H) 3.95 (s, 3 H) 8.29 (d, *J*=1.88 Hz, 1 H) 8.54 (d, *J*=2.07 Hz, 1 H)	Methyl 5-bromo-2-methoxynicotinate
Intermediate 412	 N,N-diethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide	^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ ppm 1.06 (t, *J*=7.16 Hz, 6 H) 1.33 (s, 12 H) 3.20 (q, *J*=7.03 Hz, 4 H) 7.94 (s, 1 H) 8.22 (s, 1 H) 8.96 (s, 1 H)	5-Bromo-N,N-diethylpyridine-3-sulfonamide

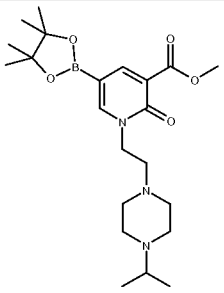
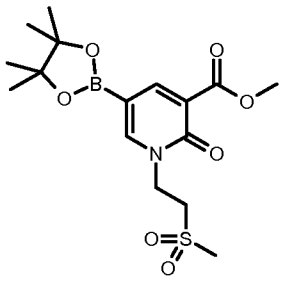
Int	Compound	Data	SM
Intermediate 413	 4-(5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-ylsulfonyl)morpholine	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.33 (s, 12 H) 2.81 - 3.08 (m, 4 H) 3.60 - 3.77 (m, 4 H) 7.94 (s, 1 H) 8.16 (s, 1 H) 9.03 (s, 1 H)	4-(5-Bromopyridin-3-ylsulfonyl)morpholine
Intermediate 414	 Ethyl 1-(2-(dimethylamino)ethyl)-4-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydroquinoline-3-carboxylate	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.21 - 1.35 (m, 15 H) 2.20 (s, 6 H) 2.54 - 2.68 (m, 2 H) 4.23 (q, J=6.97 Hz, 2 H) 4.38 - 4.59 (m, 2 H) 7.79 (d, J=8.85 Hz, 1 H) 7.90 - 8.00 (m, 1 H) 8.53 - 8.65 (m, 2 H)	Ethyl 1-(2-(dimethylamino)ethyl)-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylate **Intermediate 388**
Intermediate 415	 2-(Methylsulfonyl)-1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)ethanone	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.34 (s, 12 H) 3.14 (s, 3 H) 5.22 (br. s., 2 H) 8.49 (br. s., 1 H) 8.98 (br. s., 1 H) 9.28 (br. s., 1 H)	1-(5-Bromopyridin-3-yl)-2-(methylsulfonyl)ethanone
Intermediate 416	 Ethyl 1-(2-(4-methylpiperazin-1-yl)ethyl)-4-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydroquinoline-3-carboxylate	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.22 - 1.40 (m, 15 H) 2.02 - 2.47 (m, 11 H) 2.56 - 2.76 (m, 2 H) 4.12 - 4.33 (m, 2 H) 4.32 - 4.61 (m, 2 H) 7.71 - 8.71 (m, 4 H)	Ethyl 6-iodo-1-(2-(4-methylpiperazin-1-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **Intermediate 389**

Int	Compound	Data	SM
Intermediate 417	 Methyl 3-oxo-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)propanoate	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.33 (s, 12 H) 3.65 (s, 3 H) 4.33 (s, 2 H) 8.42 (s, 1 H) 8.98 (br. s., 1 H) 9.23 (br. s., 1 H)	Methyl 5-bromonicotinoyl acetate
Intermediate 418	 Ethyl 2-oxo-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamino)acetate	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.23 - 1.42 (m, 15 H) 4.31 (q, *J*=7.10 Hz, 2 H) 7.25 - 7.48 (m, 2 H) 7.76 - 7.87 (m, 1 H) 7.91 (s, 1 H) 10.73 (s, 1 H)	Ethyl 2-(3-bromophenylamino)-2-oxoacetate **Intermediate 393**
Intermediate 419	 N-(ethylcarbamoyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide	MS(ES): 355 (M+1) for $C_{15}H_{23}BN_2O_5S$	3-Bromo-N-(ethylcarbamoyl)benzenesulfonamide **Intermediate 394**
Intermediate 420	 Methyl 2-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.28 (s, 12 H) 3.83 (s, 3 H) 7.50 (s, 2 H) 8.28 (d, *J*=1.88 Hz, 1 H) 8.38 (d, *J*=2.07 Hz, 1 H)	Methyl 2-amino-5-bromo nicotinate
Intermediate 421	 N-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.98 (t, 3 H) 1.21 - 1.45 (m, 12 H) 2.66 - 2.90 (m, 2 H) 7.84 (t, *J*=5.46 Hz, 1 H) 8.23 - 8.40 (m, 1 H) 8.94 (d, *J*=1.13 Hz, 1 H) 9.01 (d, *J*=2.26 Hz, 1 H)	5-Bromo-N-ethylpyridine-3-sulfonamide **Intermediate 395**

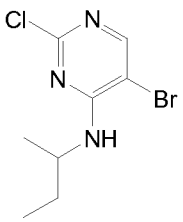
Int	Compound	Data	SM
Intermediate 422	 Methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.29 (s, 12 H) 3.78 (s, 3 H) 3.85 (s, 3 H) 7.16 (d, *J*=8.48 Hz, 1 H) 7.81 (dd, *J*=8.38, 1.98 Hz, 1 H) 7.96 (d, *J*=1.70 Hz, 1 H)	Methyl 5-iodo-2-methoxybenzoate
Intermediate 423	 N-(methylsulfonyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide	^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.38 (s, 12 H) 3.71 (s, 3 H) 7.53 (t, *J*=7.63 Hz, 1 H) 7.98 - 8.09 (m, 2 H) 8.16 (s, 1 H)	3-Bromo-N-(methylsulfonyl)benzamide **Intermediate 396**
Intermediate 424	 tert-butyl 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylsulfonyl)acetate	^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.36 (d, *J*=5.27 Hz, 21 H) 4.05 (s, 2 H) 7.58 (t, *J*=7.63 Hz, 1 H) 7.97 - 8.16 (m, 2 H) 8.38 (s, 1 H)	tert-Butyl 2-(3-bromophenylsulfonyl)acetate **Intermediate 392**
Intermediate 425	 Methyl 1-(2-morpholinoethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.28 (s, 12 H) 2.33 - 2.46 (m, 4 H) 2.46 - 2.60 (m, 2 H) 3.42 - 3.55 (m, 4 H) 3.74 (s, 3 H) 4.09 (t, *J*=6.03 Hz, 2 H) 8.12 (d, *J*=2.26 Hz, 1 H) 8.19 (d, *J*=2.07 Hz, 1 H)	Methyl 5-bromo-1-(2-morpholinoethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Intermediate 398**

Int	Compound	Data	SM
Intermediate 426	 Methyl 2-(2-morpholinoethylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.21 - 1.36 (m, 12 H) 2.29 - 2.66 (m, 6 H) 3.42 - 3.72 (m, 6 H) 3.84 (s, 3 H) 8.29 (d, *J*=2.07 Hz, 1 H) 8.33 - 8.54 (m, 2 H)	methyl 5-bromo-2-(2-morpholinoethylamino)nicotinate **Intermediate 399**
Intermediate 427	 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)isoindoline-1,3-dione	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.33 (s, 12 H) 7.83 (d, *J*=7.35 Hz, 1 H) 7.96 (s, 1 H) 8.08 (dd, *J*=7.35, 0.75 Hz, 1 H) 11.46 (br. s., 1 H)	4-bromophthalimide
Intermediate 428	 Methyl 2-(2-methoxyethylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.28 (s, 12 H) 3.29 (s, 3 H) 3.51 (t, *J*=5.46 Hz, 2 H) 3.66 (q, *J*=5.46 Hz, 2 H) 3.83 (s, 3 H) 8.23 - 8.37 (m, 2 H) 8.45 (d, *J*=1.88 Hz, 1 H)	Methyl 5-bromo-2-(2-methoxyethylamino)nicotinate **Intermediate 400**
Intermediate 429	 Ethyl 1-(2-methoxyethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.21 - 1.38 (m, 15 H) 3.23 (s, 3 H) 3.50 - 3.66 (m, 2 H) 4.09 - 4.28 (m, 4 H) 8.08 (d, *J*=2.07 Hz, 1 H) 8.12 (d, *J*=2.26 Hz, 1 H)	Ethyl 5-bromo-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Intermediate 401**

Int	Compound	Data	SM
Intermediate 430	 Ethyl 1-(2-hydroxyethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.21 - 1.35 (m, 15 H) 3.62 (q, *J*=5.15 Hz, 2 H) 4.03 (t, *J*=4.99 Hz, 2 H) 4.21 (q, *J*=7.10 Hz, 2 H) 4.86 (t, *J*=5.46 Hz, 1 H) 8.03 - 8.18 (m, 2 H)	Ethyl 5-bromo-1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Intermediate 402**
Intermediate 431	 N-(ethylsulfonyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinamide	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.20 - 1.40 (m, 15 H) 3.45 (q, *J*=7.16 Hz, 2 H) 3.96 (s, 3 H) 8.05 (d, *J*=1.88 Hz, 1 H) 8.51 (d, *J*=1.88 Hz, 1 H) 11.75 (s, 1 H)	5-Bromo-N-(ethylsulfonyl)-2-methoxynicotinamide **Intermediate 406**
Intermediate 432	 1-Methyl-N-(methylsulfonyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxamide	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.30 (s, 12 H) 3.36 (br. s., 3 H) 3.63 (s, 3 H) 8.31 - 8.61 (m, 2 H) 12.55 (br. s., 1 H)	5-Bromo-1-methyl-N-(methylsulfonyl)-2-oxo-1,2-dihydropyridine-3-carboxamide **Intermediate 407**

Int	Compound	Data	SM
Intermediate 433	 Methyl 1-(2-(4-isopropylpiperazin-1-yl)ethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.93 (d, *J*=6.59 Hz, 6 H) 1.21 - 1.29 (m, 12 H) 1.79 (br. s., 2 H) 2.29 - 2.44 (m, 8 H) 2.52 - 2.66 (m, 1 H) 3.73 (s, 3 H) 4.07 (t, *J*=5.84 Hz, 2 H) 8.05 - 8.19 (m, 2 H)	Methyl 5-bromo-1-(2-(4-isopropylpiperazin-1-yl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Intermediate 403**
Intermediate 434	 Methyl 1-(2-(methylsulfonyl)ethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate	^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.29 (s, 12 H) 3.07 (s, 3 H) 3.56 (t, *J*=6.88 Hz, 2 H) 3.75 (s, 3 H) 4.38 (t, *J*=6.97 Hz, 2 H) 8.14 (d, *J*=2.07 Hz, 1 H) 8.32 (d, *J*=2.07 Hz, 1 H)	Methyl 5-bromo-1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Intermediate 404**

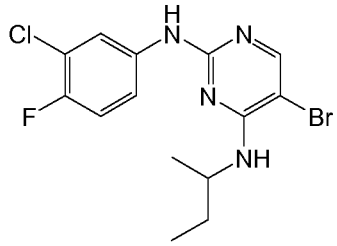
Intermediate 435: 5-bromo-N-butan-2-yl-2-chloropyrimidin-4-amine



Prepared using the general method described above for **Intermediate 1** using 5-bromo-2,4-dichloro-pyrimidine and butan-2-amine. MS(ES): 265.8 (M+2) for $C_8H_{11}BrClN_3$.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 0.93 - 1.03 (m, 3 H), 1.26 (d, *J*=6.59 Hz, 3 H), 1.55 - 1.70 (m, 2 H), 4.06 - 4.36 (m, 1 H), 5.30 (s, 1 H), 8.12 (s, 1 H).

Intermediate 436: 5-bromo-N'-butan-2-yl-N-(3-chloro-4-fluorophenyl)pyrimidine-2,4-diamine

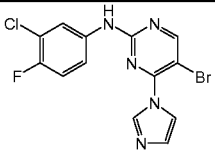


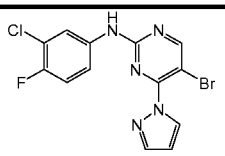
Prepared using the general method described above for **Intermediate 26** using **Intermediate 435** and 3-chloro-4-fluoroaniline.

MS(ES): 375 (M+2) for $C_{14}H_{15}BrClFN_4$.

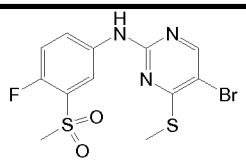
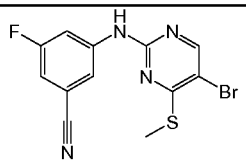
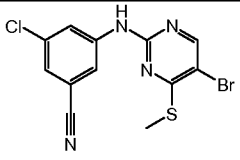
1H NMR (300 MHz, CHLOROFORM-D) δ ppm 0.98 - 1.03 (m, 3 H), 1.29 (d, *J*=6.59 Hz, 3 H), 1.55 - 1.70 (m, 2 H), 4.06 - 4.30 (m, 1 H), 5.17 (m, 1 H), 7.07 (m, 1 H), 7.23 (m, 2 H), 7.97-8.00 (m, 2 H).

The following intermediates were prepared using the general method described above for **Intermediate 112** using **Intermediate 69** and the starting material (SM) indicated.

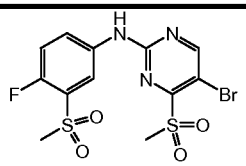
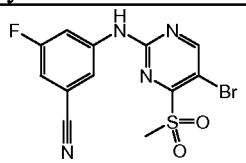
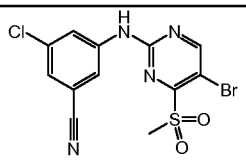
Int	Compound	Data	SM
Intermediate 437	 5-bromo-N-(3-chloro-4-fluorophenyl)-4-imidazol-1-ylpyrimidin-2-amine	MS(ES): 370 (M+2) for $C_{13}H_8BrClFN_5$. 1H NMR (300 MHz, DMSO-D6) δ ppm 7.18 (s, 1 H), 7.40 (t, *J*=9.14 Hz, 1 H), 7.58 - 7.67 (m, 1 H), 7.82 (s, 1 H), 7.98 (dd, *J*=6.78, 2.64 Hz, 1 H), 8.39 (s, 1 H), 8.86 (s, 1 H), 10.33 (s, 1 H).	imidazole

Int	Compound	Data	SM
Intermediate 438	 5-bromo-N-(3-chloro-4-fluorophenyl)-4-pyrazol-1-ylpyrimidin-2-amine	MS(ES): 369.9 (M+2) for $C_{13}H_8BrClFN_5$. 1H NMR (300 MHz, DMSO-D6) δ ppm 6.67 (dd, *J*=2.64, 1.70 Hz, 1 H), 7.40 (t, *J*=9.14 Hz, 1 H), 7.57 - 7.73 (m, 1 H), 7.94 (d, *J*=0.94 Hz, 1 H), 8.00 (dd, *J*=6.78, 2.64 Hz, 1 H), 8.47 (d, *J*=2.07 Hz, 1 H), 8.83 (s, 1 H), 10.28 (s, 1 H).	pyrazole

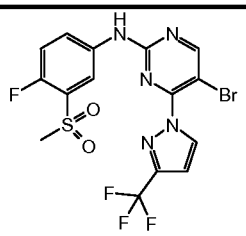
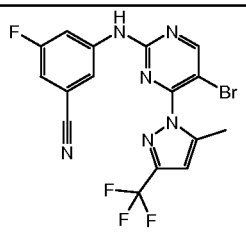
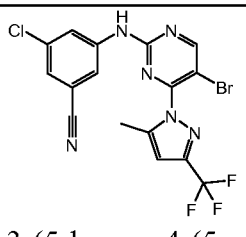
The following intermediates were prepared using the general method described above for **Intermediate 65** using 5-bromo-2-chloro-4-(methylthio)pyrimidine and the starting material (SM) indicated.

Int	Compound	Data	SM
Intermediate 439	 5-bromo-N-(4-fluoro-3-methylsulfonylphenyl)-4-methylsulfanylpyrimidin-2-amine	MS(ES): 393.8 (M+2) for $C_{12}H_{11}BrFN_3O_2S_2$. 1H NMR (300 MHz, DMSO-D6) δ ppm 2.59 (s, 3 H), 3.32 (s, 3 H), 7.35 - 7.61 (m, 1 H), 7.83 - 8.02 (m, 1 H), 8.36 (s, 1 H), 8.46 (dd, *J*=6.22, 2.83 Hz, 1 H), 10.16 (s, 1 H).	4-fluoro-3-(methylsulfonyl)aniline
Intermediate 440	 3-(5-bromo-4-(methylthio)pyrimidin-2-ylamino)-5-fluorobenzonitrile	MS(ES): 340.8 (M+2) for $C_{12}H_8BrFN_4S$. 1H NMR (300 MHz, DMSO-D6) δ ppm 2.60 (s, 3 H), 7.32 - 7.49 (m, 1 H), 7.93 - 8.00 (m, 1 H), 8.02 (t, *J*=1.60 Hz, 1 H), 8.42 (s, 1 H), 10.31 (s, 1 H).	3-amino-5-fluorobenzonitrile
Intermediate 441	 3-(5-bromo-4-(methylthio)pyrimidin-2-ylamino)-5-chlorobenzonitrile	MS(ES): 357 (M+2) for $C_{12}H_8BrClN_4S$. 1H NMR (300 MHz, DMSO-D6) δ ppm 2.60 (s, 3 H), 7.48 - 7.68 (m, 1 H), 8.08 - 8.14 (m, 1 H), 8.19 (t, *J*=1.98 Hz, 1 H), 8.43 (s, 1 H), 10.29 (s, 1 H).	3-amino-5-chlorobenzonitrile

The following intermediates were prepared using the general method described above for **Intermediate 69** using m-CPBA and the starting material (SM) indicated.

Int	Compound	Data	SM
Intermediate 442	 5-bromo-N-(4-fluoro-3-(methylsulfonyl)phenyl)-4-(methylsulfonyl)pyrimidin-2-amine	MS(ES): 426 (M+2) for $C_{12}H_{11}BrFN_3O_4S_2$. 1H NMR (300 MHz, DMSO-D6) δ ppm 3.34 (s, 3 H), 3.45 - 3.52 (m, 3 H), 7.53 (t, *J*=9.42 Hz, 1 H), 7.85 - 8.02 (m, 1 H), 8.30 (dd, *J*=6.12, 2.73 Hz, 1 H), 8.96 (s, 1 H), 10.70 (s, 1 H).	**Intermediate 439**
Intermediate 443	 3-(5-bromo-4-(methylsulfonyl)pyrimidin-2-ylamino)-5-fluorobenzonitrile	MS(ES): 372.7 (M+2) for $C_{12}H_8BrFN_4O_2S$. 1H NMR (300 MHz, DMSO-D6) δ ppm 3.49 (s, 3 H), 7.41 - 7.58 (m, 1 H), 7.89 - 8.07 (m, 2 H), 9.03 (s, 1 H), 10.88 (s, 1 H).	**Intermediate 440**
Intermediate 444	 3-(5-bromo-4-(methylsulfonyl)pyrimidin-2-ylamino)-5-chlorobenzonitrile	MS(ES): 389 (M+2) for $C_{12}H_8BrClN_4O_2S$.	**Intermediate 441**

The following intermediates were prepared using the general method described above for **Intermediate 112** using the starting materials (SM) indicated.

Int	Compound	Data	SM
Intermediate 445	 5-bromo-N-(4-fluoro-3-(methylsulfonyl)phenyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine	MS(ES): 481.7 (M+2) for $C_{15}H_{10}BrF_4N_5O_2S$. 1H NMR (300 MHz, DMSO-D6) δ ppm 3.35 (s, 3 H), 7.15 (d, *J*=2.64 Hz, 1 H), 7.52 (t, *J*=9.42 Hz, 1 H), 7.84 - 8.12 (m, 1 H), 8.43 (dd, *J*=6.12, 2.73 Hz, 1 H), 8.68 (d, *J*=1.51 Hz, 1 H), 8.93 (s, 1 H), 10.61 (s, 1 H).	**Intermediate 443** and 3-(trifluoromethyl)-1H-pyrazole
Intermediate 446	 3-(5-bromo-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-5-fluorobenzonitrile	MS(ES): 443 (M+2) for $C_{16}H_9BrF_4N_6$. 1H NMR (300 MHz, DMSO-D6) δ ppm 2.42 (s, 3 H), 6.88 (s, 1 H), 7.37 - 7.60 (m, 1 H), 7.80 - 8.15 (m, 2 H), 9.07 (s, 1 H), 10.79 (s, 1 H).	**Intermediate 443** and 5-methyl-3-(trifluoromethyl)-1H-pyrazole
Intermediate 447	 3-(5-bromo-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-ylamino)-5-chlorobenzonitrile	MS(ES): 459 (M+2) for $C_{16}H_9BrClF_3N_6$. 1H NMR (300 MHz, DMSO-D6) δ ppm 2.42 (s, 3 H), 6.88 (s, 1 H), 7.66 (s, 1 H), 8.00 - 8.23 (m, 2 H), 9.07 (s, 1 H), 10.75 (s, 1 H).	**Intermediate 444** and 5-methyl-3-(trifluoromethyl)-1H-pyrazole

Intermediate 448: 5-bromo-N-(3,5-dimethoxyphenyl)-4-hydrazinylpyrimidin-2-amine

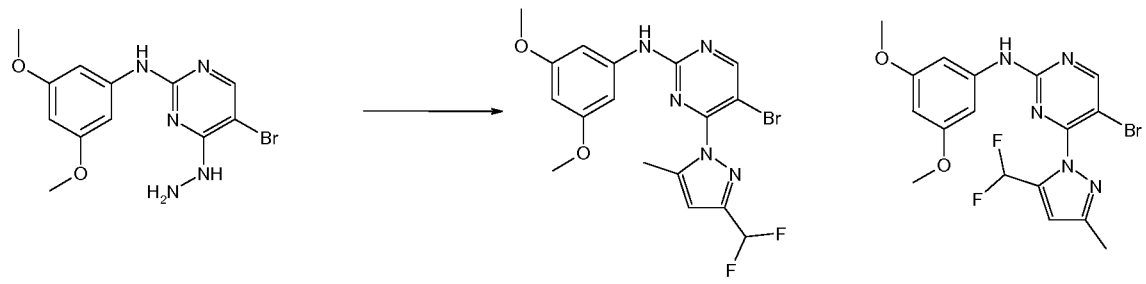


5-bromo-N-(3,5-dimethoxyphenyl)-4-(methylthio)pyrimidin-2-amine **Intermediate 363** (1 g, 2.81 mmol), hydrazine anhydrous (12 ml, 382.34 mmol) and dioxane (4 mL) were combined to give a white suspension. The reaction mixture was heat at 100 °C for 2 hours. The reaction mixture was cooled over an ice bath and 60 ml of water was slowly added. The precipitated solid was filtered and washed with water to give the crude title compound (462 mg), used without further purification in the next step.

MS (Electrospray): 341.18 (MH^+) for $C_{12}H_{14}BrN_5O_2$

Intermediate 449: 5-bromo-4-(3-(difluoromethyl)-5-methyl-1H-pyrazol-1-yl)-N-(3,5-dimethoxyphenyl)pyrimidin-2-amine

Intermediated 450: 5-bromo-4-(5-(difluoromethyl)-3-methyl-1H-pyrazol-1-yl)-N-(3,5 dimethoxyphenyl)pyrimidin-2-amine



5-bromo-N-(3-chloro-4-fluorophenyl)-4-hydrazinylpyrimidin-2-amine (487 mg, 1.43 mmol), 1,1-difluoropentane-2,4-dione (214 mg, 1.57 mmol), acetic acid (0.082 mL, 1.43 mmol) and butan-1-ol (4 mL) were combined to give a yellow suspension. The mixture was heated at 150 °C for one hour. The resulting mixture of two product isomers was separated using flash chromatography, silica gel, 5-45% ethyl acetate in hexanes.

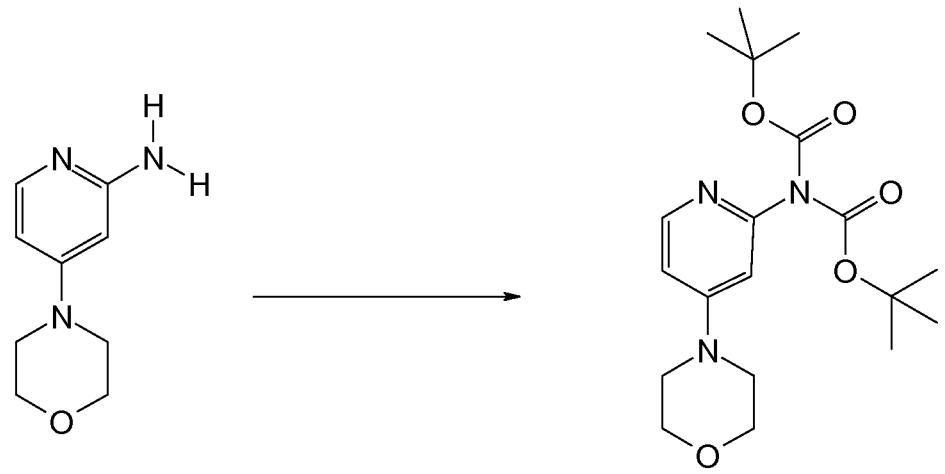
Intermediate 449 was isolated as a solid (210 mg).

Intermediate 450 was isolated as a solid (102 mg).

MS:ES+ 440 for $C_{17}H_{16}BrF_2N_5O_2$

These materials gave the same mass spectral results and were taken onto the next step without further characterization. The assigned regioisomeric identities of these intermediates were based on NMR analysis of the products obtained in the next reactions.

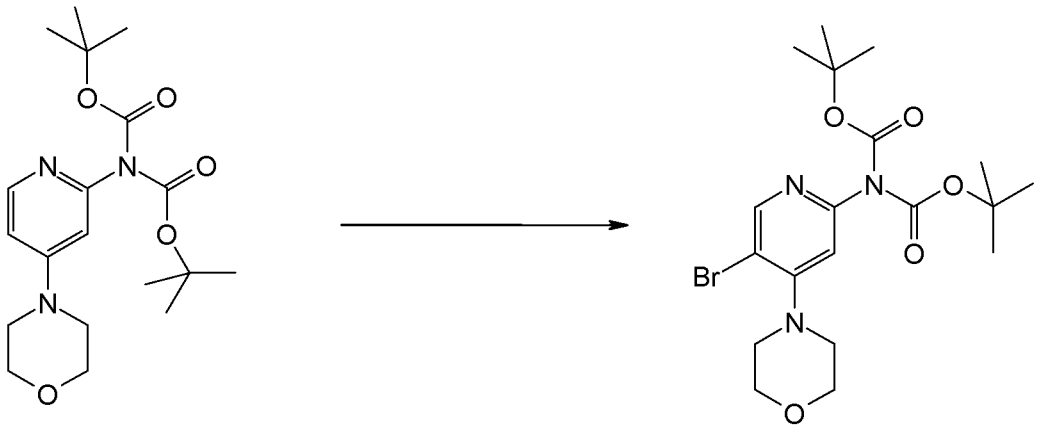
Intermediate 451: tert-butyl N-[(2-methylpropan-2-yl)oxycarbonyl]-N-(4-morpholin-4-ylpyridin-2-yl)carbamate



4-morpholinopyridin-2-amine (prepared according to literature procedure *: Bioorganic & Medicinal Chemistry Letters*, 16(4), 839-844, **2006**) (1.082 g, 6.04 mmol), di-t-butyl-dicarbonate (1.542 mL, 6.64 mmol), and TEA (1.010 mL, 7.24 mmol) were combined in Dioxane (20 mL) to give a colorless solution. DMAP (0.738 g, 6.04 mmol) was added and the mixture allowed to stir at RT for 2 hours, then heated to 70 °C for 1 hour. An additional amount of di-t-butyl-dicarbonate (2 g, 9.17 mmol) was added and the mixture was heated at 70 °C overnight. The reaction mixture was concentrated and diluted with methylene chloride and water. The layers were separated and the organic layer was washed with water, dried over Na_2SO_4 then concentrated. The resulting residue was triturated with diethyl ether, filtered and further washed with diethyl ether to give the pure title compound. (1.654 g).

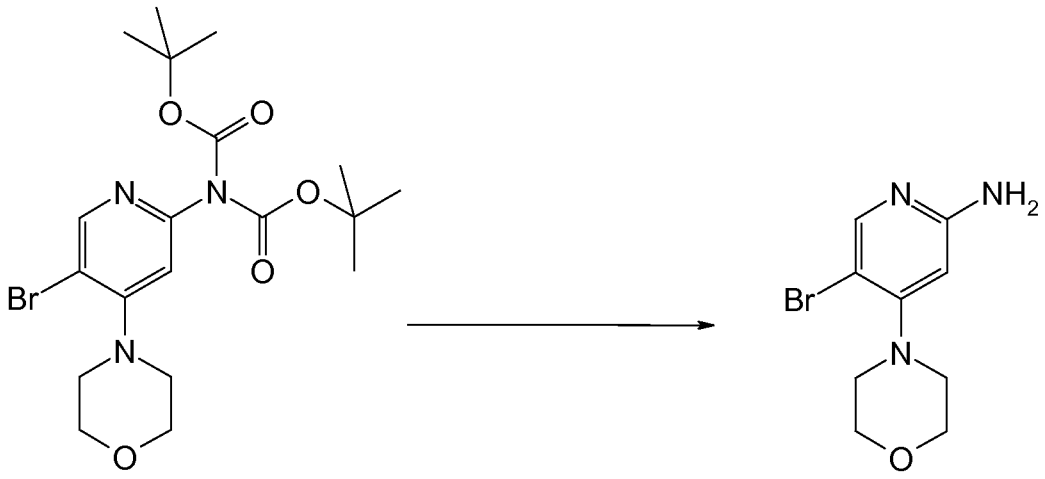
MS (Electrospray): 380.45 (MH^+) for $C_{19}H_{29}N_3O_5$

Intermediate 452: tert-butyl N-(5-bromo-4-morpholin-4-ylpyridin-2-yl)-N-[(2-methylpropan-2-yl)oxycarbonyl]carbamate



tert-butyl N-[(2-methylpropan-2-yl)oxycarbonyl]-N-(4-morpholin-4-ylpyridin-2-yl)carbamate **Intermediate 451** (51 mg, 0.29 mmol) was dissolved in DMF (20 mL). N-bromosuccinimide (51.6 mg, 0.29 mmol) was added and the mixture was heated to 85 °C for 1 hour. The mixture was concentrated and purified by flash chromatography (silica gel column, 40 g, eluted with 0-40% ethyl acetate in hexanes) to give the title compound. (95 mg). MS (Electrospray): 459.35 (MH^+) for $C_{19}H_{28}BrN_3O_5$

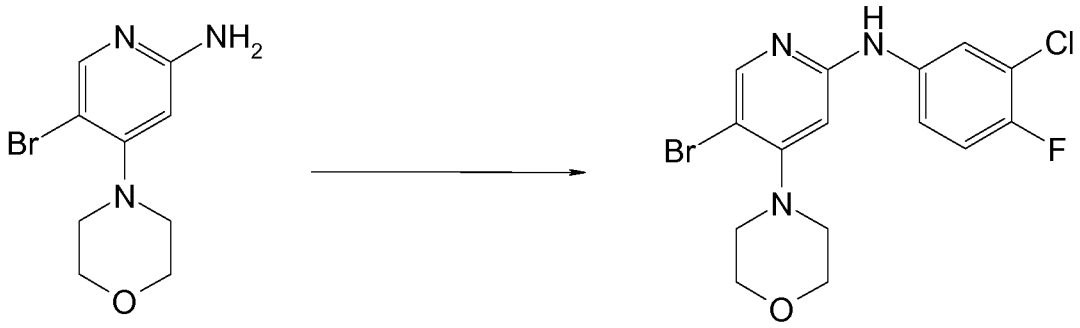
Intermediate 453: 5-bromo-4-morpholinopyridin-2-amine



tert-butyl N-(5-bromo-4-morpholin-4-ylpyridin-2-yl)-N-[(2-methylpropan-2-yl)oxycarbonyl]carbamate **Intermediate 452** (1.632 g, 3.56 mmol) was dissolved in anhydrous MeOH (10 ml) and HCl 4M in Dioxane (2.67 ml, 10.68 mmol) was added. The

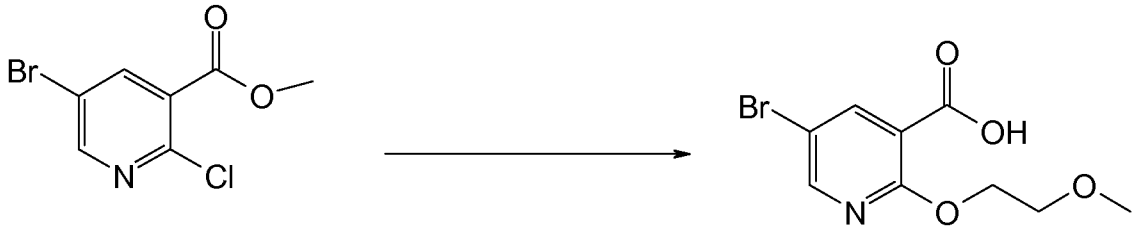
mixture was allowed to stir at rt ovenight, then heat at 50 °C for 7 hours. The reaction mixture was concentrated to give the crude title compound (926 mg) which was used in the next step without further purification. MS (Electrospray): 259.12 (MH^+) for $C_9H_{12}BrN_3O$

Intermediate 454: 5-bromo-N-(3-chloro-4-fluorophenyl)-4-morpholinopyridin-2-amine



5-bromo-4-morpholinopyridin-2-amine **Intermediate 453** (320 mg, 0.97 mmol), 3-chloro-4-fluorophenylboronic acid (337 mg, 1.93 mmol), and 5-bromo-4-morpholinopyridin-2-amine (320 mg, 0.97 mmol) were combined with methylene chloride (5 ml) to give a yellow solution. Copper (II) acetate (176 mg, 0.97 mmol) was added followed by anhydrous powdered 3 angstrom molecular sieves (200 mg). The mixture was allowed to stir at rt overnight. Filtration, evaporation and purification by flash chromatography (0-100% ethyl acetate in hexanes) afforded the title compound (82 mg). MS (Electrospray): 387.65 (MH^+) for $C_{15}H_{14}BrClFN_3O$

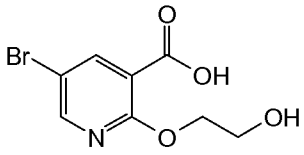
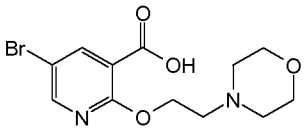
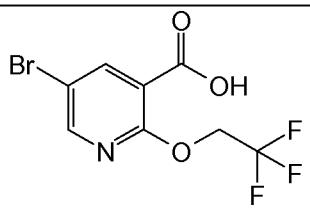
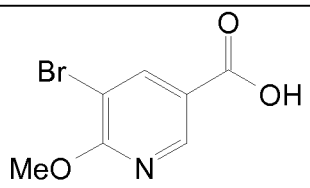
Intermediate 455: 5-bromo-2-(2-methoxyethoxy)nicotinic acid



methyl 5-bromo-2-chloronicotinate (500 mg, 2.00 mmol) and 2-methoxyethanol (456 mg, 5.99 mmol) were combined in tert-butanol (20 mL) to give a yellow solution. Sodium 2-methylpropan-2-olate (576 mg, 5.99 mmol) was added. The mixture was heated at 90 °C for 1 hour then concentrated. 1 N HCl was added to the residue followed by extraction with ethyl acetate. The organic layer was washed with water then brine, dried with $MgSO_4$ and

concentrated to give the title compound (454 mg). MS (Electrospray): 277.08 (MH^+) for $C_9H_{10}BrNO_4$

The compounds in the table below were prepared using this procedure and the specified starting materials.

Compound	Structure	Mass spectrum and ^1H NMR	SM
Intermediate 456	 5-bromo-2-(2-hydroxyethoxy)nicotinic acid	MS(ES): 263.06 (M+1) for $C_8H_8BrNO_4$	5-bromo-2-chloronicotinic acid and ethylene glycol
Intermediate 457	 5-bromo-2-(2-morpholinoethoxy)nicotinic acid	MS(ES); 331.16 (M+1) for $C_{12}H_{15}BrN_2O_4$	5-bromo-2-chloronicotinic acid and 2-morpholino ethanol
Intermediate 458	 5-bromo-2-(2,2,2-trifluoroethoxy)nicotinic acid	MS(ES); 301.03 (M+1) for $C_8H_5BrF_3NO_3$	5-bromo-2-chloronicotinic acid and 2,2,2-trifluoroethanol
Intermediate 459	 5-bromo-6-methoxynicotinic acid	MS(ES): 232.03 (M+1)for $C_7H_6BrNO_3$	5-bromo-2-chloronicotinic acid and methanol

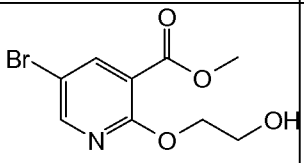
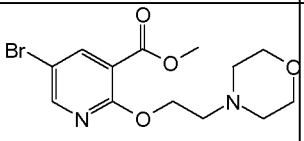
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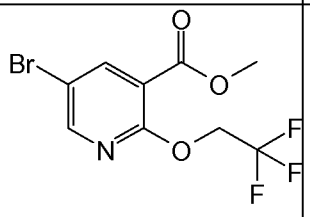
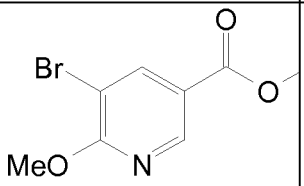
Intermediate 460: methyl 5-bromo-2-(2-methoxyethoxy)nicotinate



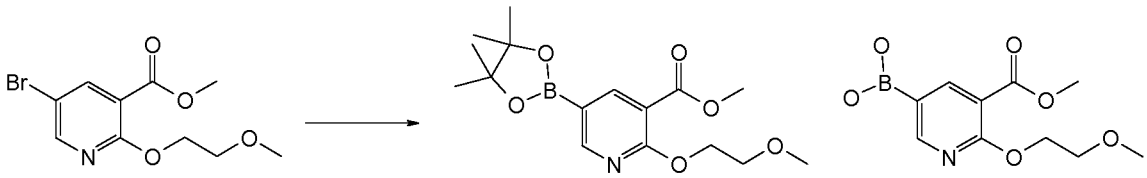
5-bromo-2-(2-methoxyethoxy)nicotinic acid **Intermediate 455** (454 mg, 1.64 mmol) was dissolved in anhydrous methanol (20 mL) and H_2SO_4 (0.088 mL, 1.64 mmol) was added to give a brown solution. The mixture was stirred overnight at room temperature. An additional amount of H_2SO_4 (0.088 mL, 1.64 mmol) was added and the mixture was heated at 60 °C for 5 hours. The reaction mixture was concentrated down to dryness, ethyl acetate followed by water was added and the layers were separated. The organic layer was washed with water, then brine and dried over $MgSO_4$. Evaporation gave the title compound (440 mg). MS (Electrospray): 291.11 (MH^+) for $C_{10}H_{12}BrNO_4$

The compounds in the table below were prepared using this procedure and the specified starting materials.

Compound	Structure	Mass spectrum and ^1H NMR	SM
Intermediate 461	 methyl 5-bromo-2-(2-hydroxyethoxy)nicotinate	MS(ES): 277.08 (M+1) for $C_9H_{10}BrNO_4$	5-bromo-2-(2-hydroxyethoxy)nicotinic acid **Intermediate 456**
Intermediate 462	 methyl 5-bromo-2-(2-morpholinoethoxy)nicotinate	MS(ES): 346.19 (M+1) for $C_{13}H_{17}BrN_2O_4$	5-bromo-2-(2-morpholinoethoxy)nicotinic acid **Intermediate 457**

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 463	 methyl 5-bromo-2-(2,2,2-trifluoroethoxy)nicotinate	MS(ES): 315.06 (M+1) for $C_9H_7BrF_3NO_3$	5-bromo-2-(2,2,2-trifluoroethoxy)nicotinic acid **Intermediate 458**
Intermediate 464	 methyl 5-bromo-6-methoxynicotinate	MS(ES): 246.06 (M+1)for $C_8H_8BrNO_3$	5-bromo-6-methoxynic otinic acid Intermediate 459

Intermediate 465: methyl 2-(2-methoxyethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate and 5-(methoxycarbonyl)-6-(2-methoxyethoxy)pyridin-3-ylboronic acid

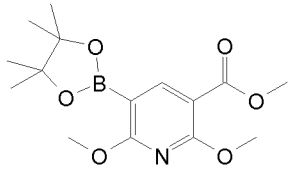
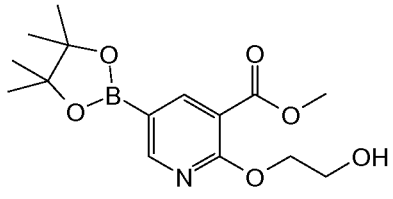
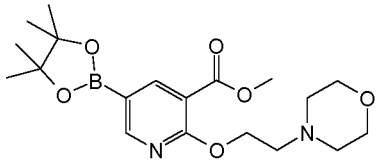
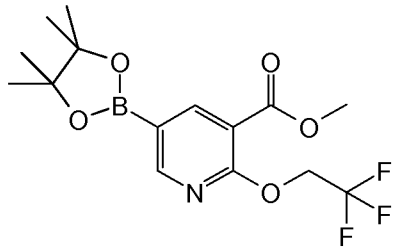


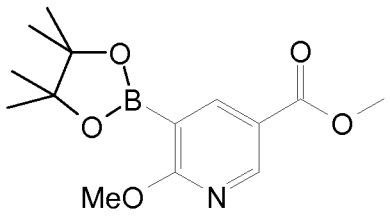
methyl 5-bromo-2-(2-methoxyethoxy)nicotinate **Intermediate 460** (440 mg, 1.52 mmol), bis(pinacolato)diboron (539 mg, 2.12 mmol), and potassium acetate (447 mg, 4.55 mmol) were combined in 1,4-dioxane (20 mL). PdCl2(dppf)-CH_2Cl_2 Adduct (1239 mg, 1.52 mmol) was added and the reaction was degassed with argon then heated to 90 °C for 3 hours. Purification by flash chromatography (10-100% ethyl acetate in hexanes) afforded the title compound as a mixture of boronic acid and pinacol ester (365 mg, ester: acid 1:1 mixture).

MS (Electrospray): 338.18 (MH^+) for $C_{16}H_{24}BNO_6$

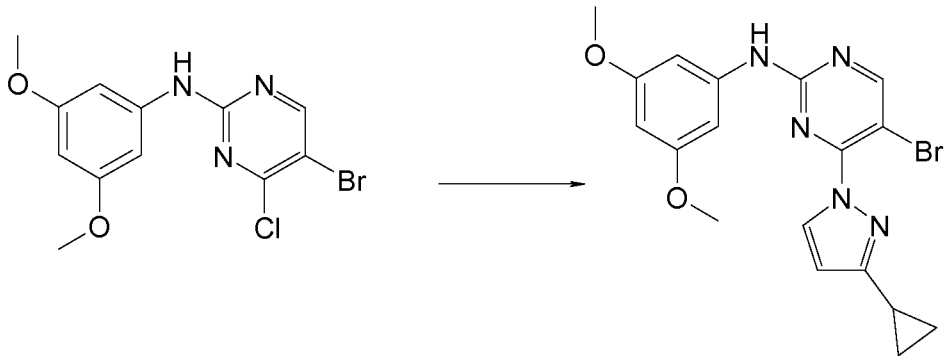
MS (Electrospray): 256.03 (MH^+) for $C_{10}H_{14}BNO_6$

The compounds in the below table were prepared using this procedure and the specified starting materials.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 466	 methyl 2,6-dimethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate	MS(ES):323.15 (M) for $C_{15}H_{22}BNO_6$	methyl 5-bromo-2,6-dimethoxynicotinate
Intermediate 467	 methyl 2-(2-hydroxyethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate	MS(ES): 323.15 (M) for $C_{15}H_{22}BNO_6$	methyl 5-bromo-2-(2-hydroxyethoxy)nicotinate **Intermediate 461**
Intermediate 468	 methyl 2-(2-morpholinoethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate	MS(ES): 392.25 (M) for $C_{19}H_{29}BN_2O_6$	methyl 5-bromo-2-(2-morpholinoethoxy)nicotinate **Intermediate 462**
Intermediate 469	 methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(2,2,2-trifluoroethoxy)nicotinate	MS(ES): 361.12 (M) for $C_{15}H_{19}BF_3NO_5$	methyl 5-bromo-2-(2,2,2-trifluoroethoxy)nicotinate **Intermediate 463**

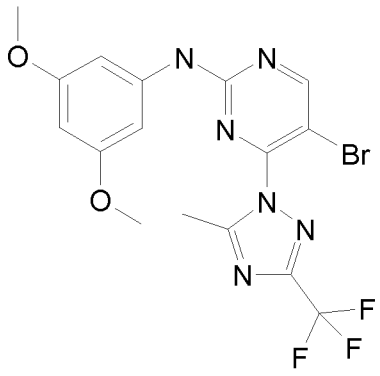
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 470	 methyl 6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate	MS(ES):293.12 (M) for $C_{14}H_{20}BNO_5$	methyl 5-bromo-6-methoxynicotinate **Intermediate 464**

Intermediate 471: 5-bromo-4-(3-cyclopropyl-1H-pyrazol-1-yl)-N-(3,5-dimethoxyphenyl)pyrimidin-2-amine



NaH (0.07 g, 1.75 mmol) was suspended in anhydrous NMP (5 mL) and cooled to 0 °C, 3-cyclopropyl-1H-pyrazole (0.235 g, 2.18 mmol) was then added slowly and the mixture was stirred for 15 minutes. 5-Bromo-4-chloro-N-(3,5-dimethoxyphenyl)pyrimidin-2-amine **Intermediate 213** (0.5 g, 1.45 mmol) in a solution of 10 ml of NMP under argon was added and the reaction mixture was allowed to warm to room temperature overnight. Water (60 ml) was added to give a precipitate, which was filtered, washed with water and dried under vacuum to give the title compound as an off- white solid (503 mg). MS (Electrospray): 417.27 (MH^+) for $C_{18}H_{18}BrN_5O_2$

The compound below was prepared according the above procedure for **Intermediate 471** using the specified starting materials.

Compound	Structure	Mass spectrum	SM
Intermediate 472	 5-bromo-N-(3,5-dimethoxyphenyl)-4-(5-methyl-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)pyrimidin-2-amine	MS: ES+460.22 for (M+1) $C_{16}H_{14}BrF_3N_6O_2$	5-bromo-4-chloro-N-(3,5-dimethoxyphenyl) pyrimidin-2-amine **Intermediate 213** and 5-methyl-3-(trifluoromethyl)-1H-1,2,4-triazole

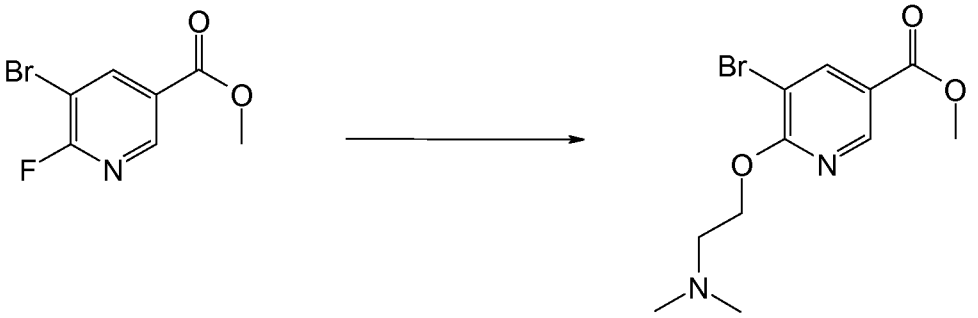
Intermediate 473: methyl 5-bromo-6-fluoronicotinate



Methyl 5-bromo-6-chloronicotinate (2.885 g, 11.52 mmol), potassium fluoride (2.68 g, 46.07 mmol), and tetraphenylphosphonium bromide (2.90 g, 6.91 mmol) combined in acetonitrile (75 mL) to give a yellow suspension. The reaction mixture was warmed at reflux or overnight. Additional potassium fluoride(1 g, 17 mmol) was added and the mixture was refluxed for 5 days more. Evaporation and purification by flash chromatography (0-25% ethyl acetate in hexanes) afforded the title compound (1.53 g).

MS (Electrospray): 235.02 (MH^+) for $C_7H_5BrFNO_2$

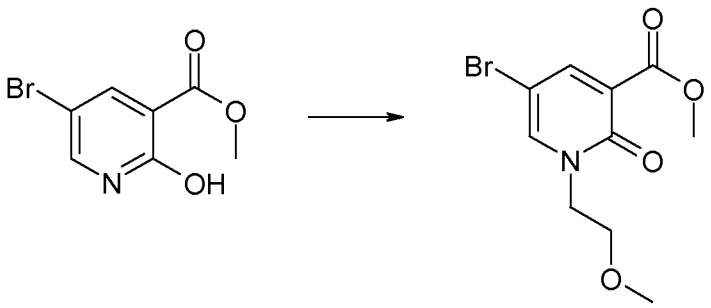
Intermediate 474: Methyl 5-bromo-6-(2-(dimethylamino)ethoxy)nicotinate



2-(dimethylamino)ethanol (503 mg, 5.64 mmol) was dissolved in THF (6 mL) and cooled to 0 °C. 1M Lithium bis(trimethylsilyl)amide in THF (6.41 mL, 6.41 mmol) was added slowly and the mixture was allowed stir for 15 minutes. A solution of methyl 5-bromo-6-fluoronicotinate **Intermediate 473** (600 mg, 2.56 mmol) in THF (4ml) was then added to the reaction mixture. The reaction was allowed to reach room temperature over 4 hours, 1M NH_4Cl and dichloromethane were added and the layers were separated. The water layer was extracted with 5% methanol in methylene chloride. The pooled organic layers were dried over $MgSO_4$ and purified by flash chromatography (3-10% methanol in methylene chloride) to afford the title compound (312 mg).

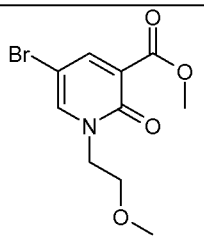
MS (Electrospray): 304.15 (MH^+) for $C_{11}H_{15}BrN_2O_3$

Intermediate 475: methyl 5-bromo-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

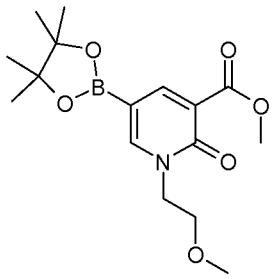


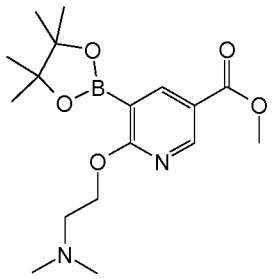
Sodium hydride (0.207 g, 5.17 mmol) was suspended in DMF (12 mL) in an oven dried flask under nitrogen and treated with methyl 5-bromo-2-hydroxynicotinate (1.2 g, 5.17 mmol). The mixture was stirred at room temperature for 30 minutes then 2-Bromoethyl methylether (1.458 mL, 15.52 mmol) was added dropwise. The mixture was then heated at 60 °C overnight. The mixture was diluted with water and extracted with EtOAc. The extracts were

washed with brine, dried over sodium sulfate, and the solvent removed at reduced pressure. The residue was purified by flash chromatography, silica gel, 20-100 % EtOAc in DCM to afford the desired product.

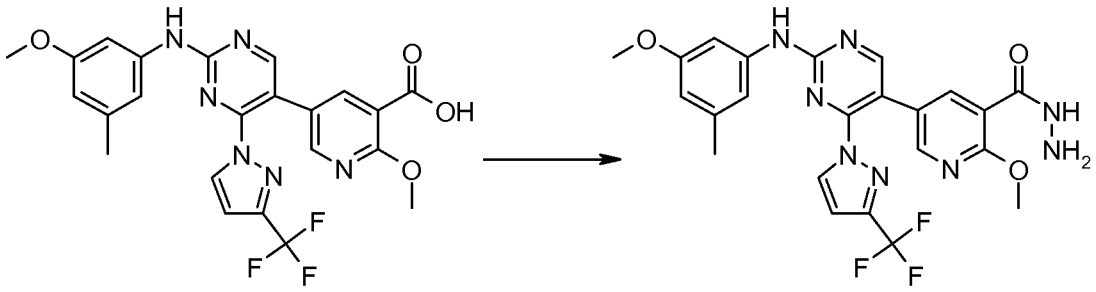
Compound	Structure	^{1}H NMR	SM
Intermediate 475	 methyl 5-bromo-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate	1H NMR (300 MHz, DMSO-d6) δ ppm 3.24 (s, 3 H) 3.57 (t, J=5.27 Hz, 2 H) 3.75 (s, 3 H) 4.10 (t, J=5.27 Hz, 2 H) 8.05 (d, J=2.83 Hz, 1 H) 8.22 (d, J=2.83 Hz, 1 H)	methyl 5-bromo-2-hydroxynicotinate

The following compounds were prepared using the general method described above for **Intermediate 134** using bis(pinacolato)diboron, 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride, potassium acetate and the starting material (SM) indicated.

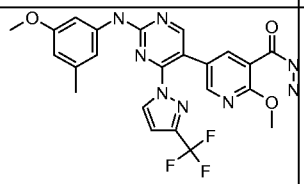
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 476	 methyl 1-(2-methoxyethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate	MS(ES): 338 (M+1) for $C_{16}H_{24}BNO_6$. 1H NMR (300 MHz, DMSO-d6) δ ppm 1.28 (s, 12 H) 3.23 (s, 3 H) 3.56 (t, J=5.18 Hz, 2 H) 3.74 (s, 3 H) 4.17 (t, J=5.18 Hz, 2 H) 8.13 (q, J=2.07 Hz, 2 H)	methyl 5-bromo-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Intermediate 476-B	 methyl 6-(2-(dimethylamino)ethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate	MS(ES): 351 (M+1) for $C_{17}H_{27}BN_2O_5$.	**Intermediate 474** methyl 5-bromo-6-(2-(dimethylamino)ethoxy)nicotinate

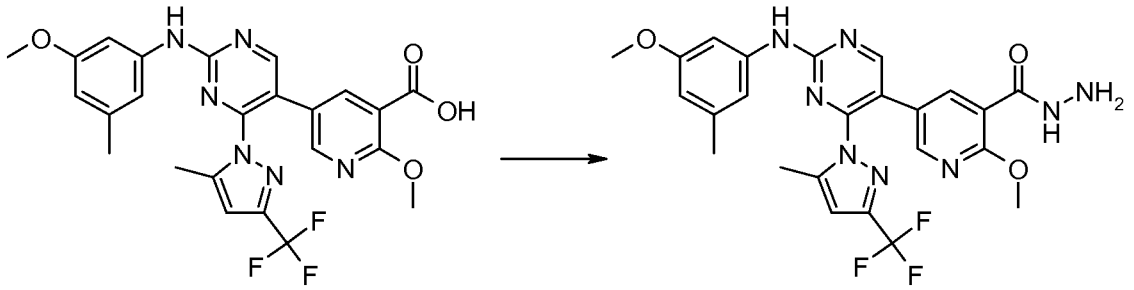
Intermediate 477: 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carbohydrazide



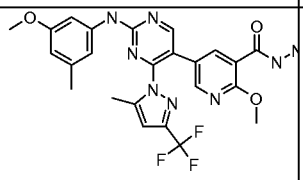
To a solution of 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid (**Example 760**, 0.15 mmol, 75 mg) in CH_2Cl_2 (10 mL), were added Hydrazine monohydrate (0.38 mmol, 19 mg), triethylamine (0.6 mmol, 0.08 mL), 2-chloro-1-methylpyridinium iodide (0.19 mmol, 48 mg) and 4-(Dimethylamino)pyridine (0.03 mmol, 4 mg) and stirred overnight at RT. Six batches of the same size were run and all the reaction mixtures were combined, diluted with dichloromethane (10 mL) and further washed with 25% citric acid solution (2 x 10 mL), water (15 mL) and brine (15 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by flash chromatography (product eluted with 2 -3% MeOH in $CHCl_3$) to afford 300 mg of the title compound.

Compound	Structure	Mass spectrum	SM
Intermediate 477	 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carbohydrazide	MS (ES): 515 (M+1) for $C_{23}H_{21}F_3N_8O_3$.	**Example 760** 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoro methyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

Intermediate 478: 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carbohydrazide

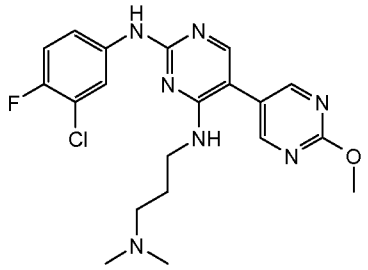


To a solution of 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid (**Example 761**, 0.19 mmol, 100 mg) in DMSO (2 mL) was added triethylamine (0.97 mmol, 98 mg) and stirred for 10 min. To this, 2-chloro-1-methyl-pyridinium iodide (0.23 mmol, 60 mg), 4-(dimethylamino)pyridine (0.038 mmol, 5 mg) and hydrazine hydrate (0.48 mmol, 24 mg, 0.023 mL) were added and stirred for 4 h at RT. The reaction mixture was diluted with DCM (25 mL) and further washed with 25% citric acid solution (2 x 15 mL), water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by flash chromatography (product eluted with 1-2% MeOH in $CHCl_3$) to afford the title compound as 85 mg of white solid.

Compound	Structure	Mass spectrum	SM
Intermediate 478	 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carbohydrazide	MS(ES): 529(M+1) for $C_{24}H_{23}F_3N_8O_3$. (66 % pure by LCMS).	**Example 761** 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

Examples

Example 1: N^2-(3-chloro-4-fluorophenyl)-N^4-(3-(dimethylamino)propyl)-2'-methoxy-5,5'-bipyrimidine-2,4-diamine

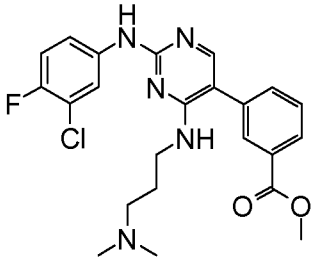
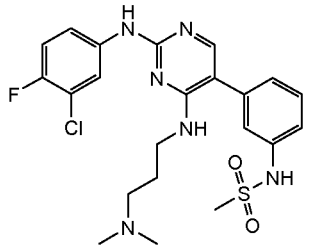


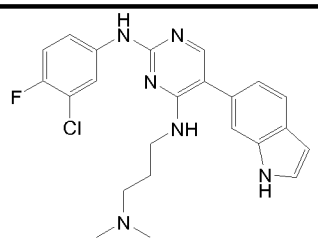
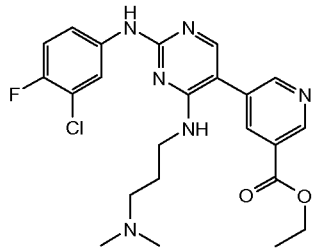
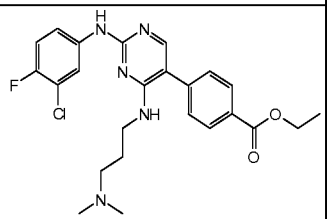
A suspension of 5-bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(3-dimethylamino-propyl)-pyrimidine-2,4-diamine (**Intermediate 26**, 160 mg, 0.40 mmol), 2-methoxy-5-pyrimidineboronic acid (92 mg, 0.60 mmol), tris(dibenzylideneacetone)dipalladium(0) (36.3 mg, 0.04 mmol), 2-dicyclohexylphosphino-2',4',6'-triiso-propyl-1,1'-biphenyl (56.7 mg, 0.12 mmol) and sodium carbonate (42.0 mg, 0.40 mmol) in acetonitrile/water (4ml:1ml) was degassed with bubbling nitrogen for 10 min. and then heated to 90 °C. After 1 h LC-MS indicated complete reaction, and the reaction mixture was diluted with ethyl acetate (50 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated. Flash chromatography (12g column, 0-6% MeOH/CH_2Cl_2 with 0.75% triethylamine) provided 125 mg of the desired product.

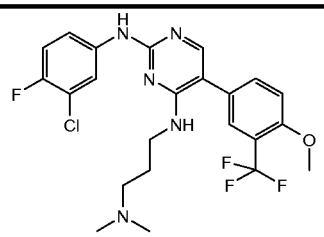
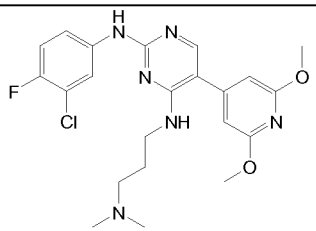
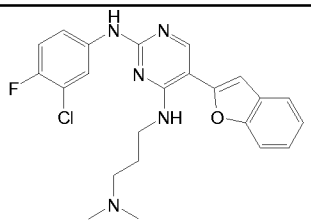
MS: ES+ 432 for $C_{20}H_{23}ClFN_7O$.

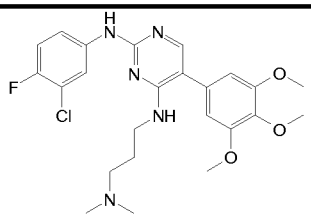
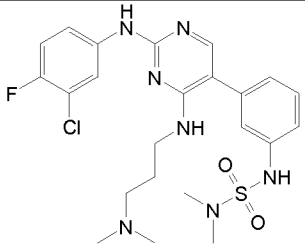
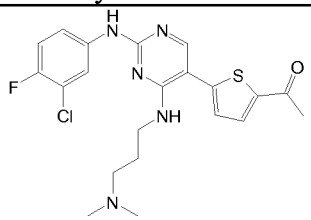
1H NMR (300 MHz, DMSO-D6) δ ppm 1.58 - 1.75 (m, 2 H) 2.02 (s, 6 H) 2.27 (t, *J*=6.59 Hz, 2 H) 3.34 - 3.44 (m, 2 H) 3.95 (s, 3 H) 7.23 - 7.37 (m, 2 H) 7.55 - 7.67 (m, 1 H) 7.74 - 7.80 (m, 1 H) 8.25 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.56 (s, 2 H) 9.42 (s, 1 H).

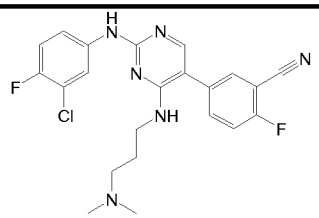
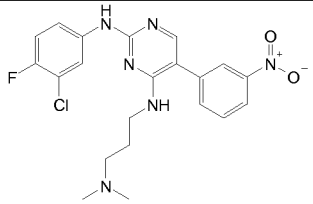
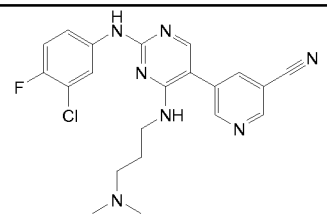
The following examples were prepared using the general method described above for Example 1 using 5-bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(3-dimethylamino-propyl)-pyrimidine-2,4-diamine (**Intermediate 26**) and the starting material (SM) indicated.

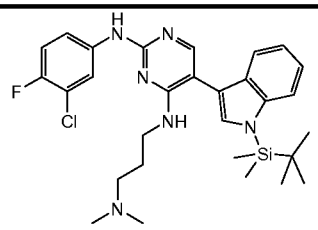
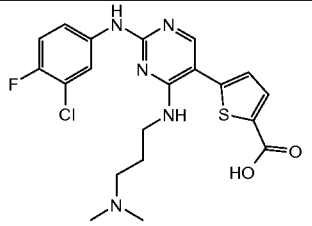
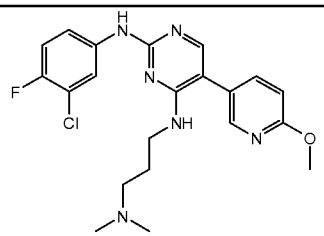
Ex	Compound	Data	SM
2	 methyl 3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino) propylamino) pyrimidin-5-yl)benzoate	MS: ES+ 458 for $C_{23}H_{25}ClFN_5O_2$ 1H NMR (300 MHz, DMSO-D6) δ ppm 1.59 - 1.74 (m, 2 H) 1.93 (s, 6 H) 2.27 (t, *J*=6.31 Hz, 2 H) 3.37 - 3.49 (m, 2 H) 3.86 (s, 3 H) 7.19 - 7.34 (m, 2 H) 7.56 - 7.70 (m, 3 H) 7.78 (s, 1 H) 7.85 - 8.00 (m, 2 H) 8.25 (dd, *J*=6.97, 2.64 Hz, 1 H) 9.40 (s, 1 H)	3-(methoxy carbonyl) phenylboronic acid
3	 N-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino) propylamino) pyrimidin-5-yl)phenyl) methanesulfonamide	MS: ES+ 494 for $C_{22}H_{26}ClFN_6O_2S$ 1H NMR (300 MHz, DMSO-D6) δ ppm 1.84 - 2.03 (m, 2 H) 2.75 (d, *J*=4.71 Hz, 6 H) 2.95 - 3.14 (m, 5 H) 3.33 - 3.49 (m, 2 H) 7.13 (d, *J*=7.72 Hz, 1 H) 7.18 - 7.30 (m, 2 H) 7.37 - 7.50 (m, 2 H) 7.51 - 7.75 (m, 2 H) 7.86 (s, 1 H) 8.04 (dd, *J*=6.78, 2.45 Hz, 1 H) 9.50 (s, 1 H) 9.95 (s, 1 H) 10.30 (s, 1 H)	3-(methyl-sulfonamido) phenylboronic acid

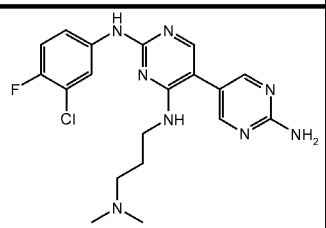
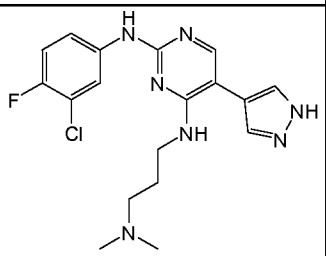
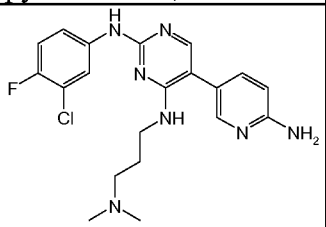
Ex	Compound	Data	SM
4	 N^2-(3-chloro-4-fluorophenyl)-N^4-(3-(dimethylamino)propyl)-5-(1*H*-indol-6-yl)pyrimidine-2,4-diamine	MS: ES+ 439 for $C_{23}H_{24}ClFN_6$ 1H NMR (300 MHz, DMSO-D6) δ ppm 1.60 - 1.73 (m, 2 H) 1.92 (s, 6 H) 2.29 (t, *J*=6.31 Hz, 2 H) 3.38 - 3.50 (m, 2 H) 6.41 - 6.49 (m, 1 H) 6.95 (dd, *J*=8.10, 1.51 Hz, 1 H) 7.07 (t, *J*=5.09 Hz, 1 H) 7.28 (t, *J*=9.14 Hz, 1 H) 7.33 - 7.39 (m, 2 H) 7.56 - 7.68 (m, 2 H) 7.76 (s, 1 H) 8.27 (dd, *J*=6.97, 2.64 Hz, 1 H) 9.30 (s, 1 H) 11.17 (s, 1 H)	1*H*-indol-6-ylboronic acid
5	 Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino) propylamino) pyrimidin-5-yl) nicotinate	MS: ES+ 473 for $C_{23}H_{26}ClFN_6O_2$ 1H NMR (300 MHz, DMSO-D6) δ ppm 1.34 (t, *J*=7.06 Hz, 3 H) 1.85 - 2.01 (m, 2 H) 2.75 (d, *J*=4.71 Hz, 6 H) 2.96 - 3.10 (m, 2 H) 3.33 - 3.49 (m, 2 H) 4.38 (q, *J*=7.16 Hz, 2 H) 7.38 - 7.63 (m, 2 H) 7.91 - 8.16 (m, 3 H) 8.32 (t, *J*=1.98 Hz, 1 H) 8.85 (s, 1 H) 9.14 (s, 1 H) 9.73 (s, 1 H) 10.74 (s, 1 H)	ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate
6	 Ethyl 4-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino) propylamino) pyrimidin-5-yl) benzoate	MS: ES+ 472 for $C_{24}H_{27}ClFN_5O_2$ 1H NMR (300 MHz, DMSO-D6) δ ppm 1.32 (t, *J*=7.06 Hz, 3 H) 1.60 - 1.75 (m, 2 H) 1.96 (s, 6 H) 2.28 (t, *J*=6.41 Hz, 2 H) 3.37 - 3.52 (m, 2 H) 4.33 (q, *J*=7.10 Hz, 2 H) 7.22 - 7.36 (m, 2 H) 7.52 (d, *J*=8.48 Hz, 2 H) 7.57 - 7.68 (m, 1 H) 7.83 (s, 1 H) 8.01 (d, *J*=8.48 Hz, 2 H) 8.25 (dd, *J*=6.97, 2.64 Hz, 1 H) 9.44 (s, 1 H)	4-(ethoxy carbonyl) phenyl boronic acid

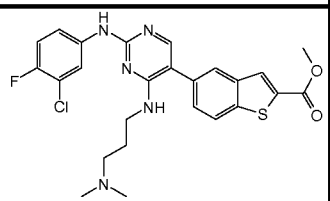
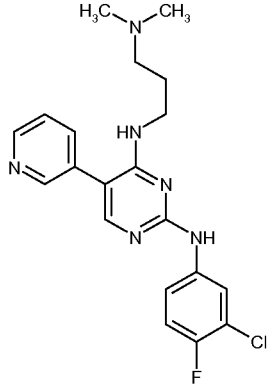
Ex	Compound	Data	SM
7	 N^2-(3-chloro-4-fluorophenyl)-N^4-(3-(dimethylamino) propyl)-5-(4-methoxy-3(trifluoromethyl) phenyl)pyrimidine-2,4-diamine	MS: ES+ 498 for $C_{23}H_{24}ClF_4N_5O$ 1H NMR (300 MHz, DMSO-D6) δ ppm 1.91 (m, 2 H) 2.74 (d, *J*=4.71 Hz, 6 H) 2.95 - 3.11 (m, 2 H) 3.33 - 3.47 (m, 2 H) 3.94 (s, 3 H) 7.43 (dd, *J*=20.25, 8.76 Hz, 2 H) 7.50 - 7.59 (m, 1 H) 7.59 - 7.81 (m, 3 H) 7.87 (s, 1 H) 8.02 (dd, *J*=6.78, 2.26 Hz, 1 H) 9.37 - 9.59 (m, 1 H) 10.35 (s, 1 H)	4-methoxy-3-(trifluoro methyl)pheny lboronic acid
8	 N^2-(3-chloro-4-fluorophenyl)-5-(2,6-dimethoxypyridin-4-yl)-N^4-(3-(dimethylamino)propyl)pyrimidine-2,4-diamine	MS: ES+ 461 for $C_{22}H_{26}ClFN_6O_2$ 1H NMR (300 MHz, DMSO-D6) δ ppm 1.58 - 1.70 (m, 2 H) 1.98 (s, 6 H) 2.25 (t, *J*=6.50 Hz, 2 H) 3.34 - 3.44 (m, 2 H) 3.76 - 3.94 (m, 6 H) 6.36 - 6.49 (m, 1 H) 6.82 (t, *J*=5.18 Hz, 1 H) 7.26 (t, *J*=9.14 Hz, 1 H) 7.43 - 7.55 (m, 1 H) 7.56 - 7.66 (m, 2 H) 8.26 (dd, *J*=6.88, 2.54 Hz, 1 H) 9.27 (s, 1 H)	2,6-dimethoxy pyridin-4-yl boronic acid
9	 5-(benzofuran-2-yl)-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-(dimethylamino) propyl)pyrimidine-2,4-diamine	MS: ES+ 440 for $C_{23}H_{23}ClFN_5O$ 1H NMR (300 MHz, DMSO-D6) δ ppm 1.69 - 1.82 (m, 2 H) 2.08 (s, 6 H) 2.35 (t, *J*=6.59 Hz, 2 H) 3.49 - 3.62 (m, 2 H) 7.08 (d, *J*=0.75 Hz, 1 H) 7.21 - 7.45 (m, 3 H) 7.49 - 7.76 (m, 4 H) 8.24 (dd, *J*=6.97, 2.64 Hz, 1 H) 8.35 (s, 1 H) 9.64 (s, 1 H)	benzofuran-2-ylboronic acid

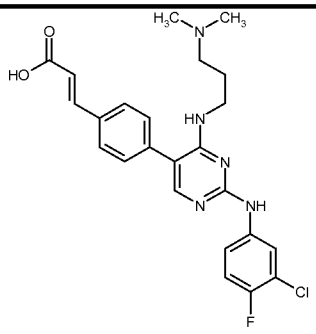
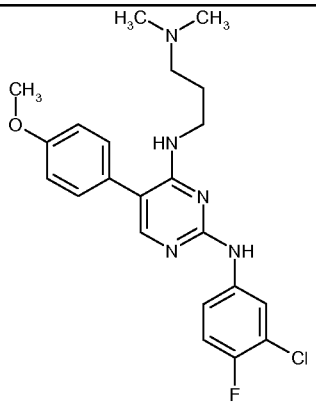
Ex	Compound	Data	SM
10	 N^2-(3-chloro-4-fluorophenyl)-N^4-(3-(dimethylamino) propyl)-5-(3,4,5-trimethoxyphenyl) pyrimidine-2,4-diamine	MS: ES+ 490 for $C_{24}H_{29}ClFN_5O_3$ 1H NMR (300 MHz, DMSO-D6) δ ppm 1.61 - 1.75 (m, 2 H) 1.99 (s, 6 H) 2.28 (t, *J*=6.69 Hz, 2 H) 3.42 (q, *J*=6.15 Hz, 2 H) 3.68 (s, 3 H) 3.80 (s, 6 H) 6.62 (s, 2 H) 7.12 (s, 1 H) 7.27 (t, *J*=9.14 Hz, 1 H) 7.47 - 7.65 (m, 1 H) 7.79 (s, 1 H) 8.27 (dd, *J*=6.97, 2.64 Hz, 1 H) 9.33 (s, 1 H)	3,4,5-trimethoxy phenylboronic acid
11	 *N*'-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[3-(dimethylamino) propyl]amino} pyrimidin-5-yl) phenyl]-*N*,*N*-dimethylsulfamide	MS: ES+ 522 for $C_{23}H_{29}ClFN_7O_2S$ 1H NMR (300 MHz, DMSO-D6) δ ppm 1.88 - 2.03 (m, 2 H) 2.72 (s, 12 H) 2.98 - 3.12 (m, 2 H) 3.39 - 3.52 (m, 2 H) 6.64 - 6.79 (m, 1 H) 7.07 (d, *J*=7.54 Hz, 1 H) 7.12 - 7.23 (m, 1 H) 7.25 - 7.44 (m, 2 H) 7.56 - 7.68 (m, 1 H) 7.75 (s, 1 H) 8.18 (dd, *J*=6.78, 2.45 Hz, 1 H) 9.44 (s, 1 H) 9.79 (s, 1 H) 10.03 (s, 1 H)	3-(*N*,*N*-dimethyl sulfamoyl amino)phenyl boronic acid
12	 1-{5-[2-(3-chloro-4-fluorophenylamino)-4-[3-(dimethylamino) propylamino) pyrimidin-5-yl] thiophen-2-yl}ethanone	MS: ES+ 448 for $C_{21}H_{23}ClFN_5OS$ 1H NMR (300 MHz, DMSO-D6) δ ppm 1.64 - 1.78 (m, Hz, 2 H) 2.04 (s, 6 H) 2.32 (t, *J*=6.31 Hz, 2 H) 2.54 (s, 3 H) 3.40 - 3.53 (m, 2 H) 7.20 - 7.36 (m, 2 H) 7.53 - 7.67 (m, 2 H) 7.95 - 8.04 (m, 2 H) 8.21 (dd, *J*=6.97, 2.64 Hz, 1 H) 9.58 (s, 1 H)	5-acetyl thiophen-2-yl boronic acid

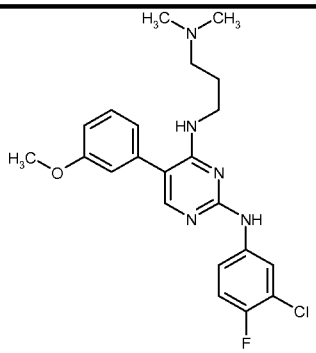
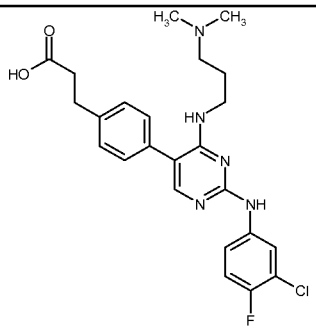
Ex	Compound	Data	SM
13	 5-{2-(3-chloro-4-fluorophenylamino)-4-[3-(dimethylamino)propyl amino]pyrimidin-5-yl}-2-fluorobenzonitrile	MS: ES+ 443 for $C_{22}H_{21}ClF_2N_6$	3-cyano-4-fluorophenyl boronic acid
14	 N^2-(3-chloro-4-fluorophenyl)-N^4-[3-(dimethylamino)propyl]-5-(3-nitrophenyl) pyrimidine-2,4-diamine	MS: ES+ 445 for $C_{21}H_{22}ClFN_6O_2$ 1H NMR (300 MHz, DMSO-D6) δ ppm 1.59 - 1.75 (m, Hz, 2 H) 1.98 (s, 6 H) 2.28 (t, *J*=6.50 Hz, 2 H) 3.37 - 3.51 (m, 2 H) 7.24 - 7.36 (m, 2 H) 7.57 - 7.67 (m, 1 H) 7.74 (t, *J*=7.82 Hz, 1 H) 7.80 - 7.91 (m, 2 H) 8.13 - 8.33 (m, 3 H) 9.47 (s, 1 H)	3-nitrophenyl boronic acid
15	 5-{2-(3-chloro-4-fluorophenylamino)-4-[3-(dimethylamino) propylamino] pyrimidin-5-yl} nicotinonitrile	MS: ES+ 426 for $C_{21}H_{21}ClFN_7$ 1H NMR (300 MHz, DMSO-D6) δ ppm 1.85 - 2.02 (m, 2 H) 2.75 (d, *J*=4.33 Hz, 6 H) 3.05 (dd, *J*=9.70, 4.80 Hz, 2 H) 3.41 (t, *J*=5.97 Hz, 2 H) 7.44 (t, *J*=9.04 Hz, 1 H) 7.52 - 7.63 (m, 1 H) 7.87 - 8.08 (m, 3 H) 8.39 (t, *J*=1.98 Hz, 1 H) 8.89 (d, *J*=2.07 Hz, 1 H) 9.07 (d, *J*=1.88 Hz, 1 H) 9.88 (s, 1 H) 10.61 (s, 1 H)	5-cyano pyridin-3-yl boronic acid

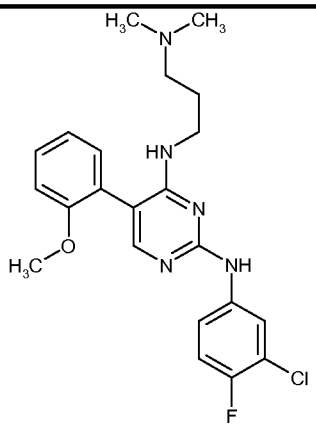
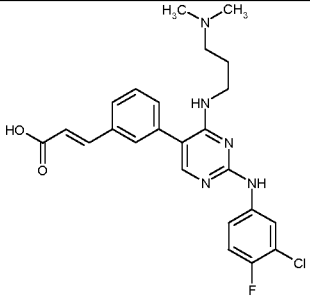
Ex	Compound	Data	SM
16	 5-[1-(*tert*-butyldimethylsilyl)-1*H*-indol-3-yl]-N^2-(3-chloro-4-fluorophenyl)-N^4-[3-(dimethyl amino)propyl] pyrimidine-2,4-diamine	MS: ES+ 553 for $C_{29}H_{38}ClFN_6Si$ 1H NMR (300 MHz, DMSO-D6) δ ppm 0.64 (s, 6 H) 0.93 (s, 9 H) 1.86 - 2.02 (m, 2 H) 2.74 (d, *J*=4.71 Hz, 6 H) 2.93 - 3.12 (m, 2 H) 3.32 - 3.50 (m, 2 H) 7.08 - 7.28 (m, 2 H) 7.43 - 7.51 (m, 1 H) 7.51 - 7.60 (m, 2 H) 7.63 (d, *J*=8.29 Hz, 1 H) 7.87 - 7.97 (m, 2 H) 8.01 (dd, *J*=6.69, 2.35 Hz, 1 H) 9.68 (s, 1 H) 10.79 (s, 1 H)	1-(*tert*-butyldimethy lsilyl)-1*H*-indol-3-yl boronic acid
17	 5-{2-(3-chloro-4-fluorophenylamino)-4-[3-(dimethylamino) propylamino] pyrimidin-5-yl} thiophene-2-carboxylic acid	MS: ES+ 450 for $C_{20}H_{21}ClFN5O_2S$ 1H NMR (300 MHz, DMSO-D6) δ ppm 1.89 - 2.04 (m, 2 H) 2.75 (d, *J*=4.71 Hz, 6 H) 3.00 - 3.14 (m, 2 H) 3.38 - 3.51 (m, 2 H) 7.26 (d, *J*=3.77 Hz, 1 H) 7.33 - 7.48 (m, 2 H) 7.53 - 7.64 (m, 1 H) 7.76 (d, *J*=3.77 Hz, 1 H) 8.03 (s, 1 H) 8.10 (dd, *J*=6.88, 2.54 Hz, 1 H) 9.50 (s, 1 H) 9.96 (s, 1 H)	5-borono thiophene-2-carboxylic acid
18	 N^2-(3-chloro-4-fluorophenyl)-N^4-[3-(dimethylamino) propyl]-5-(6-methoxy pyridin-3-yl) pyrimidine-2,4-diamine	MS: ES+ 431 for $C_{21}H_{24}ClFN_6O$ 1H NMR (300 MHz, DMSO-D6) δ ppm 1.84 - 1.99 (m, 2 H) 2.74 (d, *J*=4.71 Hz, 6 H) 2.94 - 3.09 (m, 2 H) 3.32 - 3.46 (m, 2 H) 3.90 (s, 3 H) 6.95 (d, *J*=8.67 Hz, 1 H) 7.40 - 7.59 (m, 2 H) 7.73 (dd, *J*=8.67, 2.45 Hz, 1 H) 7.81 - 8.05 (m, 3 H) 8.20 (d, *J*=2.26 Hz, 1 H) 9.66 (s, 1 H) 10.63 (s, 1 H)	2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyridine

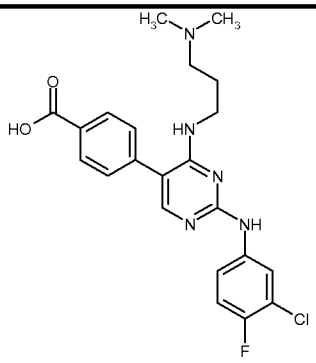
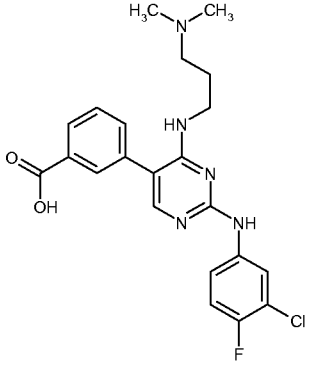
Ex	Compound	Data	SM
19	 N^2-(3-chloro-4-fluorophenyl)-N^4-[3-(dimethylamino) propyl]-5,5'-bipyrimidine-2,2',4-triamine	MS: ES+ 417 for $C_{19}H_{22}ClFN_8$ 1H NMR (300 MHz, DMSO-D6) δ ppm 1.82 - 1.99 (m, 2 H) 2.74 (d, *J*=2.83 Hz, 6 H) 2.93 - 3.15 (m, 2 H) 3.30 - 3.46 (m, 2 H) 6.87 (s, 1 H) 7.25 - 7.49 (m, 2 H) 7.52 - 7.62 (m, 1 H) 7.78 (s, 1 H) 8.06 - 8.16 (m, 2 H) 8.21 (s, 2 H) 9.64 (s, 1 H) 9.87 (s, 1 H)	2-amino pyrimidin-5-yl boronic acid
20	 N^2-(3-chloro-4-fluorophenyl)-N^4-[3-(dimethylamino) propyl]-5-(1*H*-pyrazol-4-yl) pyrimidine-2,4-diamine	MS: ES+ 390 for $C_{18}H_{21}ClFN_7$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 1.92 (m, 2 H) 2.75 (d, *J*=4.52 Hz, 6 H) 2.99 - 3.10 (m, 2 H) 3.36 - 3.50 (m, 2 H) 7.40 - 7.59 (m, 2 H) 7.76 - 7.94 (m, 3 H) 7.99 (dd, *J*=6.78, 2.45 Hz, 1 H) 9.57 (br. s., 1 H) 10.58 (br. s., 1 H)	4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole
21	 5-(6-aminopyridin-3-yl)-N^2-(3-chloro-4-fluorophenyl)-N^4-[3-(dimethylamino) propyl]pyrimidine-2,4-diamine	MS: ES+ 416 for $C_{20}H_{23}ClFN_7$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 1.86 - 2.01 (m, 2 H) 2.75 (d, *J*=3.96 Hz, 6 H) 2.99 - 3.12 (m, 2 H) 3.32 - 3.49 (m, 2 H) 7.09 (d, *J*=9.04 Hz, 1 H) 7.40 - 7.59 (m, 2 H) 7.80 - 8.00 (m, 3 H) 8.05 (d, *J*=1.51 Hz, 1 H) 8.36 (br. s., 1 H) 8.54 (br. s., 2 H) 10.12 (br. s., 1 H) 11.15 (br. s., 1 H)	5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine

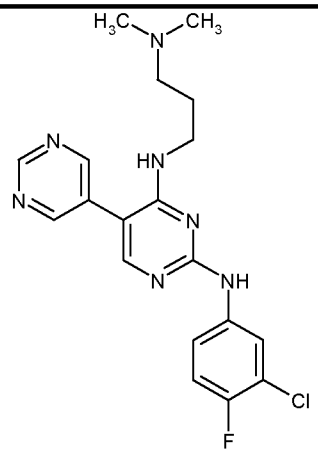
Ex	Compound	Data	SM
22	 Methyl 5-{2-(3-chloro-4-fluorophenylamino)-4-[3-(dimethylamino) propylamino] pyrimidin-5-yl} benzo[b]thiophene-2-carboxylate	MS: ES+ 514 for $C_{25}H_{25}ClFN_5O_2S$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 1.85 - 1.99 (m, 2 H) 2.75 (d, *J*=4.71 Hz, 6 H) 2.97 - 3.08 (m, 2 H) 3.36 - 3.46 (m, 2 H) 3.90 (s, 3 H) 7.44 (t, *J*=9.04 Hz, 1 H) 7.52 - 7.72 (m, 3 H) 7.92 (s, 1 H) 8.02 - 8.10 (m, 2 H) 8.21 (d, *J*=8.48 Hz, 1 H) 8.27 (s, 1 H) 9.51 (br. s., 1 H) 10.26 (br. s., 1 H)	Methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-benzo thiophene-2-carboxylate
23	 N^2-(3-chloro-4-fluorophenyl)-N^4-[3-(dimethylamino)propyl]-5-pyridin-3-ylpyrimidine-2,4-diamine	MS (ES) $(M+H)^+$ 401 for $C_{20}H_{22}ClFN_6$ ^{1}H-NMR (DMSO-d_6) δ: 11.04 (s, 1 H), 10.66 (s, 1 H), 8.95 (s, 1 H), 8.89 (d, *J*=4.71 Hz, 1 H), 8.55 (s, 1 H), 8.39 (d, *J*=6.97 Hz, 1H), 8.02 - 8.07 (m, 1 H), 7.90 - 8.02 (m, *J*=11.87 Hz, 2 H), 7.44 - 7.64 (m, 2 H), 3.26 - 3.53 (m, 2 H), 2.92 - 3.13 (m, 2 H), 2.69 (s, *J*=3.00 Hz, 6 H),1.83 - 2.06 (m, *J*=5.65 Hz, 2 H). ^{19}F NMR (DMSO-*d* 6) δ: 121.61 (s, 1 F).	3-pyridyl boronic acid

Ex	Compound	Data	SM
24	 (2E)-3-[4-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[3-(dimethylamino)propyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoic acid	MS (ES) $(M+H)^+$ 470 for $C_{24}H_{26}ClFN_5O_2$ MS (ES) $(M-H)^-$ 468 for $C_{24}H_{24}ClFN_5O_2$ ^{1}H-NMR (DMSO-d_6) δ:9.36 (s, 1 H), 8.25 (dd, *J*=6.88, 2.54 Hz, 1 H), 7.77 (s, 1 H), 7.60 - 7.68 (m, *J*=9.23 Hz, 1 H), 7.57 (d,*J*=8.29 Hz, 2 H), 7.32 (d, *J*=8.29 Hz, 2 H), 7.22 - 7.30 (m, 3 H), 7.16 (d, *J*=15.82 Hz, 1 H), 6.42 (d, *J*=15.82 Hz, 1 H), 3.43 (td, *J*=6.78, 5.09 Hz, 2H), 2.28 (t, *J*=5.65 Hz, 2 H), 1.96 (s, 6 H), 1.66 (tt, *J*=7.35, 6.78, 6.22, 5.09 Hz, 2 H). ^{19}F NMR (DMSO-d 6) δ: 127.21 (s, 1 F).	(E)-3-(4-boronophenyl)prop-2-enoic acid
25	 N^2-(3-chloro-4-fluorophenyl)-N^4-[3-(dimethylamino)propyl]-5-(4-methoxyphenyl)pyrimidine-2,4-diamine	MS (ES) $(M+H)^+$ 430 for $C_{22}H_{25}ClFN_5O$ ^{1}H-NMR (DMSO-d_6) δ:9.30 (s, 1 H), 8.25 (dd, *J*=6.78, 2.64 Hz, 1 H), 7.70 (s, 1 H), 7.61 (td, *J*=6.45, 2.73 Hz, 1 H), 7.20 - 7.34 (m,3 H), 7.09 (t, *J*=4.52 Hz, 1 H), 7.02 (d, *J*=8.67 Hz, 2 H), 3.78 (s, 3 H), 3.42 (q, *J*=5.78 Hz, 2 H), 2.28 (t, *J*=5.93 Hz, 2 H), 1.98 (s, 6 H), 1.66 (ddd,*J*=12.39, 6.08, 5.84 Hz, 2 H). ^{19}F NMR (DMSO-*d* 6) δ: 127.37 (s, 1 F).	(4-methoxyphenyl)boronic acid

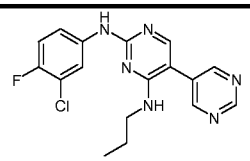
Ex	Compound	Data	SM
26	 N^2-(3-chloro-4-fluorophenyl)-N^4-[3-(dimethylamino)propyl]-5-(3-methoxyphenyl)pyrimidine-2,4-diamine	MS (ES) $(M+H)^+$ 430 for $C_{22}H_{25}ClFN_5O$ ^{1}H-NMR (DMSO-d_6) δ:9.34 (s, 1 H), 8.25 (dd, *J*=6.88, 2.35 Hz, 1 H), 7.77 (s, 1 H), 7.56 - 7.66 (m, 1 H), 7.37 (t, *J*=7.72 Hz, 1 H),7.28 (t, *J*=9.14 Hz, 1 H), 7.20 (t, *J*=5.27 Hz, 1 H), 6.87 - 6.96 (m, 3 H), 3.78 (s, 3 H), 3.43 (q, *J*=6.41 Hz, 2 H), 2.28 (t, *J*=6.97, 6.41 Hz, 2 H), 1.97(s, 6 H), 1.67 (tt, *J*=6.59, 6.03 Hz, 2 H). ^{19}F NMR (DMSO-*d* 6) δ: $^-$ 127.22 (s, 1 F).	(3-methoxyphenyl)boronic acid
27	 3-[4-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[3-(dimethylamino)propyl]amino}pyrimidin-5-yl)phenyl]propanoic acid	MS (ES) $(M+H)^+$ 472 for $C_{24}H_{28}ClFN_5O_2$ MS (ES) $(M-H)^-$ 470 for $C_{24}H_{26}ClFN_5O_2$ ^{1}H-NMR (DMSO-d_6) δ:9.31 (s, 1 H), 8.24 (dd, *J*=6.78, 1.88 Hz, 1 H), 7.71 (s, 1 H), 7.53 - 7.66 (m, 1 H), 7.25 - 7.33 (m, 2 H), 7.15- 7.25 (m, 4 H), 3.42 (q, *J*=5.71 Hz, 2 H), 2.79 (t, *J*=7.72 Hz, 2 H), 2.27 (t, *J*=6.78, 5.65 Hz, 2 H), 2.20 (t, *J*=8.67, 7.54 Hz, 2 H), 1.95 (s, 6 H), 1.65(tt, *J*=6.03 Hz, 2 H). ^{19}F NMR (DMSO-*d* 6) δ: $^-$ 127.35 (s, 1 F).	3-(4-boronophenyl)propanoic acid

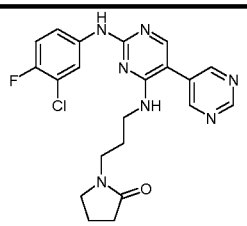
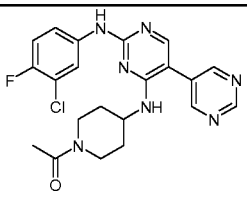
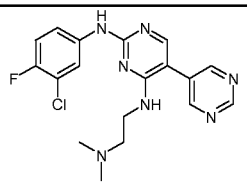
Ex	Compound	Data	SM
28	 N^2-(3-chloro-4-fluorophenyl)-N^4-[3-(dimethylamino)propyl]-5-(2-methoxyphenyl)pyrimidine-2,4-diamine	MS (ES) $(M+H)^+$ 430 for $C_{22}H_{25}ClFN_5O$ MS (ES) (M-H)- 428 for $C_{22}H_{23}ClFN_5O$ ^{1}H-NMR (DMSO-d_6) δ: 9.75 (s, 1 H), 8.01 (br. s., 1 H), 7.73 (s, 1 H), 7.51 - 7.60 (m, 1 H), 7.40 - 7.52 (m, 2 H), 7.20 - 7.26 (m, 1H), 7.15 (d, *J*=8.67 Hz, 1 H), 7.06 (t, *J*=7.35 Hz, 1 H), 3.78 (s, 3 H), 3.40 (d, *J*=6.22 Hz, 2 H), 2.90 - 3.05 (m, 2 H), 2.72 (d, *J*=4.71 Hz, 6 H), 1.81 -2.02 (m, 2 H).	(2-methoxyphenyl)boronic acid
29	 (2E)-3-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[3-(dimethylamino)propyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoic acid	MS (ES) $(M+H)^+$ 470 for $C_{24}H_{26}ClFN_5O_2$ MS (ES) $(M-H)^-$ 468 for $C_{24}H_{24}ClFN_5O_2$ ^{1}H-NMR (DMSO-d_6) δ:9.37 (s, 1 H), 8.25 (dd, *J*=6.88, 2.54 Hz, 1 H), 7.78 (s, 1 H), 7.54 - 7.68 (m, 3 H), 7.41 - 7.52 (m, 2 H), 7.19- 7.40 (m, 4 H), 6.55 (d, *J*=16.20 Hz, 1 H), 3.43 (q, *J*=5.65 Hz, 2 H), 2.28 (t, *J*=6.22, 5.09 Hz, 2 H), 1.95 (s, 6 H), 1.59 - 1.73 (m, 2 H). ^{19}F NMR (DMSO-*d* 6) δ: $^-$ 127.19 (s, 1 F).	(E)-3-(3-boronophenyl)prop-2-enoic acid

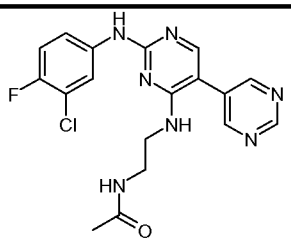
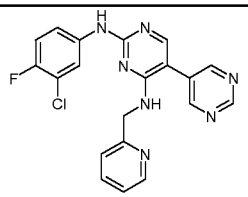
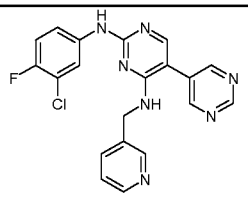
Ex	Compound	Data	SM
30	 4-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[3-(dimethylamino)propyl]amino}pyrimidin-5-yl)benzoic acid	MS (ES) $(M+H)^+$ 444 for $C_{22}H_{24}ClFN_5O_2$ MS (ES) $(M-H)^-$ 442 for $C_{22}H_{22}ClFN_5O_2$ ^{1}H-NMR (DMSO-d_6) δ:9.38 (s, 1 H), 8.24 (dd, *J*=6.97, 2.45 Hz, 1 H), 7.95 (d, *J*=8.10 Hz, 2 H), 7.78 (s, 1 H), 7.54 - 7.68 (m, 1 H),7.35 (d, *J*=7.91 Hz, 2 H), 7.20 - 7.32 (m, *J*=9.04, 9.04 Hz, 2 H), 3.43 (td, *J*=6.41, 5.27 Hz, 2 H), 2.29 (t, *J*=6.41 Hz, 2 H), 1.96 (s, 6 H), 1.67 (tt,*J*=6.22 Hz, 2 H). ^{19}F NMR (DMSO-*d* 6) δ: 127.16 (s, 1 F).	4-borono-benzoic acid
31	 3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[3-(dimethylamino)propyl]amino}pyrimidin-5-yl)benzoic acid	MS (ES) $(M+H)^+$ 444 for $C_{22}H_{24}ClFN_5O_2$ MS (ES) $(M-H)^-$ 442 for $C_{22}H_{22}ClFN_5O_2$ ^{1}H-NMR (DMSO-d_6) δ:9.33 (s, 1 H), 8.24 (dd, *J*=7.06, 2.35 Hz, 1 H), 7.78 - 7.92 (m, 2 H), 7.71 (s, 1 H), 7.56 - 7.68 (m, 1 H), 7.36(t, *J*=7.54 Hz, 1 H), 7.22 - 7.32 (m, 2 H), 7.18 (t, *J*=4.90 Hz, 1 H), 3.43 (td, *J*=6.59, 5.09 Hz, 2 H), 2.26 (t, *J*=5.75 Hz, 2 H), 1.91 (s, 6 H), 1.64 (dt,*J*=12.57, 6.43 Hz, 2 H). ^{19}F NMR (DMSO-*d* 6) δ: 127.36 (s, 1 F).	3-borono-benzoic acid

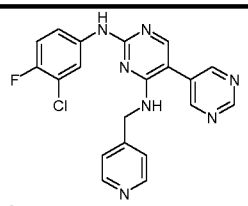
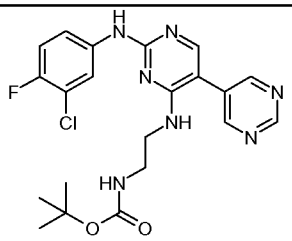
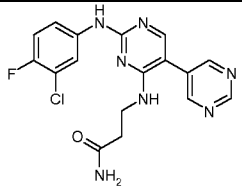
Ex	Compound	Data	SM
32	 N^2-(3-chloro-4-fluorophenyl)-N^4-[3-(dimethylamino)propyl]-5,5'-bipyrimidine-2,4-diamine	MS (ES) $(M+H)^+$ 402 for $C_{19}H_{22}ClFN_7$ ^{1}H-NMR (DMSO-d_6) δ: 9.50 (s, 1 H), 9.17 (s, 1 H), 8.81 (s, 2 H), 8.24 (dd, *J*=6.88, 2.54 Hz, 1 H), 7.86 (s, 1 H), 7.62 (ddd, *J*=9.00,4.10, 2.73 Hz, 1 H), 7.45 (t, *J*=4.33 Hz, 1 H), 7.30 (t, *J*=9.14 Hz, 1 H), 3.41 (dt, *J*=6.41, 5.27 Hz, 2 H), 2.42 (t, *J*=5.56 Hz, 2 H), 2.14 (s, 6 H), 1.73(tt, *J*=6.59 Hz, 2 H). ^{19}F NMR (DMSO-*d* 6) δ: 126.69 (s, 1 F).	pyrimidin-5-ylboronic acid

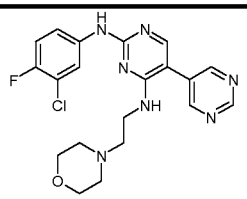
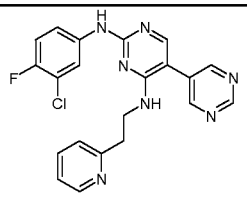
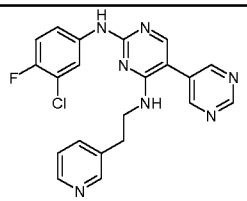
The following examples were prepared using the general method described above for **Example 1** using pyrimidin-5-ylboronic acid and the starting material (SM) indicated.

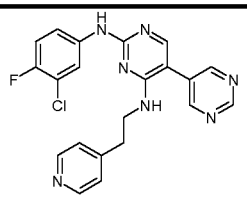
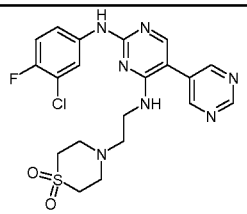
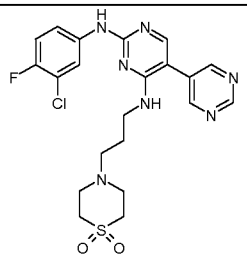
Ex	Compound	Data	SM
33	 N^2-(3-chloro-4-fluorophenyl)-N^4-propyl-5-pyrimidin-5-ylpyrimidine-2,4-diamine	MS(ES): 359 (M+1) for $C_{17}H_{16}ClFN_6$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.86-0.91 (m, 3H), 1.23 (d, *J* = 6.92 Hz, 2H), 1.58 (q, *J* = 7.44 Hz, 2H), 7.12 (t, *J* = 5.68 Hz, 1H), 7.29 (t, *J* = 9.12 Hz, 1H), 7.55-7.59 (m, 1H), 7.82 (s, 1H), 8.28 (dd, *J* = 6.9, 2.56 Hz, 1H), 8.78 (s, 2H), 9.15 (s, 1H), 9.48 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-propyl-pyrimidine-2,4-diamine (**Intermediate 35**)

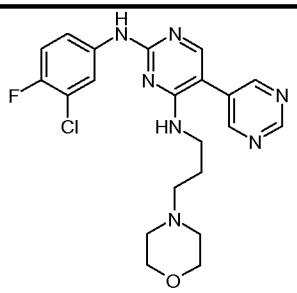
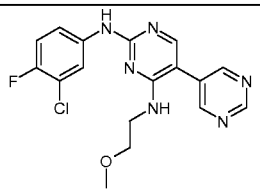
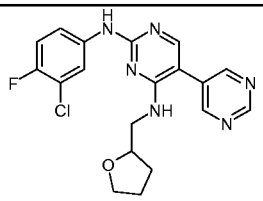
Ex	Compound	Data	SM
34	 1-[3-[[2-[(3-chloro-4-fluorophenyl)amino]-5-pyrimidin-5-ylpyrimidin-4-yl]amino]propyl]pyrrolidin-2-one	MS(ES): 442 (M+1) for $C_{21}H_{21}ClFN_7O$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.72-1.77 (m, 2H), 1.85-1.89 (m, 2H), 2.16 (t, J = 8.2 Hz, 2H), 3.15 (s, 1H), 3.22 (t, J = 7.04 Hz, 2H), 3.28 (m, 3H), 7.07 (br s, 1H), 7.32 (t, J = 9.16 Hz, 1H), 7.6-7.64 (m, 1H), 7.85 (s, 1H), 8.19 (dd, J = 6.86, 2.48 Hz, H), 8.82 (s, 2H), 9.16 (s, 1H), 9.53 (s, 1H).	1-{3-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-propyl}-pyrrolidin-2-one **(Intermediate 36)**
35	 1-[4-[[2-[(3-chloro-4-fluorophenyl)amino]-5-pyrimidin-5-ylpyrimidin-4-yl]amino]piperidin-1-yl]ethanone	MS(ES): 442 (M+1) for $C_{21}H_{21}ClFN_7O$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.36-1.46 (m, 2H), 1.84-1.93 (m, 2H), 1.98 (s, 3H), 2.64 (t, J = 10.56 Hz, 1H), 3.12 (t, J = 11.40 Hz, 1H), 3.85 (d, J = 13.48 Hz, 1H), 4.20 (m, 1H), 4.36 (d, J = 13.68 Hz, 1H), 6.84 (d, J = 7.72 Hz, 1H), 7.33 (t, J = 9.08 Hz, 1H), 7.56 (m, 1H), 7.86 (s, 1H), 8.23 (dd, J = 6.90, 2.04 Hz, 1H), 8.79 (s, 2H), 9.15 (s, 1H), 9.54 (s, 1H).	1-{4-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-piperidin-1-yl}-ethanone **(Intermediate 72)**
36	 N^2-(3-chloro-4-fluorophenyl)-N^4-(2-dimethylaminoethyl)-5-pyrimidin-5-ylpyrimidine-2,4-diamine	MS(ES): 388(M+1) for $C_{18}H_{19}ClFN_7$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.31 (br s, 6H), 2.65 (br s, 2H), 3.49–3.51 (br s, 2H), 6.98 (br s, 1H), 7.3 (t, J = 9.1 Hz, 1H), 7.64 (ddd, J = 9.02, 4.12, 2.72 Hz, 1H), 7.87 (s, 1H), 8.15 (dd, J = 6.88, 2.5 Hz, 1H), 8.81 (s, 2H), 9.16 (s, 1H), 9.49 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-dimethylamino-ethyl)-pyrimidine-2,4-diamine **(Intermediate 37)**

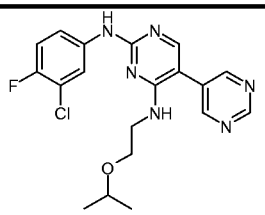
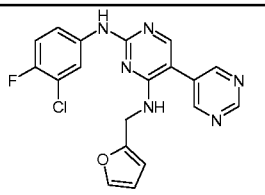
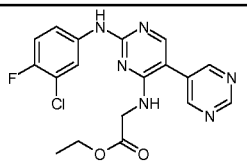
Ex	Compound	Data	SM
37	 N-[2-[[2-[(3-chloro-4-fluorophenyl)amino]-5-pyrimidin-5-ylpyrimidin-4-yl]amino]ethyl]acetamide	MS(ES): 402 (M+1) for $C_{18}H_{17}ClFN_7O$ ^{1}H NMR (400 MHz, MeOD): δ 1.9 (s, 3H), 3.43 (t, *J* = 5.52 Hz, 2H), 3.57 (q, *J* = 5.33 Hz, 2H), 7.16 (t, *J* = 9 Hz, 1H), 7.5 (ddd, *J* = 9, 4.1, 2.68 Hz, 1H), 7.82 (s, 1H), 8.05 (dd, *J* = 6.74, 2.68 Hz, 1H), 8.85 (s, 2H), 9.14 (s, 1H).	N-{2-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-ethyl}-acetamide **(Intermediate 38)**
38	 N^2-(3-chloro-4-fluorophenyl)-N^4-(pyridin-2-ylmethyl)-5-pyrimidin-5-ylpyrimidine-2,4-diamine	MS(ES): 408 (M+1) for $C_{20}H_{15}ClFN_7$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.66 (d, *J* = 5.96 Hz, 2H), 7.15 (t, *J* = 9.24 Hz, 1H), 7.21-7.24 (m, 1H), 7.35 (d, *J* = 7.84 Hz, 1H), 7.48-7.52 (m, 1H), 7.66-7.74 (m, 2H), 7.92 (m, 2H), 8.52 (d, *J* = 4.8 Hz, 1H), 8.91 (s, 2H), 9.19 (s, 1H), 9.45 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine **(Intermediate 39)**
39	 N^2-(3-chloro-4-fluorophenyl)-N^4-(pyridin-3-ylmethyl)-5-pyrimidin-5-ylpyrimidine-2,4-diamine	MS(ES): 408 (M+1) for $C_{20}H_{15}ClFN_7$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.59 (d, *J* = 5.64 Hz, 2H), 7.22 (t, *J* = 9.00 Hz, 1H), 7.32-7.35 (m, 1H), 7.52 (dd, *J* = 6.6, 3.96 Hz, 1H), 7.67 (d, *J* = 5.2 Hz, 1H), 7.75 (d, *J* = 7.52 Hz, 1H), 7.91 (s, 1H), 8.01 (d, *J* = 6.56 Hz, 1H), 8.42 (d, *J* = 3.36 Hz, 1H), 8.58 (s, 1H), 8.86 (s, 2H), 9.18 (s, 1H), 9.49 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(pyridin-3-ylmethyl)-pyrimidine-2,4-diamine hydrochloride salt **(Intermediate 40)**

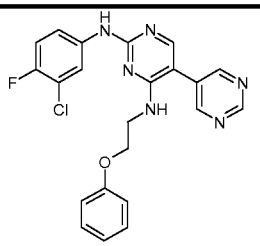
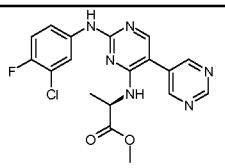
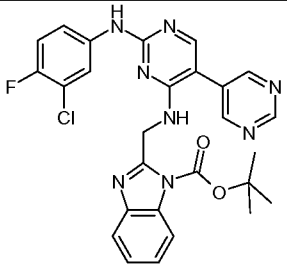
Ex	Compound	Data	SM
40	 N^2-(3-chloro-4-fluorophenyl)-N^4-(pyridin-4-ylmethyl)-5-pyrimidin-5-ylpyrimidine-2,4-diamine	MS(ES): 408 (M+1) for $C_{20}H_{15}ClFN_7$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.78 (d, J = 5.64 Hz, 2H), 7.28-7.32 (m, 2H), 7.60 (br s, 1H), 7.97 (d, J = 6.44 Hz, 2H), 8.08 (s, 1H), 8.6 (br s, 1H), 8.83 (d, J = 6.64 Hz, 2H), 8.97 (s, 2H), 9.28 (s, 1H), 10.4 (br s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-pyridin-4-ylmethyl-pyrimidine-2,4-diamine hydrochloride salt **(Intermediate 41)**
41	 *tert*-butyl N-[2-[[2-[(3-chloro-4-fluorophenyl)amino]-5-pyrimidin-5-ylpyrimidin-4-yl]amino]ethyl]carbamate	MS(ES): 460 (M+1) for $C_{21}H_{23}ClFN_7O_2$ ^{1}H NMR (400 MHz, MeOD): δ 1.38 (s, 9H), 3.53 (t, J = 6.04 Hz, 2H), 7.16 (t, J = 9 Hz, 1H), 7.5 (m, 1H), 7.8 (s, 1H), 8.05 (dd, J = 6.74, 2.48 Hz, 1H), 8.85 (s, 2H), 9.14 (s, 1H).	{2-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-ethyl}-carbamic acid *tert*-butyl ester **(Intermediate 73)**
42	 3-[[2-[(3-chloro-4-fluorophenyl)amino]-5-pyrimidin-5-ylpyrimidin-4-yl]amino]propanamide	MS(ES): 388(M+1) for $C_{17}H_{15}ClFN_7O$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.41 (t, J = 6.88 Hz, 2H), 3.56 (br s, 2H), 6.87 (br s, 1H), 7.17 (br s, 1H), 7.3 (t, J = 9.12 Hz, 1H), 7.34 (s, 1H), 7.7 (ddd, J = 9.06, 4.22, 2.72 Hz, 1H), 7.87 (s, 1H), 8.15 (dd, J = 6.86, 2.6 Hz, 1H), 8.8 (s, 2H), 9.16 (s, 1H), 9.54 (s, 1H).	3-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-propionamide **(Intermediate 42)**

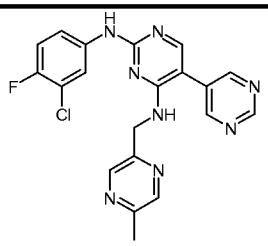
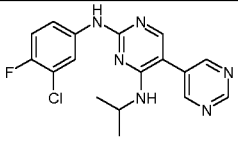
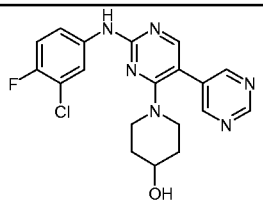
Ex	Compound	Data	SM
43	 N^2-(3-chloro-4-fluorophenyl)-N^4-(2-morpholin-4-ylethyl)-5-pyrimidin-5-ylpyrimidine-2,4-diamine	MS(ES): 430 (M+1) for $C_{20}H_{21}ClFN_7O$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.3-2.4 (m, 4H), 2.51-2.53 (m, 2H), 3.48-3.49 (m, 2H), 3.53-3.55 (m, 4H), 6.92 (t, J = 5.88 Hz, 1H), 7.29 (t, J = 9.04 Hz, 1H), 7.61-7.65 (m, 2H), 7.88 (s, 1H), 8.18 (dd, J = 6.84, 2.44 Hz, 1H), 8.83 (s, 2H), 9.17 (s, 1H), 9.48 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-morpholin-4-yl-ethyl)-pyrimidine-2,4-diamine **(Intermediate 43)**
44	 N^2-(3-chloro-4-fluorophenyl)-N^4-(2-pyridin-2-ylethyl)-5-pyrimidin-5-ylpyrimidine-2,4-diamine	MS(ES): 422.2(M) for $C_{21}H_{17}ClFN_7$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.04 (t, J = 7.12 Hz, 2H), 3.72 (q, J = 6.72 Hz, 2H), 7.20-7.27 (m, 4H), 7.66-7.71 (m, 2H), 7.86 (s, 1H), 8.17 (dd, J = 6.97, 2.68 Hz, 1H), 8.46 (dd, J = 4.82, 0.84 Hz, 1H), 8.75 (s, 2H), 9.15 (s, 1H), 9.49 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine **(Intermediate 44)**
45	 N^2-(3-chloro-4-fluorophenyl)-N^4-(2-pyridin-3-ylethyl)-5-pyrimidin-5-ylpyrimidine-2,4-diamine	MS(ES): 422.2(M) for $C_{21}H_{17}ClFN_7$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.91 (t, J = 7.12 Hz, 2H), 3.58-3.63 (m, 2H), 7.18 (t, J = 5.12 Hz, 1H), 7.27 (d, J = 9.08 Hz, 1H), 7.30-7.35 (m, 1H), 7.59-7.66 (m, 2H), 7.87 (s, 1H), 8.20 (dd, J = 6.86, 2.48 Hz, 1H), 8.42-8.45 (m, 2H), 8.73 (s, 2H), 9.15 (s, 1H), 9.52 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-pyridin-3-yl-ethyl)-pyrimidine-2,4-diamine **(Intermediate 45)**

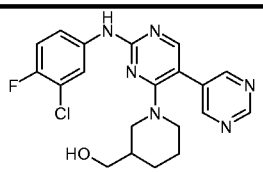
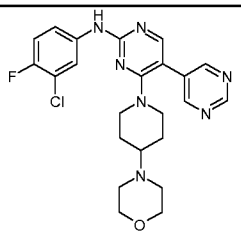
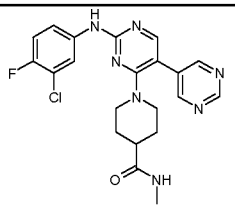
Ex	Compound	Data	SM
46	 N^2-(3-chloro-4-fluorophenyl)-N^4-(2-pyridin-4-ylethyl)-5-pyrimidin-5-ylpyrimidine-2,4-diamine	MS(ES): 422.2(M) for $C_{21}H_{17}ClFN_7$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.92 (t, J = 7.16 Hz, 2H), 3.59-3.64 (m, 2H), 7.14-7.17 (m, 1H), 7.26-7.30 (m, 3H), 7.58-7.62 (m, 1H), 7.87 (s, 1H), 8.18 (dd, J = 6.88, 2.68 Hz, 1H), 8.47 (dd, J = 4.52, 1.48 Hz, 2H), 8.73 (s, 2H), 9.15 (s, 1H), 9.51 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-pyridin-4-yl-ethyl)-pyrimidine-2,4-diamine hydrochloride salt **(Intermediate 46)**
47	 N^2-(3-chloro-4-fluorophenyl)-N^4-[2-(1,1-dioxo-1,4-thiazinan-4-yl)ethyl]-5-pyrimidin-5-ylpyrimidine-2,4-diamine	MS(ES):478 (M+1) for $C_{20}H_{21}ClFN_7O_2S$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.71 (br s, 2H), 2.95 (br s, 4H), 3.06 (br s, 4H), 3.47 (br s, 2H), 7.02 (br s, 1H), 7.32 (t, J = 9.04 Hz, 1H), 7.62 (ddd, J = 9.06, 4.22, 2.72 Hz, 1H), 7.89 (s, 1H), 8.15 (dd, J = 6.84, 2.6 Hz, 1H), 8.83 (s, 2H), 9.18 (s, 1H), 9.53 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-[2-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-ethyl]-pyrimidine-2,4-diamine **(Intermediate 47)**
48	 N^2-(3-chloro-4-fluorophenyl)-N^4-[3-(1,1-dioxo-1,4-thiazinan-4-yl)propyl]-5-pyrimidin-5-ylpyrimidine-2,4-diamine	MS(ES): 492 (M+1) for. $C_{21}H_{23}ClFN_7O_2S$. ^{1}H 400 MHz, DMSO-d_6): δ 1.69-1.73 (m, 2H), 2.50-2.52 (m, 2H), 2.82 (br s, 4H), 3.0 (br s, 4H), 3.36-3.38 (br s, 2H), 7.0 (br s, 1H), 7.30 (t, J = 9.12 Hz, 1H), 7.55-7.6 (m, 1H), 7.83 (s, 1H), 8.24 (dd, J = 2.44, 6.88 Hz, 1H), 8.79 (s, 2H), 9.1(s, 1H), 9.47 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-[3-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-propyl]-pyrimidine-2,4-diamine **(Intermediate 49)**

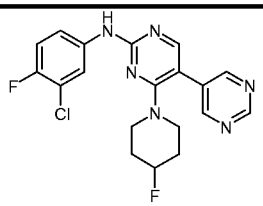
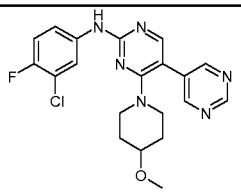
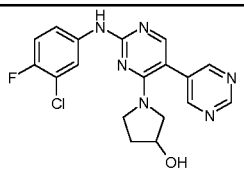
Ex	Compound	Data	SM
49	 N^2-(3-chloro-4-fluorophenyl)-N^4-(3-morpholin-4-ylpropyl)-5-pyrimidin-5-ylpyrimidine-2,4-diamine	MS(ES): 444 (M+1) for $C_{21}H_{23}ClFN_7O$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.73 (br s, 2H), 2.32 (br s, 5H), 3.40 (q, J = 5.88 Hz, 2H), 3.48 (s, 4H), 7.09 (br s, 1H), 7.31 (t, J = 9.12 Hz, 1H), 7.59 (ddd, J = 2.72, 4.12, 9.07 Hz, 1H), 7.85 (s, 1H), 8.26 (dd, J = 2.40, 6.84 Hz, 1H), 8.81 (s, 2H), 9.17 (s, 1H), 9.50 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(3-morpholin-4-yl-propyl)-pyrimidine-2,4-diamine **(Intermediate 48)**
50	 N^2-(3-chloro-4-fluorophenyl)-N^4-(2-methoxyethyl)-5-pyrimidin-5-ylpyrimidine-2,4-diamine	MS(ES): 375 (M+1) for $C_{17}H_{16}ClFN_6O$ ^{1}H NMR (400 MHz DMSO-d_6): δ 3.25 (s, 3H), 3.48-3.54 (m, 4H), 7.13 (br s, 1H), 7.27-7.32 (t, 1H, J =9.1 Hz), 7.59-7.62 (m, 1H), 7.86 (s, 1H), 8.18-8.20 (dd, J = 3.96, 6.92 Hz, 1H), 8.78 (s, 2H), 9.16 (s, 1H), 9.52 (br s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-methoxy-ethyl)-pyrimidine-2,4-diamine **(Intermediate 50)**
51	 N-(3-chloro-4-fluorophenyl)-N'-(oxolan-2-ylmethyl)-5-pyrimidin-5-ylpyrimidine-2,4-diamine	MS(ES): 401 (M+1) for $C_{19}H_{18}ClFN_6O$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.57–1.60 (t, J = 11.92 Hz, 1H), 1.77–1.91 (m, 3H), 3.38–3.42 (m, 2H), 3.60–3.63 (m, 1H), 3.72–3.75 (m, 1H), 4.07–4.10 (m, 1H), 7.0–7.12 (t, J = 11.04 Hz, 1H), 7.27–7.31 (t, J = 18.2 Hz, 1H), 7.58–7.62 (m, 1H), 7.85 (s, 1H), 8.19–8.21 (q, J = 9.48 Hz, 1H), 8.78 (s, 2H), 9.16 (s, 1H), 9.49 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(tetrahydro-furan-2-ylmethyl)-pyrimidine-2,4-diamine **(Intermediate 75)**

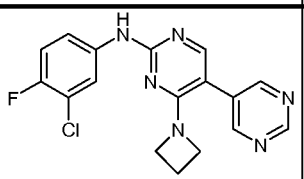
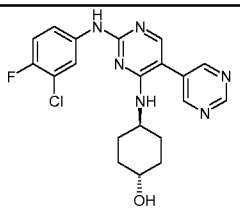
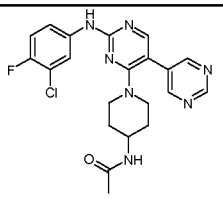
Ex	Compound	Data	SM
52	 N^2-(3-chloro-4-fluorophenyl)-*N4*-(2-propan-2-yloxyethyl)-5-pyrimidin-5-ylpyrimidine-2,4-diamine	MS(ES): 403 (M+1) for $C_{19}H_{20}ClFN_6O$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.06 (d, *J* = 6.08 Hz, 6H), 3.48-3.57 (m, 5H), 7.06 (m, 1H), 7.29 (t, *J* = 9.12 Hz, 1H), 7.62 (ddd, *J* = 9.06, 4.24, 2.72 Hz, 1H), 7.87 (s, 1H), 8.19 (dd, *J* = 6.92, 2.64 Hz, 1H), 8.80 (s, 2H), 9.17 (s, 1H), 9.52 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-isopropoxy-ethyl)-pyrimidine-2,4-diamine **(Intermediate 51)**
53	 N^2-(3-chloro-4-fluorophenyl)-N^4-(furan-2-ylmethyl)-5-pyrimidin-5-ylpyrimidine-2,4-diamine	MS(ES): 397 (M+1) for $C_{19}H_{14}ClFN_6O$ ^{1}H NMR (400 MHz DMSO-d_6): δ 4.55 (d, *J* = 5.68 Hz, 2H), 6.28 (d, *J* = 2.88 Hz, 1H), 6.37 (dd, *J* = 3.10, 1.84 Hz, 1H), 7.29 (t, *J* = 9.08 Hz, 1H), 7.56-7.66 (m, 3H), 7.90 (s, 1H), 8.11 (dd, *J* = 6.86, 2.52 Hz, 1H), 8.81 (s, 2H), 9.18 (s, 1H), 9.57 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(furan-2-ylmethyl)-pyrimidine-2,4-diamine **(Intermediate 52)**
54	 ethyl 2-[[2-[(3-chloro-4-fluorophenyl)amino]-5-pyrimidin-5-ylpyrimidin-4-yl]amino]acetate	MS(ES):403 (M+1) for $C_{18}H_{16}ClFN_6O_2$. ^{1}H NMR (400 MHz MeOD): δ 1.22 (t, *J* = 7.08 Hz, 3H), 4.15 (m, 4H), 7.15 (t, *J* = 8.96 Hz, 1H), 7.45-7.48 (m, 1H), 7.89-7.93 (m, 2H), 8.90 (s, 2H), 9.17 (s, 1H).	[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-acetic acid ethyl ester **(Intermediate 76)**

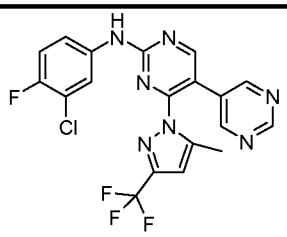
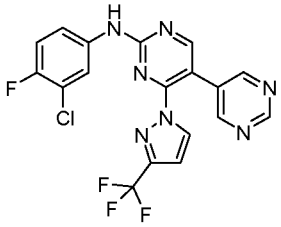
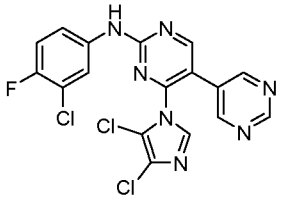
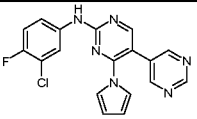
Ex	Compound	Data	SM
55	 N^2-(3-chloro-4-fluorophenyl)-N^4-(2-phenoxyethyl)-5-pyrimidin-5-ylpyrimidine-2,4-diamine	MS(ES): 437 (M+1) for $C_{22}H_{18}ClFN_6O$. ^{1}H NMR (400 MHz DMSO-d_6): δ 3.75(m, 2H), 4.14 (t, J = 6.2Hz, 2H), 6.9 (m, 3H), 7.26 (m, 5H), 7.61 (m, 1H), 7.89 (s, 1H), 8.2 (dd, J = 2.6 Hz, 1H), 8.72 (s, 2H), 9.17 (s, 1H), 9.53 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-phenoxy-ethyl)-pyrimidine-2,4-diamine **(Intermediate 53)**
56	 methyl (2R)-2-[[2-[(3-chloro-4-fluorophenyl)amino]-5-pyrimidin-5-ylpyrimidin-4-yl]amino]propanoate	MS(ES): 403 (M+1) for $C_{18}H_{16}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.40 (d, J = 7.32 Hz, 3H), 3.58 (s, 3H), 4.73 (t, J = 7.28 Hz, 1H), 7.28 (t, J = 9.04 Hz, 1H), 7.34 (d, J = 7.40 Hz, 1H), 7.59 (m, 1H), 7.93 (s, 1H), 8.02 (dd, J = 6.76, 4.44 Hz, 1H), 8.83 (s, 1H), 9.17 (s, 1H), 9.51 (s, 1H).	Methyl (2R)-2-[[2-[(3-chloro-4-fluorophenyl) amino]-5-bromo-pyrimidin-4-yl]amino]propanoate **(Intermediate 54)**
57	 *tert*-butyl 2-[[[2-[(3-chloro-4-fluorophenyl)amino]-5-pyrimidin-5-ylpyrimidin-4-yl]amino]methyl]benzimidazole-1-carboxylate	MS(ES): 547 for $C_{27}H_{24}ClFN_8O_2$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.66 (s, 9H), 5.00 (d, J = 5.56 Hz, 2H), 7.09 (t, J = 9.08 Hz, 1H), 7.28-7.38 (m, 3H), 7.65 (d, J = 7.84 Hz, 2H), 7.86 (br s, 1H), 7.93 (d, J = 7.88 Hz, 1H), 7.99 (s, 1H), 8.31 (s, 1H), 8.98 (s, 2H), 9.20 (s, 1H), 9.50 (s, 1H).	N^4-(1H-Benzoimidazol-2-ylmethyl)-5-bromo-N^2-(3-chloro-4-fluoro-phenyl)-pyrimidine-2,4-diamine **(Intermediate 126)**

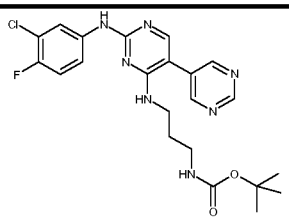
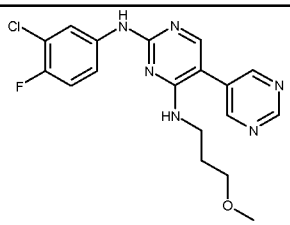
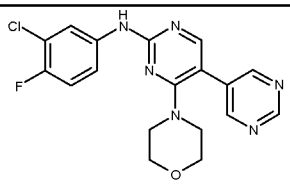
Ex	Compound	Data	SM
58	 N^2-(3-chloro-4-fluorophenyl)-N^4-[(5-methylpyrazin-2-yl)methyl]-5-pyrimidin-5-ylpyrimidine-2,4-diamine	MS(ES): 423(M+1) for $C_{20}H_{16}ClFN_8$. ^{1}H NMR (400 MHz DMSO-d_6) δ 2.44 (s, 3H), 4.66 (d, J = 5.72 Hz, 2H), 7.21 (t, J = 9.12 Hz, 1H), 7.50 (dt, J = 8.57, 4.00 Hz, 1H), 7.73 (s, 1H), 7.94 (m, 2H), 8.49 (d, J = 10.72 Hz, 2H), 8.89 (s, 2H), 9.19 (s, 1H), 9.49 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(5-methyl-pyrazin-2-ylmethyl)-pyrimidine-2,4-diamine **(Intermediate 77)**
59	 N^2-(3-chloro-4-fluorophenyl)-N^4-propan-2-yl-5-pyrimidin-5-ylpyrimidine-2,4-diamine	MS(ES): 359.1 (M+1) for $C_{17}H_{16}ClFN_6$ ^{1}H NMR (400 MHz DMSO-d_6): δ 1.18(d, J = 6.52 Hz, 6H), 4.30-4.36 (m, 1H), 6.77 (d, J = 7.72 Hz, 1H), 7.3 (t, J = 9.08 Hz, 1H), 7.54-7.58 (m, 1H), 7.82 (s, 1H),8.28 (dd, J = 6.92, 2.6 Hz, 1H), 8.78 (s, 2H), 9.15 (s,1H), 9.48 (s, 1H).	(5-Bromo-2-chloro-pyrimidin-4-yl)-isopropyl-amine **(Intermediate 56)**
60	 1-[2-[(3-chloro-4-fluorophenyl)amino]-5-pyrimidin-5-ylpyrimidin-4-yl]piperidin-4-ol	MS(ES): 401(M+1) for $C_{19}H_{18}ClFN_6O$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.33(m, 2H), 1.67(m, 2H), 3.0 (m, 2H), 3.3 (m, 2H), 3.52 (m, 1H), 4.7 (br s, 1H), 7.33(t, J = 9.12 Hz, 1H), 7.58 (ddd, 1H), 8.11 (s, 1H), 8.2 (dd, J = 2.64, 6.92 Hz, 1H), 8.9 (s, 2H), 9.11(s, 1H), 9.7 (s, 1H).	1-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-yl]-piperidin-4-ol **(Intermediate 78)**

Ex	Compound	Data	SM
61	 [1-[2-[(3-chloro-4-fluorophenyl)amino]-5-pyrimidin-5-ylpyrimidin-4-yl]piperidin-3-yl]methanol	MS(ES): 413(M-1) for $C_{20}H_{20}ClFN_6O$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.13 (m, 1H), 1.42 (m, 1H), 1.56 (m, 2H), 1.67 (m, 1H), 2.58 (m, 1H), 2.82 (m, 1H), 3.10 (m, 1H), 3.20 (m, 1H), 3.65 (d, *J* = 3.52 Hz, 1H), 3.74 (d, *J* = 11.64 Hz, 1H), 4.41 (t, *J* = 4.96 Hz, 1H), 7.32 (t, *J* = 9.12 Hz, 1H), 7.66 (ddd, *J* = 9.08, 4.26, 2.72 Hz, 1H), 8.10 (s, 1H), 8.16 (dd, *J* = 6.86, 2.60 Hz, 1H), 8.88 (s, 2H), 9.10 (s, 1H), 9.68 (s, 1H).	{1-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-yl]-piperidin-3-yl}-methanol **(Intermediate 79)**
62	 N-(3-chloro-4-fluorophenyl)-4-(4-morpholin-4-ylpiperidin-1-yl)-5-pyrimidin-5-ylpyrimidin-2-amine	MS(ES): 470.2 (M+1) for $C_{23}H_{25}ClFN_7O$. ^{1}H NMR (400 MHz $CDCl_3$): δ 1.49 (m, 2H), 1.84 (m, 2H), 2.36 (m, 1H), 2.54 (br s, 4H), 2.84 (t, *J* = 12.12 Hz, 2H), 3.72 (br s, 4H), 3.86 (d, *J* = 13.72 Hz, 2H), 7.00 (d, *J* = 6.04 Hz, 1H), 7.10 (t, *J* = 8.76 Hz, 1H), 7.27 (m, 1H), 7.97 (s, 1H), 8.05 (dd, *J* = 6.60, 2.60 Hz, 1H), 8.83 (s, 2H), 9.17 (s, 1H).	[5-Bromo-4-(4-morpholin-4-yl-piperidin-1-yl)-pyrimidin-2-yl]-(3-chloro-4-fluoro-phenyl)-amine **(Intermediate 80)**
63	 1-[2-[(3-chloro-4-fluorophenyl)amino]-5-pyrimidin-5-ylpyrimidin-4-yl]-N-methylpiperidine-4-carboxamide	MS(ES): 442.3 (M+1) for $C_{21}H_{21}ClFN_7O$ ^{1}H NMR (400 MHz DMSO-*d_6*): δ 1.55 (m, 4H), 2.3 (m, 1H), 2.53 (d, *J* = 4.52 Hz, 3H), 2.82 (t, *J* = 10.6 Hz, 2H), 3.71 (d, *J* = 13.24 Hz, 2H), 7.3 (t, *J* = 9.08 Hz, 1H), 7.6 (ddd, *J* = 9.06, 4.2, 2.8 Hz, 1H), 7.72 (m, 1H), 8.13 (s, 1H), 8.21 (dd, *J* = 6.88, 2.6 Hz, 1H), 8.91 (s,2H), 9.12 (s, 1H), 9.72 (s, 1H).	1-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid methylamide **(Intermediate 81)**

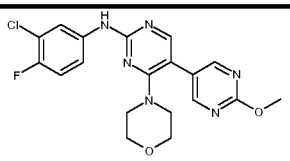
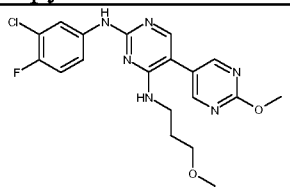
Ex	Compound	Data	SM
64	 N-(3-chloro-4-fluorophenyl)-4-(4-fluoropiperidin-1-yl)-5-pyrimidin-5-ylpyrimidin-2-amine	MS(ES):403 (M+1) for $C_{19}H_{17}ClF_2N_6$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.66 (m, 2H), 1.81-1.92 (m, 2H), 3.20 (m, 2H), 3.30 (m, 2H), 4.85 (d, J = 48.08 Hz, 1H), 7.34 (t, J = 9.08 Hz, 1H), 7.61 (m, 1H), 8.15-8.19 (m, 2H), 8.93 (s, 2H), 9.13 (s, 1H), 9.73 (s, 1H).	[5-Bromo-4-(4-fluoro-piperidin-1-yl)-pyrimidin-2-yl]-(3-chloro-4-fluoro-phenyl)-amine **(Intermediate 82)**
65	 N-(3-chloro-4-fluorophenyl)-4-(4-methoxypiperidin-1-yl)-5-pyrimidin-5-ylpyrimidin-2-amine	MS(ES):415.2 (M+1) for $C_{20}H_{20}ClFN_6O$ ^{1}H NMR (400 MHz DMSO-d_6): δ 1.35-1.43 (m, 2H), 1.78-1.81 (m, 2H), 2.99-3.05 (m, 2H), 3.21 (s, 3H), 3.47-3.5 (m, 2H), 7.33 (t, J = 9.12 Hz, 1H), 7.6 (ddd, J = 9.04, 4.22, 2.68 Hz, 1H), 8.12 (s, 1H), 8.2 (dd, J = 6.9, 2.6 Hz, 1H), 8.91 (s, 2H), 9.12 (s, 1H), 9.71 (s,1H).	[5-Bromo-4-(4-methoxy-piperidin-1-yl)-pyrimidin-2-yl]-(3-chloro-4-fluoro-phenyl)-amine **(Intermediate 83)**
66	 1-[2-[(3-chloro-4-fluorophenyl)amino]-5-pyrimidin-5-ylpyrimidin-4-yl]pyrrolidin-3-ol	MS(ES): 387(M+1) for $C_{18}H_{16}ClFN_6O$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.65-1.77 (br s, 1H), 1.85-1.89 (m, 1H), 2.91 (br s, 1H), 3.25 (br s, 2H), 3.41 (br s, 1H), 4.22 (br s, 1H), 4.92 (br s, 1H), 7.32 (t, J = 9.12 Hz, 1H), 7.65 (ddd, J = 8.98, 4.14, 2.68 Hz, 1H), 7.97 (d, J = 1.44 Hz, 1H), 8.24 (dd, J = 6.92, 2.56 Hz, 1H), 8.79 (s, 2H), 9.13 (d, J = 1.32 Hz, 1H), 9.60 (s, 1H).	1-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-yl]-pyrrolidin-3-ol **(Intermediate 84)**

Ex	Compound	Data	SM
67	 4-(azetidin-1-yl)-N-(3-chloro-4-fluorophenyl)-5-pyrimidin-5-ylpyrimidin-2-amine	MS(ES):357 (M+1) for $C_{17}H_{14}ClFN_6$. ^{1}H NMR (400 MHz DMSO-d_6): δ 2.19 (m, 2H), 3.79 (t, J = 7.36 Hz, 4H), 7.31 (t, J = 10.28 Hz, 1H), 7.64 (ddd, J = 9.06, 4.16, 2.76 Hz, 1H), 7.98 (s, 1H), 8.24 (dd, J = 6.92, 2.60 Hz, 1H), 8.80 (s, 2H), 9.13 (s, 1H), 9.64 (s, 1H).	(4-Azetidin-1-yl-5-bromo-pyrimidin-2-yl)-(3-chloro-4-fluoro-phenyl)-amine **(Intermediate 87)**
68	 *trans*-4-[[2-[(3-chloro-4-fluorophenyl)amino]-5-pyrimidin-5-ylpyrimidin-4-yl]amino]cyclohexan-1-ol	MS(ES): 415 (M+1) for $C_{20}H_{20}ClFN_6O$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.3 (m, 4H), 1.8 (m, 4H), 3.9 (m, 1H), 4.5 (d, J = 4.36 Hz, 1H), 6.7 (d, J = 7.6 Hz, 1H), 7.29 (t, J = 9.12 Hz, 1H), 7.54 (m, 1H), 7.82 (s, 1H), 8.26 (dd, J = 2.36, 6.84 Hz, 1H), 8.76 (s, 2H), 9.14 (s, 1H), 9.49 (s, 1H).	*Trans*-4-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-cyclohexanol **(Intermediate 89)**
69	 N-[1-[2-[(3-chloro-4-fluorophenyl)amino]-5-pyrimidin-5-ylpyrimidin-4-yl]piperidin-4-yl]acetamide	MS(ES): 442.2 (M+1) for $C_{21}H_{21}ClFN_7O$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (m, 2H), 1.66 (m, 2H), 1.75 (s, 3H), 2.93 (t, J = 11.60 Hz, 2H), 3.67 (d, J = 38.64 Hz, 2H), 3.73 (br s, 1H), 7.34 (t, J = 9.12 Hz, 1H), 7.61 (dt, J = 8.60, 4.16 Hz, 1H), 7.82 (d, J = 7.76 Hz, 1H), 8.14 (s, 1H), 8.19 (dd, J = 6.86, 2.56 Hz, 1H), 8.91 (s, 2H), 9.12 (s, 1H), 9.74 (s, 1H).	N-{1-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-yl]-piperidin-4-yl}-acetamide **(Intermediate 90)**

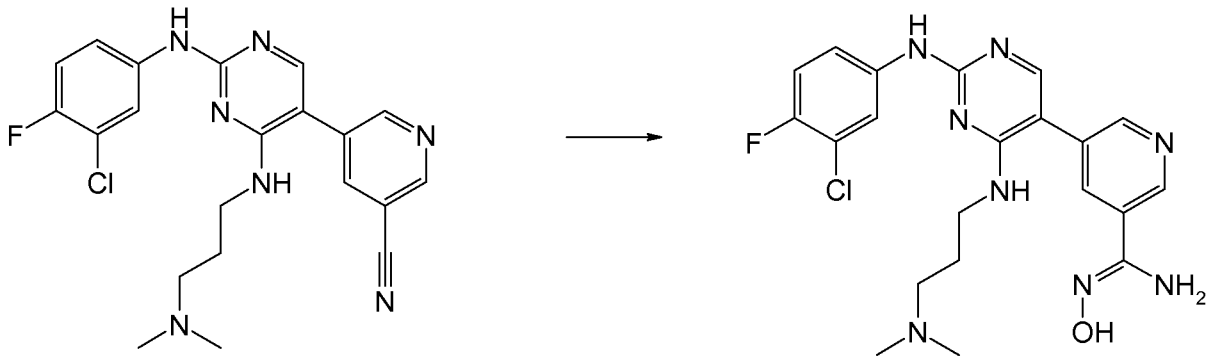
Ex	Compound	Data	SM
70	 *N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-5,5'-bipyrimidin-2-amine	MS(ES): 450 (M+1) for $C_{19}H_{12}ClF_4N_7$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.52 (s, 3H), 6.45 (s, 1H), 7.17 (t, *J* = 8.72 Hz, 1H), 7.36-7.40 (m, 1H), 7.44 (br s, 1H), 7.86 (dd, *J* = 2.60, 6.40 Hz, 1H), 8.47 (br s, 2H), 8.62 (br s, 1H), 9.17 (s, 1H).	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **(Intermediate 113)**
71	 *N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-5,5'-bipyrimidin-2-amine	MS(ES): 436 (M+1) for $C_{18}H_{10}ClF_4N_7$. ^{1}H NMR (400 MHz DMSO-d_6): δ 7.07 (d, *J* = 2.68 Hz 1H), 7.43(t, *J* = 9.12 Hz, 1H), 7.71-7.75(m, 1H), 8.05 (dd, *J* = 6.64, 2.36 Hz, 1H), 8.60 (d, *J* = 1.76, 1H), 8.68 (s, 2H), 8.81 (s, 1H), 9.14 (s, 1H), 10.48 (s, 1H).	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **(Intermediate 115)**
72	 *N*-(3-chloro-4-fluorophenyl)-4-(4,5-dichloro-1*H*-imidazol-1-yl)-5,5'-bipyrimidin-2-amine	MS(ES): 436 (M+1) for $C_{17}H_9Cl_3FN_7$. ^{1}H NMR (400 MHz DMSO-d_6): δ 7.43 (t, *J* = 9.08 Hz 1H), 7.68(m, 1H), 8.05(br s, 1H), 8.15 (s, 1H), 8.63 (s, 2H), 9.04 (s, 1H), 9.17 (s, 1H), 10.67 (s, 1H).	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(4,5-dichloro-1*H*-imidazol-1-yl)pyrimidin-2-amine **(Intermediate 116)**
73	 *N*-(3-chloro-4-fluorophenyl)-4-(1*H*-pyrrol-1-yl)-5,5'-bipyrimidin-2-amine	MS(ES): 367 (M+1) for $C_{18}H_{12}ClFN_6$. ^{1}H NMR (400 MHz DMSO-d_6): δ 6.23 (t, *J* = 1.88 Hz, 2H), 6.94 (t, *J* = 1.88 Hz, 2H), 7.41 (t, *J* = 9.04 Hz, 1H), 7.68 (m, 1H), 8.11 (dd, *J* = 8.52, 2.44 Hz, 1H), 8.66 (s, 2H), 8.70 (s, 1H), 9.16 (s, 1H), 10.30 (s, 1H).	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(1*H*-pyrrol-1-yl)pyrimidin-2-amine **(Intermediate 117)**

Ex	Compound	Data	SM
74	 *tert*-butyl 3-(2-(3-chloro-4-fluorophenylamino)-5,5'-bipyrimidin-4-ylamino)propylcarbamate	MS(ES): 474 (M+1) for $C_{22}H_{25}ClFN_7O_2$ ^{1}H NMR (300 MHz, DMSO- *d6*) δ ppm 1.33 (s, 9 H) 1.49 - 1.83 (m, 2 H) 2.79 - 3.12 (m, 2 H) 3.31 - 3.49 (m, 2 H) 6.80 (t, J=5.65 Hz, 1 H) 7.02 (t, J=5.65 Hz, 1 H) 7.31 (t, J=9.04 Hz, 1 H) 7.49 - 7.72 (m, 1 H) 7.84 (s, 1 H) 8.20 (dd, J=6.69, 2.35 Hz, 1 H) 8.80 (s, 2 H) 9.16 (s, 1 H) 9.49 (s, 1 H)	*tert*-Butyl 3-(5-bromo-2-(3-chloro-4-fluorophenylamino)pyrimidin-4-ylamino)propylcarbamate **(Intermediate 97)**
75	 N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)-5,5'-bipyrimidine-2,4-diamine	MS(ES): 389 (M+1) for $C_{18}H_{18}ClFN_6O$ ^{1}H NMR (300 MHz, DMSO- *d6*) δ ppm 1.33 (t, J=7.06 Hz, 3 H) 1.95 (s, 3 H) 3.24 (d, J=10.93 Hz, 4 H) 3.42 (d, J=11.49 Hz, 4 H) 4.37 (q, J=6.97 Hz, 2 H) 7.34 (t, J=9.14 Hz, 1 H) 7.49 - 7.79 (m, 1 H) 7.99 - 8.28 (m, 2 H) 8.28 - 8.46 (m, 1 H) 8.92 (d, J=2.07 Hz, 1 H) 9.01 (d, J=1.88 Hz, 1 H) 9.75 (s, 1 H)	5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)pyrimidine-2,4-diamine **(Intermediate 119)**
76	 N-(3-chloro-4-fluorophenyl)-4-morpholino-5,5'-bipyrimidin-2-amine	MS(ES): 387 (M+1) for $C_{18}H_{16}ClFN_6O$ ^{1}H NMR (300 MHz, DMSO- *d6*) δ ppm 3.07 - 3.29 (m, 4 H) 3.41 - 3.75 (m, 4 H) 7.33 (t, J=9.14 Hz, 1 H) 7.51 - 7.75 (m, 1 H) 7.98 - 8.29 (m, 2 H) 8.93 (s, 2 H) 9.12 (s, 1 H) 9.75 (s, 1 H)	5-Bromo-N-(3-chloro-4-fluorophenyl)-4-morpholin-4-ylpyrimidin-2-amine **(Intermediate 111)**

The following examples were prepared using the general method described above for Example 1 using (2-methoxypyrimidin-5-yl)boronic acid, tris(dibenzyledeneacetone)-dipalladium(0), 2-dicyclohexyl phosphino-2',4',6'-triiso-propyl-1,1'-biphenyl, sodium carbonate and the starting material (SM) indicated.

Ex.	Compound	Data	SM
77	 N-(3-chloro-4-fluorophenyl)-2'-methoxy-4-morpholino-5,5'-bipyrimidin-2-amine	MS(ES): 417 (M+1) for $C_{19}H_{18}ClFN_6O_2$ 1H NMR (300 MHz, DMSO- *d*6) δ ppm 3.15 - 3.40 (m, 4 H) 3.46 - 3.70 (m, 4 H) 3.94 (s, 3 H) 7.34 (t, J=9.14 Hz, 1 H) 7.50 - 7.73 (m, 1 H) 7.97 - 8.20 (m, 2 H) 8.71 (s, 2 H) 9.77 (s, 1 H)	5-Bromo-N-(3-chloro-4-fluorophenyl)-4-morpholin-4-ylpyrimidin-2-amine **(Intermediate 111)**
78	 N^2-(3-chloro-4-fluorophenyl)-2'-methoxy-N^4-(3-methoxypropyl)-5,5'-bipyrimidine-2,4-diamine	MS(ES): 419 (M+1) for $C_{19}H_{20}ClFN_6O_2$ 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.62 - 1.92 (m, 2 H) 3.08 - 3.23 (m, 3 H) 3.26 - 3.54 (m, 4 H) 3.97 (s, 3 H) 7.41 (t, J=9.04 Hz, 1 H) 7.47 - 7.61 (m, 1 H) 7.89 (s, 1 H) 7.96 - 8.21 (m, 2 H) 8.58 (s, 2 H) 10.59 (s, 1 H)	5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)pyrimidine-2,4-diamine **(Intermediate 119)**

Example 79: (Z)-5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino)propylamino)pyrimidin-5-yl)-N'-hydroxynicotinimidamide



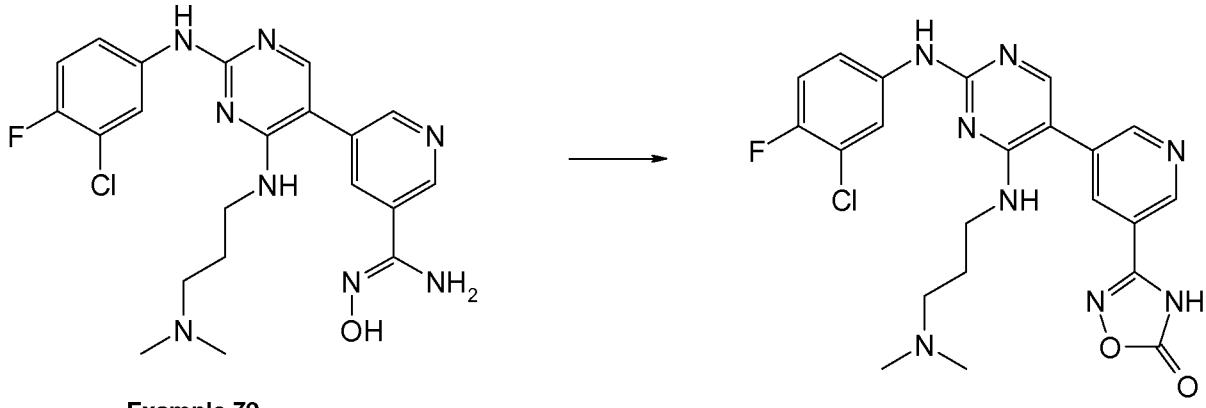
Example 15 Example 79

A stirred mixture of 5-{2-(3-chloro-4-fluorophenylamino)-4-[3-(dimethylamino) propylamino]pyrimidin-5-yl}nicotinonitrile **(Example 15**, 350 mg, 0.82 mmol) and aqueous hydroxylamine 50 weight % (0.097 mL, 1.64 mmol) in dioxane (3 mL) was prepared under

nitrogen and heated to 80 °C. After three hours, dioxane was removed under vacuum, and the residue was suspended in methanol. The mixture was cooled to near-zero while being stirred. The title compound was collected as a white solid (200 mg, 53 %).

MS: ES+ 459 for $C_{21}H_{24}ClFN_8O$.

Example 80: 3-(5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino)propylamino)pyrimidin-5-yl)pyridin-3-yl)-1,2,4-oxadiazol-5(4H)-one



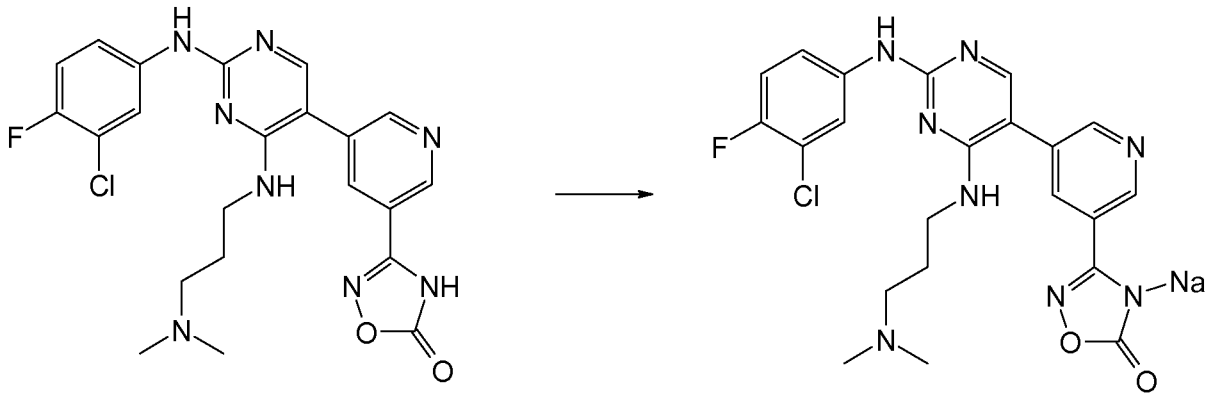
Example 79 Example 80

A stirred suspension of (Z)-5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino)propylamino)pyrimidin-5-yl)-N'-hydroxynicotinimidamide (**Example 79**, 100 mg, 0.22 mmol), triethylamine (0.045 mL, 0.33 mmol), and 1,1'-carbonyldiimidazole (35 mg, 0.22 mmol) in dioxane (2 mL) were combined under nitrogen and heated to 80 degrees C. The suspension became a solution, and after 2 hours, the solvent was removed under vacuum. Reverse-phase chromatography (acetonitrile and water with ammonium acetate additive) was used to isolate the title compound (25 mg, 98%).

MS: ES+ 485 for $C_{22}H_{22}ClFN_8O_2$.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.86 - 1.99 (m, 2 H) 2.72 (s, 6 H) 2.98 - 3.09 (m, 2 H) 3.39 - 3.51 (m, 2 H) 7.06 (t, *J*=5.46 Hz, 1 H) 7.33 (t, *J*=9.14 Hz, 1 H) 7.56 - 7.70 (m, 1 H) 7.90 (s, 1 H) 8.13 (s, 1 H) 8.21 (dd, *J*=6.88, 2.54 Hz, 1 H) 8.60 (s, 1 H) 8.92 (s, 1 H) 9.50 (s, 1 H).

Example 81: Sodium 3-(5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino)propylamino)pyrimidin-5-yl)pyridin-3-yl)-5-oxo-1,2,4-oxadiazol-4-ide



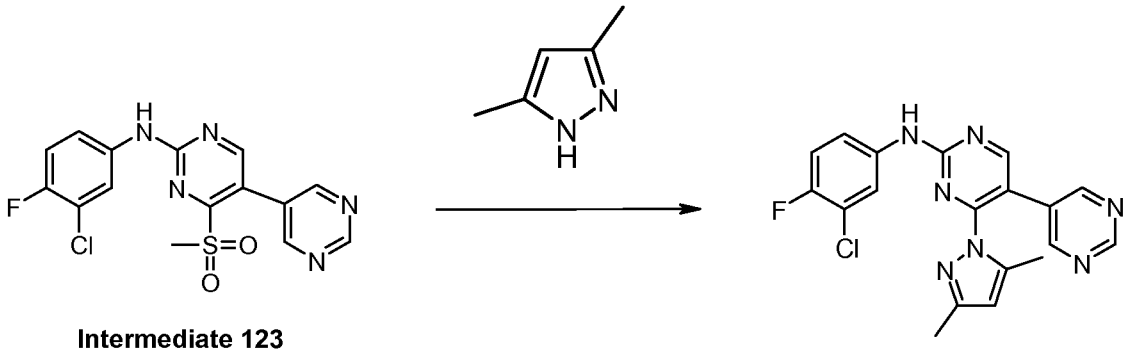
Example 80 Example 81

3-(5-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(dimethylamino)propylamino)pyrimidin-5-yl)pyridin-3-yl)-1,2,4-oxadiazol-5(4H)-one **(Example 80,** 21 mg, 0.04 mmol) was dissolved in dioxane with stirring. 0.1 N NaOH (0.4 mL, 0.04 mmol) was added to the stirred solution. After another 20 minutes of stirring the solvent was removed under vacuum. The residue was placed under high vacuum overnight and characterized (21 mg, 91%).

MS: ES+ 485 for $C_{22}H_{22}ClFN_8O_2$ (free acid detected by LCMS).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.70 - 0.86 (m, 2 H) 1.12 - 1.26 (m, 2 H) 1.59 - 1.74 (m, 2 H) 2.06 (br. s., 6 H) 7.17 - 7.34 (m, 2 H) 7.53 - 7.64 (m, 1 H) 7.77 (s, 1 H) 7.98 (t, *J*=1.88 Hz, 1 H) 8.18 (dd, 1 H) 8.47 (d, *J*=2.07 Hz, 1 H) 8.84 (d, *J*=1.70 Hz, 1 H) 9.39 (s, 1 H).

Example 82: *N*-(3-chloro-4-fluorophenyl)-4-(3,5-dimethyl-1*H*-pyrazol-1-yl)-5,5'-bipyrimidin-2-amine



Intermediate 123

Molecular Weight =379.80
Exact Mass =379

Example 82

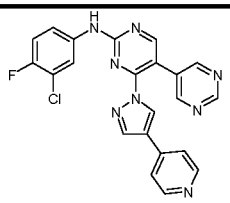
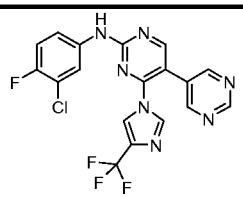
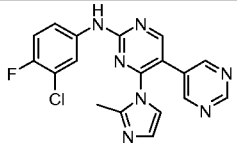
Molecular Weight =395.83
Exact Mass =395

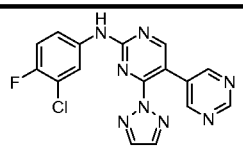
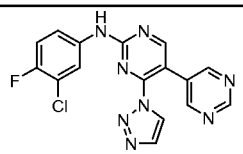
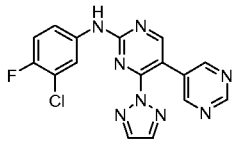
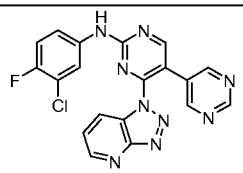
A solution of 3,5-dimethyl-1*H*-pyrazole (555 mg, 5.78 mmol, 2.2 eq) in DMF (2 mL) was added slowly to a suspension of sodium hydride (60%, 220 mg, 5.52 mmol, 2.1 eq) in DMF (1 mL) at 0 °C. The reaction mixture was stirred for 25 min at room temperature. A solution of N-(3-chloro-4-fluorophenyl)-4-methylsulfonyl-5-pyrimidin-5-ylpyrimidin-2-amine (**Intermediate 123**, 1.0 g, 2.63 mmol, 1 eq) in DMF (1 mL) was added slowly to the reaction mixture, and the mixture was stirred for 1 h. Water was added to the reaction mixture (~6 mL) and the solid formed was filtered and dried to provide the title compound (750 mg).

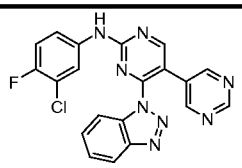
MS(ES): 396 (M+1) for $C_{19}H_{15}ClFN_7$.

^{1}H NMR 400 MHz, $CDCl_3$: δ 2.04 (s, 3H), 2.43 (s, 3H), 5.98 (s, 1H), 7.13 (t, *J* = 8.72 Hz, 1H), 7.34-7.37 (m, 1H), 7.53 (br s, 1H), 7.86 (dd, *J* = 2.52, 6.40 Hz, 1H), 8.45 (br s, 2H), 8.53 (s, 1H), 9.14 (br s, 1H).

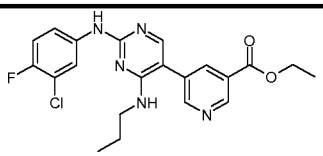
The following examples were prepared using the general method described above for **Example 82** using **Intermediate 123**, sodium hydride and the starting material (SM) indicated.

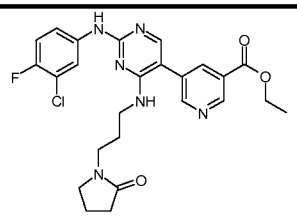
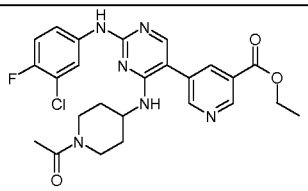
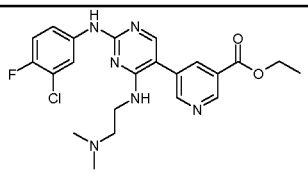
Ex	Compound	Data	SM
83	 *N*-(3-chloro-4-fluorophenyl)-4-[4-(pyridin-4-yl)-1*H*-pyrazol-1-yl]-5,5'-bipyrimidin-2-amine	MS(ES): 443 (M-1) for $C_{22}H_{14}ClFN_8$. ^{1}H NMR (400 MHz, CH_3COOH): δ 7.32 (t, *J* = 8.80 Hz, 1H), 7.65 (m, 1H), 8.12-8.16 (m, 3H), 8.30 (s, 1H), 8.64 (s, 1H), 8.92-8.97 (m, 4H), 9.32 (s, 2H).	4-(1*H*-Pyrazol-4-yl)-pyridine
84	 *N*-(3-chloro-4-fluorophenyl)-4-[4-(trifluoromethyl)-1*H*-imidazol-1-yl]-5,5'-bipyrimidin-2-amine	MS(ES): 436 (M+1) for $C_{18}H_{10}ClF_4N_7$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.43 (t, *J* = 9.08 Hz, 1H), 7.70-7.72 (m, 1H), 7.95 (s, 1H), 8.08 (d, *J* = 4.8 Hz, 1H), 8.11 (s, 1H), 8.71 (s, 2H), 8.91 (s, 1H), 9.19 (s, 1H), 10.54 (br s, 1H).	4-Trifluoromethyl-1*H*-imidazole
85	 *N*-(3-chloro-4-fluorophenyl)-4-(2-methyl-1*H*-imidazol-1-yl)-5,5'-bipyrimidin-2-amine	MS(ES): 382 (M+1) for $C_{18}H_{13}ClFN_7$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H), 6.82 (s, 1H), 7.04 (s, 1H), 7.42 (t, *J* = 9.12 Hz, 1H), 7.65-7.69 (m, 1H), 8.06 (d, *J* = 4.64 Hz, 1H), 8.55 (s, 2H), 8.93 (s, 1H), 9.12 (s, 1H), 10.46 (s, 1H).	2-Methyl-1*H*-imidazole

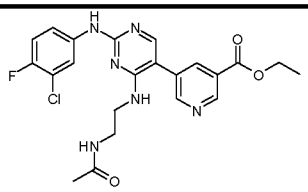
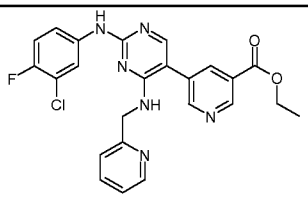
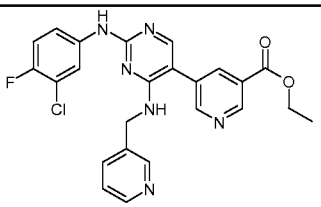
Ex	Compound	Data	SM
86	 *N*-(3-chloro-4-fluorophenyl)-4-(2*H*-1,2,3-triazol-2-yl)-5,5'-bipyrimidin-2-amine	MS(ES): 369 (M+1) for $C_{16}H_{10}ClFN_8$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.44 (t, *J* = 9.16 Hz, 1H), 7.79 (m, 1H), 8.14 (s, 2H), 8.25 (m, 1H), 8.65 (s, 2H), 8.85 (s, 1H), 9.13 (s, 1H), 10.59 (s, 1H).	1*H*-[1,2,3]Triazole
87	 *N*-(3-chloro-4-fluorophenyl)-4-(2*H*-1,2,3-triazol-1-yl)-5,5'-bipyrimidin-2-amine  *N*-(3-chloro-4-fluorophenyl)-4-(2*H*-1,2,3-triazol-2-yl)-5,5'-bipyrimidin-2-amine	MS(ES): 369 (M+1) for $C_{16}H_{10}ClFN_8$. mixture of isomers ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.39-7.45 (m, 1H), 7.71-7.75 (m, 1H), 7.97-8.14 (m, 2H), 8.65-8.68 (m, 3H), 8.90 (s, 1H), 9.14 (s, 1H), 10.59 (s, 1H).	1*H*-[1,2,3]Triazole
88	 *N*-(3-chloro-4-fluorophenyl)-4-(1*H*-[1,2,3]triazolo[4,5-*b*]pyridin-1-yl)-5,5'-bipyrimidin-2-amine	MS(ES): 418 (M-1) for $C_{19}H_{11}ClFN_9$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.44 (t, *J* = 9.04 Hz, 1H), 7.61-7.65 (m, 1H), 7.83 (dd, *J* = 4.44, 8.40 Hz, 1H), 8.10-8.15 (m, 1H), 8.83-8.86 (m, 4H), 8.92 (s, 1H), 9.18 (s, 1H), 10.53 (br s, 1H).	1*H*-[1,2,3] Triazolo[4,5-b]pyridine

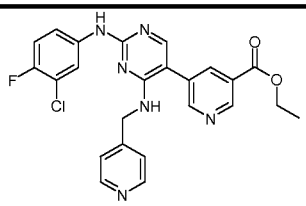
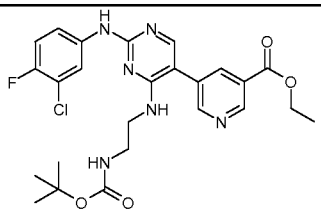
Ex	Compound	Data	SM
89	 4-(1*H*-benzotriazol-1-yl)-*N*-(3-chloro-4-fluorophenyl)-5,5'-bipyrimidin-2-amine	MS(ES): 419 (M+1) for $C_{20}H_{12}ClFN_8$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.44 (t, *J* = 9.20 Hz, 1H), 7.59 (t, *J* = 8.00 Hz, 1H), 7.61-7.70 (m, 1H), 7.76 (t, *J* = 8.00 Hz, 1H), 8.16-8.19 (m, 2H), 8.40 (br s, 1H), 8.78 (s, 2H), 8.93 (s, 1H), 9.16 (s, 1H), 10.54 (s, 1H).	1*H*-Benzotriazole

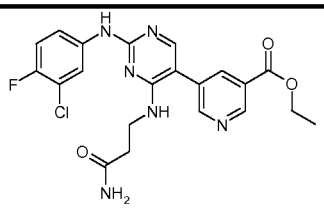
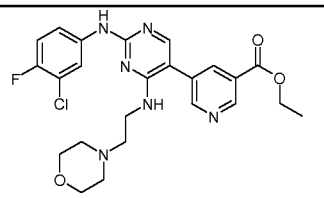
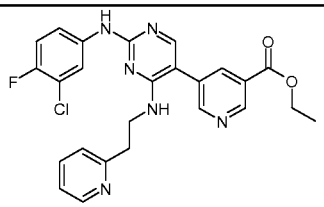
The following examples were prepared using the general method described above for **Example 1** using 3-(ethoxycarbonyl)pyridine-5-boronic acid pinacol ester, tris(dibenzyledeneacetone)-dipalladium(0), 2-dicyclohexyl phosphino-2',4',6'-triiso-propyl-1,1'-biphenyl, sodium carbonate and the starting material (SM) indicated.

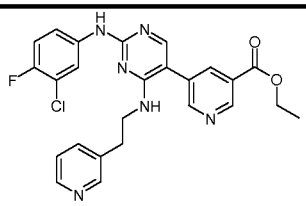
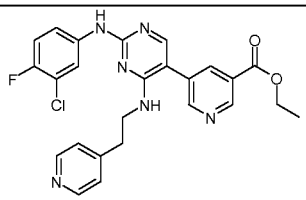
Ex	Compound	Data	SM
90	 5-[2-(3-Chloro-4-fluoro-phenylamino)-4-propylamino-pyrimidin-5-yl]-nicotinic acid ethyl ester	MS(ES): 430.2 (M+1) for $C_{21}H_{21}ClFN_5O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.9 (t, *J* = 7.44 Hz, 3H), 1.31-1.35 (m, 3H), 1.58 (q, *J* = 7.3 Hz, 2H), 4.35 (q, J = 7.12 Hz, 2H), 7.0 (t, *J* = 5.76 Hz, 1H), 7.29 (t, *J* = 9.08 Hz, 1H), 7.57 (ddd, *J* = 9.06, 4.2, 2.64 Hz, 1H), 7.83 (s, 1H), 8.21 (t, *J* = 2.12 Hz, 1H), 8.29 (dd, *J* = 6.92, 2.68 Hz, 1H), 8.77 (d, *J* = 2.2 Hz, 1H), 9.03 (d, *J* = 2 Hz, 1H), 9.48 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-propyl-pyrimidine-2,4-diamine **(Intermediate 35)**

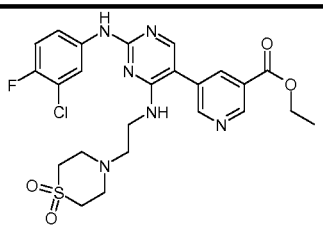
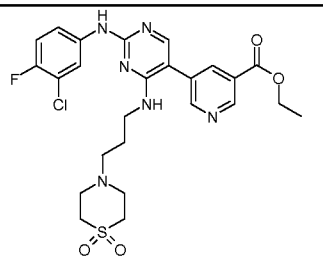
Ex	Compound	Data	SM
91	 5-{2-(3-Chloro-4-fluoro-phenylamino)-4-[3-(2-oxo-pyrrolidin-1-yl)-propylamino]-pyrimidin-5-yl}-nicotinic acid ethyl ester	MS(ES): 513(M+1) for $C_{25}H_{26}ClFN_6O_3$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.33 (t, J = 6.96 Hz, 3H), 1.74 (t, J = 6.40 Hz, 2H), 1.87 (t, J = 7.48 Hz, 2H), 2.16 (t, J = 7.88 Hz, 2H), 3.30 (m, 6H), 4.33 (m, 2H), 6.90 (br s, 1H), 7.33 (m, 1H), 7.65 (m, 1H), 7.85 (br s, 1H), 8.20 (m, 2H), 8.80 (br s, 1H), 9.05 (s, 1H), 9.50 (s, 1H).	1-{3-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-propyl}-pyrrolidin-2-one **(Intermediate 36)**
92	 5-[4-(1-Acetyl-piperidin-4-ylamino)-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester	MS(ES): 513 (M+1) for $C_{25}H_{26}ClFN_6O_3$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.33 (t, J = 7.08 Hz, 3H), 1.34-1.47 (m, 1H), 1.83-1.91 (m, 2H), 1.98 (s, 3H), 2.66 (m, 1H), 3.13 (m, 1H), 3.82 (d, J = 2.60 Hz, 1H), 4.22 (m, 1H), 4.33-4.38 (m, 3H), 6.69 (d, J = 7.76 Hz, 1H), 7.33 (t, J = 9.12 Hz, 1H), 7.56 (m, 1H), 7.87 (s, 1H), 8.21 (t, J = 2.08 Hz, 1H), 8.23 (dd, J = 7.00, 2.72 Hz, 1H), 8.78 (d, J = 2.12 Hz, 1H), 9.03 (d, J = 1.92 Hz, 1H), 9.53 (s, 1H).	1-{4-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-piperidin-1-yl}-ethanone (Intermediate 72)
93	 5-[2-(3-Chloro-4-fluoro-phenylamino)-4-(2-dimethylamino-ethylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester	MS(ES): 459.5 (M+1) for $C_{22}H_{24}ClFN_6O_2$. ^{1}H NMR (400 MHz, MeOD): δ 1.43 (t, J = 7.12 Hz, 3H), 2.38 (s, 6H), 2.72 (t, J = 6.32 Hz, 2H), 3.64 (t, J = 6.48 Hz, 2H), 4.45 (q, J = 7.12 Hz, 2H), 7.16 (t, J = 9 Hz, 1H), 7.50 (ddd, J = 8.98, 4.1, 2.68 Hz, 1H), 7.82 (s, 1H), 8.01 (dd, J = 6.7, 2.64 Hz, 1H), 8.4 (t, J = 2.04 Hz, 1H), 8.78 (d, J = 2.08 Hz, 1H), 9.1 (d, J = 1.96 Hz, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-dimethylamino-ethyl)-pyrimidine-2,4-diamine (Intermediate 37)

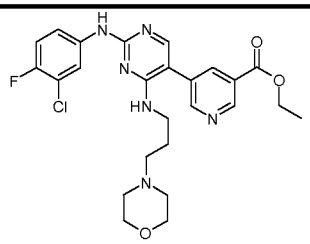
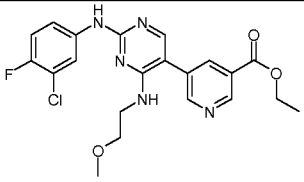
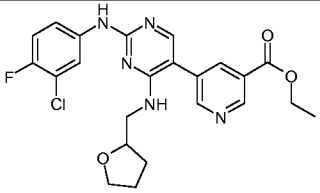
Ex	Compound	Data	SM
94	 5-[4-(2-Acetylamino-ethylamino)-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester	MS(ES): 473 (M+1) for $C_{22}H_{22}ClFN_6O_3$. ^{1}H NMR (400 MHz, MeOD): δ 1.43 (t, *J* = 7.12 Hz, 3H), 1.91 (s, 3H), 3.44 (t, *J* = 5.52 Hz, 2H), 3.57 (t, *J* = 6.24 Hz, 2H), 4.46 (q, *J* = 7.12 Hz, 2H), 7.17 (t, *J* = 9 Hz, 1H), 7.51 (ddd, *J* = 8.98, 4.1, 2.68 Hz, 1H), 7.8 (s, 1H), 8.06 (dd, *J* = 6.76, 2.68 Hz, 1H), 8.40 (t, *J* = 2.08 Hz, 1H), 8.78 (d, *J* = 2.2 Hz, 1H), 9.11 (d, *J* = 1.96 Hz, 1H).	N-{2-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-ethyl}-acetamide **(Intermediate 38)**
95	 5-{2-(3-Chloro-4-fluoro-phenylamino)-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-5-yl}-nicotinic acid ethyl ester	MS(ES): 479. (M+1) for $C_{24}H_{20}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.34 (t, *J* = 7.12 Hz, 3H), 4.38 (q, *J* = 7.08 Hz, 2H), 4.68 (d, *J* = 5.8 Hz, 2H), 7.16 (t, *J* = 9.12 Hz, 1H), 7.24 (dd, *J* = 7.02, 5.48 Hz, 1H), 7.33 (d, *J* = 7.68 Hz, 1H), 7.49-7.55 (m, 2H), 7.71-7.75 (m, 1H), 7.93-7.95 (m, 2H), 8.35 (t, *J* = 2.05 Hz, 1H), 8.52 (d, *J* = 4.92 Hz, 1H), 8.9 (d, *J* = 2.8 Hz, 1H), 9.07 (d, *J* = 1.88 Hz, 1H), 9.43 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-pyridin-2-ylmethyl-pyrimidine-2,4-diamine **(Intermediate 39)**
96	 5-{2-(3-Chloro-4-fluoro-phenylamino)-4-[(pyridin-3-ylmethyl)-amino]-pyrimidin-5-yl}-nicotinic acid ethyl ester	MS(ES): 479.5 (M+1) for $C_{24}H_{20}ClFN_6O_2$. ^{1}H NMR (400 MHz, MeOD): δ 1.42 (t, *J* = 7.12 Hz, 3H), 4.45 (q, *J* = 7.12 Hz, 2H), 4.70 (s, 2H), 7.10 (t, *J* = 8.96 Hz, 1H), 7.33-7.41 (m, 2H), 7.8-7.9 (m, 3H), 8.41-8.44 (m, 2H), 8.5 (s, 1H), 8.81 (d, *J* = 2.08 Hz, 1H), 9.13 (d, *J* = 1.92 Hz, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(pyridin-3-ylmethyl)-pyrimidine-2,4-diamine hydrochloride salt **(Intermediate 40)**

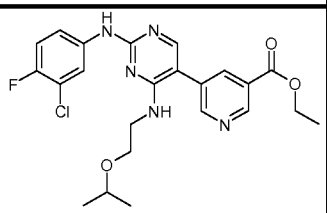
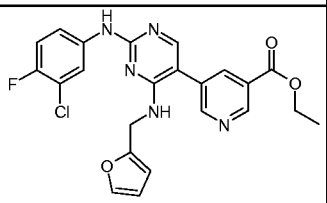
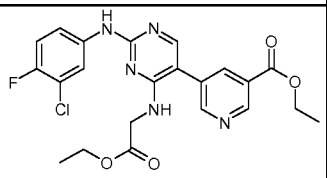
Ex	Compound	Data	SM
97	 5-{2-(3-Chloro-4-fluoro-phenylamino)-4-[(pyridin-4-ylmethyl)-amino]-pyrimidin-5-yl}-nicotinic acid ethyl ester	MS(ES):479.5 (M+1) for $C_{24}H_{20}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.34 (t, *J* = 7.08 Hz, 3H), 4.38 (q, *J* = 7.04 Hz, 2H), 4.59 (d, *J* = 5.92 Hz, 2H), 7.18 (t, *J* = 9.12 Hz, 1H), 7.34 (d, *J* = 5.96 Hz, 2H), 7.44-7.48 (m, 1H), 7.57 (t, *J* = 5.96 Hz, 1H), 7.92 (m, 2H), 8.31 (t, *J* = 2.12 Hz, 1H), 8.49 (dd, *J* = 4.48, 1.56 Hz, 2H), 8.89 (d, *J* = 2.20 Hz, 1H), 9.07 (d, *J* = 2.00 Hz, 1H), 9.45 (s, 1H).	**PE-004-025** 5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-pyridin-4-ylmethyl-pyrimidine-2,4-diamine hydrochloride salt **(Intermediate 41)**
98	 5-[4-(2-*tert*-Butoxycarbonylamino-ethylamino)-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester	MS (ES): 531 (M+1) for $C_{25}H_{28}ClFN_6O_4$. ^{1}H NMR (400 MHz, MeOD): δ 1.33 (s, 9H), 1.43 (t, *J* = 7.12 Hz, 3H), 3.54 (t, *J* = 6.08 Hz, 2H), 4.45 (q, *J* = 7.12 Hz, 2H), 7.17 (t, *J* = 8.96 Hz, 1H), 7.52 (dt, *J* = 8.84, 3.88 Hz, 1H), 7.80 (s, 1H), 8.05 (dd, *J* = 6.70, 2.64 Hz, 1H), 8.39 (t, *J* = 2.04 Hz, 1H), 8.77 (d, *J* = 2.12 Hz, 1H), 9.10 (d, *J* = 1.96 Hz, 1H).	{2-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-ethyl}-carbamic acid *tert*-butyl ester **(Intermediate 73)**

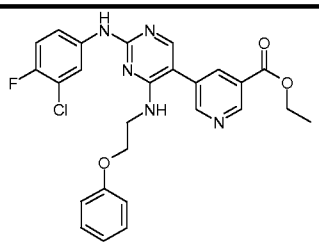
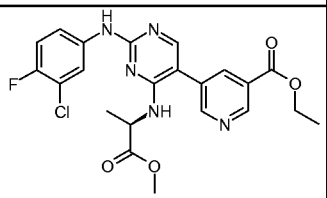
Ex	Compound	Data	SM
99	 5-[4-(2-Carbamoyl-ethylamino)-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester	MS(ES): 459(M+1) for $C_{21}H_{20}ClFN_6O_3$. ^{1}H NMR (400 MHz, MeOD): δ 1.43 (t, *J* = 7.16 Hz, 3H), 2.59 (t, *J* = 6.76 Hz, 2H), 3.73 (t, *J* = 6.72 Hz, 2H), 4.44 (q, *J* = 7.12 Hz, 2H), 7.16 (t, *J* = 9 Hz, 1H), 7.55 (ddd, *J* = 9, 4.06, 2.76 Hz, 1H), 7.81 (s, 1H), 8.04 (dd, *J* = 6.74, 2.68 Hz, 1H), 8.38 (t, *J* = 2.04 Hz, 1H), 8.75 (d, *J* = 2.16 Hz, 1H), 9.1 (d, *J* = 1.92 Hz, 1H).	3-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-propionamide **(Intermediate 42)**
100	 5-[2-(3-Chloro-4-fluoro-phenylamino)-4-(2-morpholin-4-yl-ethylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester	MS(ES): 501 (M+1) for $C_{24}H_{26}ClFN_6O_3$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.34 (t, *J* = 7.08 Hz, 3H), 2.31 (s, 4H), 3.45-3.53 (m, 6H), 4.37 (q, *J* = 7.08 Hz, 2H), 6.70 (m, 1H), 7.29 (t, *J* = 9.16 Hz, 1H), 7.61-7.64 (m, 1H), 7.87 (s, 1H), 8.18 (dd, *J* = 6.92, 2.64 Hz, 1H), 8.24 (t, *J* = 2.08 Hz, 1H), 8.81 (d, *J* = 2.20 Hz, 1H), 9.05 (d, *J* = 2.00 Hz, 1H), 9.48 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-morpholin-4-yl-ethyl)-pyrimidine-2,4-diamine **(Intermediate 43)**
101	 5-[2-(3-Chloro-4-fluoro-phenylamino)-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester	MS (ES): 493(M) for $C_{25}H_{22}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.33 (t, *J* = 7.12 Hz, 3H), 3.04 (t, *J* = 7.04 Hz, 2H), 3.72 (q, *J* = 5.84 Hz, 2H), 4.37 (q, *J* = 7.08 Hz, 2H), 7.08 (t, 1H), 7.23-7.27 (m, 3H), 7.69 (m, 2H), 7.85 (s, 1H), 8.17 (m, 2H), 8.44 (m, 1H), 8.73 (d, *J* = 2.24 Hz, 1H), 9.04 (d, *J* = 2.04 Hz, 1H), 9.48 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-pyridin-2-yl-ethyl)-pyrimidine-2,4-diamine **(Intermediate 44)**

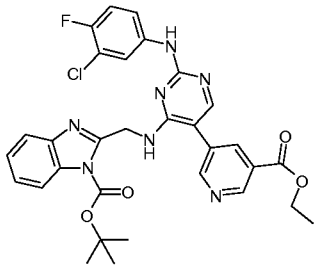
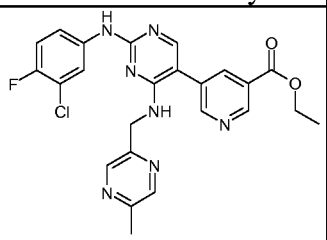
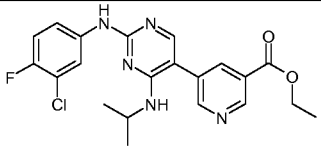
Ex	Compound	Data	SM
102	 5-[2-(3-Chloro-4-fluoro-phenylamino)-4-(2-pyridin-3-yl-ethylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester	MS(ES): 493 (M) for $C_{25}H_{22}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.34 (t, J = 7.04 Hz, 3H), 2.89 (t, J = 7.16 Hz, 2H), 3.6 (q, J = 6.72 Hz, 2 H), 4.37 (q, J = 7.12 Hz, 2H), 7.01 (t, J = 5.52 Hz, 1H), 7.28 (m, 2H), 7.60 (m, 2H), 7.85 (s, 1H), 8.15 (t, J = 2.16 Hz, 1H), 8.20 (dd, J = 6.90, 2.56 Hz, 1H), 8.40 (m, 2H), 8.71 (d, J = 2.16 Hz, 1H), 9.03 (d, J = 1.96 Hz, 1H), 9.48 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-pyridin-3-yl-ethyl)-pyrimidine-2,4-diamine **(Intermediate 45)**
103	 5-[2-(3-Chloro-4-fluoro-phenylamino)-4-(2-pyridin-4-yl-ethylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester	MS(ES): 493 (M) for $C_{25}H_{22}ClFN_6O_2$. ^{1}H NMR (400 MHz, CD_3OD) : δ 1.43 (t, J = 7.12 Hz, 3H), 3.00 (t, J = 7.32 Hz, 2H), 3.75 (t, J = 6.96 Hz, 2H), 4.45 (q, J = 7.08 Hz, 2H), 7.17 (t, J = 8.92 Hz, 1H), 7.30 (d, J = 6.0 Hz, 2H), 7.45-7.49 (m, 1H), 7.79 (s, 1H), 8.07 (dd, J = 2.68, 6.72 Hz, 1H), 8.32 (t, J = 2.00 Hz, 1H), 8.42 (d, J = 6.12 Hz, 2H), 8.69 (d, J = 2.08 Hz, 1H), 9.09 (d, J = 2.00 Hz, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-pyridin-4-yl-ethyl)-pyrimidine-2,4-diamine hydrochloride salt **(Intermediate 46)**

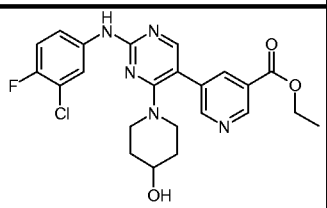
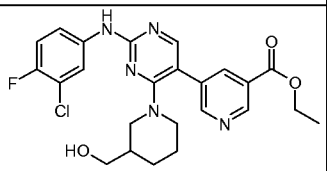
Ex	Compound	Data	SM
104	 5-{2-(3-Chloro-4-fluoro-phenylamino)-4-[2-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-ethylamino]-pyrimidin-5-yl}-nicotinic acid ethyl ester	MS(ES): 549.2 (M+1) for $C_{24}H_{26}ClFN_6O_4S$. ^{1}H NMR (400 MHz, DMSO-d_6): δ1.34 (t, J = 7.08 Hz, 3H), 2.70 (t, J = 6.40 Hz, 2H), 2.93 (br s, 4H), 3.03 (br s, 4H), 3.38-3.48 (m, 2H), 3.47 (m, 2H), 4.38 (q, J = 7.04 Hz, 2H), 6.81 (t, J = 5.44 Hz, 1H), 7.31 (t, J = 9.12 Hz, 1H), 7.64 (ddd, J = 9.10, 4.24, 2.72 Hz, 1H), 7.88 (s, 1H), 8.18 (dd, J = 6.92, 2.60 Hz, 1H), 8.25 (t, J = 2.12 Hz, 1H), 8.82 (d, J = 2.20 Hz, 1H), 9.05 (d, J = 2.0 Hz, 1H), 9.48 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-[2-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-ethyl]-pyrimidine-2,4-diamine **(Intermediate 47)**
105	 5-{2-(3-Chloro-4-fluoro-phenylamino)-4-[3-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-propylamino]-pyrimidin-5-yl}-nicotinic acid ethyl ester	MS(ES): 563 (M+1) for $C_{25}H_{28}ClFN_6O_4S$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.34 (t, J = 7.04 Hz, 3H), 1.71-1.74 (t, 2H, J = 7 Hz), 2.50-2.54 (br s, 2H), 2.83 (br s, 4H), 2.99-3.0 (br s, 4H), 3.38-3.42 (m, 2H), 4.37 (q, J = 7.04 Hz 2H), 6.95-6.97 (t, J = 5.44 Hz, 1H), 7.31 (t, J = 9.16 Hz, 1H), 7.60 (ddd, J = 9.02, 4.18, 2.76 Hz, 1H), 7.85 (s, 1H), 8.22 (t, J = 2.12 Hz, 1H), 8.27 (dd, J = 6.86, 2.60 Hz, 1H), 8.80 (d, J = 2.16 Hz, 1H), 9.0 (d, 1H, J = 1.96 Hz), 9.48 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-[3-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-propyl]-pyrimidine-2,4-diamine **(Intermediate 49)**

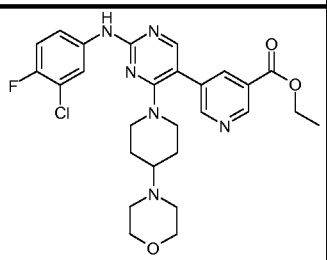
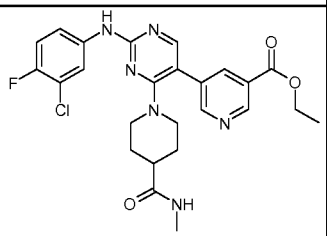
Ex	Compound	Data	SM
106	 5-[2-(3-Chloro-4-fluoro-phenylamino)-4-(3-morpholin-4-yl-propylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester	MS(ES): 515 (M+1) for $C_{25}H_{28}ClFN_6O_3$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.34 (t, *J* = 7.08 Hz, 3H), 1.73 (t, *J* = 6.56 Hz, 2H), 2.29-2.35 (m, 6H), 3.35-3.46 (m, 6H), 4.37 (q, *J* = 7.08 Hz, 2H), 6.96 (t, *J* = 5.04 Hz, 1H), 7.31 (t, *J* = 9.12 Hz, 1H), 7.60 (dt, *J* = 2.96, 6.44 Hz, 1H), 7.85 (s, 1H), 8.22 (t, *J* = 1.96 Hz, 1H), 8.27 (dd, *J* = 2.52, 6.88 Hz, 1H), 8.80 (d, *J* = 2.04 Hz, 1H), 9.05 (d, *J* = 1.88 Hz, 1H), 9.49 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(3-morpholin-4-yl-propyl)-pyrimidine-2,4-diamine **(Intermediate 48)**
107	 5-[2-(3-Chloro-4-fluoro-phenylamino)-4-(2-methoxy-ethylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester	MS(ES):446 (M+1) for $C_{21}H_{21}ClFN_5O_3$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.34 (t, *J* = 7.12 Hz, 3H), 3.25 (s, 3H), 3.50-3.54 (m, 4H), 4.37 (q, *J* = 7.08 Hz, 2H), 6.95 (br s, 1H), 7.29 (t, *J* = 9.12 Hz, 1H), 7.6 (m, 1H), 7.86 (s, 1H), 8.19 (m, 2H), 8.77 (d, *J* = 2.2 Hz, 1H), 9.04 (d, *J* = 2.04 Hz, 1H), 9.48 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-methoxy-ethyl)-pyrimidine-2,4-diamine **(Intermediate 50)**
108	 ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(oxolan-2-ylmethylamino)pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES):472 (M+1) for $C_{23}H_{23}ClFN_5O_3$ ^{1}H NMR (400 MHz DMSO-d_6): δ 1.34 (t, *J* = 7.08 Hz, 3H), 1.57-1.63 (m, 1H), 1.76-1.94 (m, 3H), 3.4-3.45 (m, 2H), 3.60-3.62 (m, 1H), 3.74-3.76 (m, 1H), 4.07-4.1 (m, 1H), 4.37 (q, *J* = 7.08 Hz, 2H), 6.95 (br s, 1H), 7.3 (t, *J* = 9.08 Hz, 1H), 7.6 (dd, *J* = 7.64, 4.88 Hz, 1H), 7.87 (s, 1H), 8.20–8.22 (m, 2H), 8.78 (d, *J* = 2.2 Hz, 1H), 9.0 (d, *J* = 2 Hz, 1H), 9.48 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(tetrahydro-furan-2-ylmethyl)-pyrimidine-2,4-diamine **(Intermediate 75)**

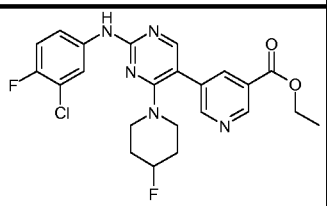
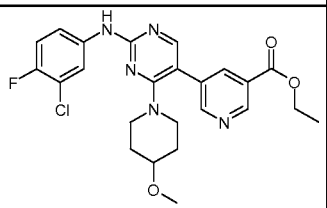
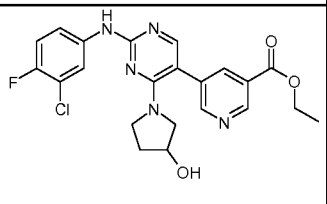
Ex	Compound	Data	SM
109	 ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(2-propan-2-yloxyethylamino)pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES): 474 (M+1) for $C_{23}H_{25}ClFN_5O_3$. ^{1}H NMR (400 MHz, DMSO-d_6):δ 1.05 (d, *J* = 6.04 Hz, 6H), 1.34 (t, *J* = 7.08 Hz, 3H), 3.48-3.55 (m, 5H), 4.37 (q, *J* = 5.12 Hz, 2H), 6.87 (d, *J* = 5.12 Hz, 1H), 7.29 (t, *J* = 9.08 Hz, 1H), 7.62 (ddd, *J* = 9.02, 4.12, 2.72 Hz, 1H), 7.86 (s, 1H), 8.18-8.21 (m, 2H), 8.78 (d, *J* = 2.16 Hz, 1H), 9.05 (d, *J* = 1.92 Hz, 1H), 9.48 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-isopropoxy-ethyl)-pyrimidine-2,4-diamine **(Intermediate 51)**
110	 ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(furan-2-ylmethylamino)pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES):468 (M+1) for $C_{23}H_{19}ClFN_5O_3$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.34 (t, *J* = 7.08 Hz, 3H), 4.37 (q, *J* = 7.08 Hz, 2H), 4.56 (d, *J* = 5.72 Hz, 2H), 6.26 (d, *J* = 3.08 Hz, 1H), 6.37 (dd, *J* = 3.10, 1.84 Hz, 1H), 7.28 (t, *J* = 9.08 Hz, 1H), 7.44 (t, *J* = 5.76 Hz, 1H), 7.55-7.61 (m, 2H), 7.90 (s, 1H), 8.14 (dd, *J* = 6.84, 2.60 Hz, 1H), 8.23 (t, *J* = 2.12 Hz, 1H), 8.79 (s, 1H), 9.05 (s, 1H), 9.50 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(furan-2-ylmethyl)-pyrimidine-2,4-diamine **(Intermediate 52)**
111	 ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[(2-ethoxy-2-oxoethyl)amino]pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES): 474 (M+1) for $C_{22}H_{21}ClFN_5O_4$. ^{1}H NMR (400 MHz MeOD): δ 1.17-1.21 (m, 3H), 1.43 (t, *J* = 7.12 Hz, 3H), 4.15 (q, *J* = 7.00 Hz, 4H), 4.45 (q, *J* = 7.12 Hz, 2H), 7.14 (t, *J* = 8.96 Hz, 1H), 7.48 (ddd, *J* = 9.06, 4.12, 2.72 Hz, 1H), 7.88 (s, 1H), 7.94 (dd, *J* = 6.68, 2.60 Hz, 1H), 8.46 (t, *J* = 2.08 Hz, 1H), 8.83 (d, *J* = 2.16 Hz, 1H), 9.12 (d, *J* = 1.88 Hz, 1H).	[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-acetic acid ethyl ester **(Intermediate 76)**

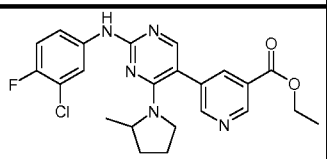
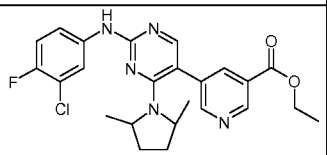
Ex	Compound	Data	SM
112	 ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[(2-ethoxy-2-oxoethyl)amino]pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES): 508 (M+1) for $C_{26}H_{23}ClFN_5O_3$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.32 (t, *J* = 7.12 Hz, 3H), 3.74 (q, *J* = 5.88 Hz, 2H), 4.16 (t, *J* = 6.24 Hz, 2H), 4.37 (q, *J* = 7.12 Hz, 2H), 6.93 (m, 3H), 7.1 (t, *J* = 5.6 Hz, 1H), 7.25 (m, 3H), 7.62 (ddd, *J* = 9.08, 4.28, 2.68 Hz, 1H), 7.89(s, 1H), 8.2 (dd, *J* = 6.9, 2.64 Hz, 1H), 8.22 (t, *J* = 2.16 Hz, 1H), 8.77 (d, *J* = 2.24 Hz, 1H), 9.05 (d, *J* = 2 Hz, 1H), 9.51 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(2-phenoxy-ethyl)-pyrimidine-2,4-diamine **(Intermediate 53)**
113	 ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[[(2R)-1-methoxy-1-oxopropan-2-yl]amino]pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES): 474.1 (M) for $C_{22}H_{21}ClFN_5O_4$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.36 (t, *J* = 7.08 Hz, 3H), 1.39 (d, *J* = 7.24 Hz, 3H), 4.37 (q, *J* = 7.08 Hz, 2H), 4.74-4.78 (m, 1H), 7.17 (d, *J* = 7.34 Hz, 1H), 7.29 (t, *J* = 9.12 Hz, 1H), 7.59 (ddd, *J* = 9.10, 4.22, 2.72 Hz, 1H), 7.94 (s, 1H), 8.02 (dd, *J* = 6.82, 2.52 Hz, 1H), 8.27 (t, *J* = 2.16 Hz, 1H), 8.82 (d, *J* = 2.16 Hz, 1H), 9.05 (d, *J* = 2 Hz, 1H).	2-(5-Bromo-2-chloro-pyrimidin-4-ylamino)-propionic acid methyl ester **(Intermediate 54)**

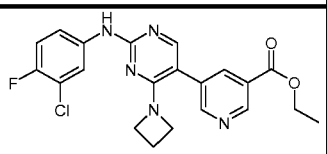
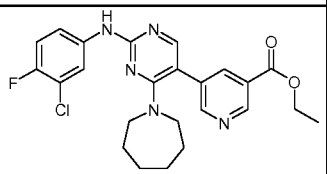
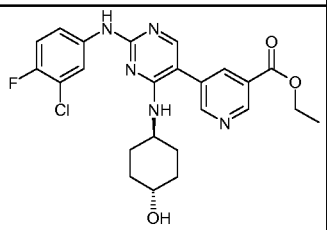
Ex	Compound	Data	SM
114	 *tert*-butyl 2-[[[2-[(3-chloro-4-fluorophenyl)amino]-5-(5-ethoxycarbonylpyridin-3-yl)pyrimidin-4-yl]amino]methyl]benzimidazole-1-carboxylate	MS(ES): 618.3 (M+1) for $C_{31}H_{29}ClFN_7O_4$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.32 (t, J = 6.96 Hz, 3H), 1.66 (s, 9H), 4.36 (q, J = 6.92 Hz, 2H), 5.01 (d, J = 4.84 Hz, 2H), 7.09 (t, J = 9.20 Hz, 1H), 7.29-7.38 (m, 3H), 7.51 (br s, 1H), 7.65 (d, J = 7.56 Hz, 1H), 7.88 (br s, 1H), 7.93 (d, J = 7.76 Hz, 1H), 7.99 (s, 1H), 8.47 (s, 1H), 8.96 (s, 1H), 9.08 (s, 1H), 9.50 (s, 1H).	*Tert*-butyl 2-[[[5-bromo-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-4-yl]amino]methyl]benzimidazole-1-carboxylate **(Intermediate 126)**
115	 ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[(5-methylpyrazin-2-yl)methylamino]pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES): 494(M+1) for $C_{24}H_{21}ClFN_7O_2$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.34 (t, *J* = 7.08 Hz, 3H), 2.44 (s, 3H), 4.37 (q, *J* = 7.12 Hz, 2H), 4.67 (d, *J* = 5.80 Hz, 2H), 7.21 (t, *J* = 9.08 Hz, 1H), 7.51 (dt, *J* = 8.59, 4.16 Hz, 1H), 7.59 (t, *J* = 5.32 Hz, 1H), 7.96 (m, 2H), 8.32 (t, *J* = 2.12 Hz, 1H), 8.48 (d, *J* = 8.32 Hz, 2H), 8.87 (d, *J* = 2.16 Hz, 1H), 9.07 (d, *J* = 1.96 Hz, 1H), 9.47 (s, 1H).	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(5-methyl-pyrazin-2-ylmethyl)-pyrimidine-2,4-diamine **(Intermediate 77)**
116	 ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(propan-2-ylamino)pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES): 430 (M+1) for $C_{21}H_{21}ClFN_5O_2$ ^{1}H NMR (400 MHz DMSO-d_6): δ 1.17 (d, *J* = 6.56 Hz, 6H), 1.34 (t, *J* = 7.12 Hz, 3H), 4.37 (m, 3H), 6.62 (d, *J* = 7.8 Hz, 1H), 7.3 (t, *J* = 11.28 Hz, 1H), 7.55-7.59 (m, 1H), 7.84 (s, 1H), 8.2 (t, *J* = 1.96 Hz, 1H), 8.28 (dd, *J* = 6.9, 2.48 Hz, 1H), 8.78 (d, *J* = 1.92 Hz, 1H), 9.04 (d, *J* = 1.76 Hz, 1H), 9.47 (s, 1H).	(5-Bromo-2-chloro-pyrimidin-4-yl)-isopropyl-amine **(Intermediate 56)**

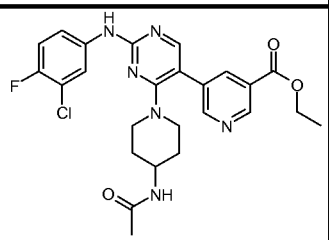
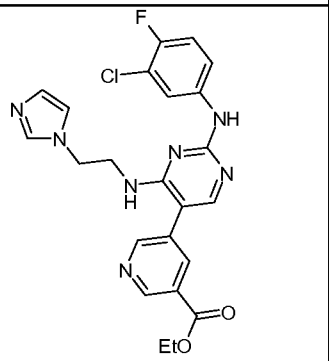
Ex	Compound	Data	SM
117	 ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(4-hydroxypiperidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES): 472 (M+1) for $C_{23}H_{23}ClFN_5O_3$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.32 (m, 2H), 1.35 (t, *J* = 7.08 Hz, 3H), 1.66-1.69 (m, 2H), 2.95 (t, *J* = 10.12 Hz, 2H), 3.5-3.53 (m, 2H), 3.63-3.64 (br s, 1H), 4.37 (q, *J* = 7.04 Hz, 2H), 4.71 (d, *J* = 3.60 Hz, 1H), 7.33 (t, *J* = 9.12 Hz, 1H), 7.60 (ddd, *J* = 9.08, 4.16, 2.76 Hz, 1H), 8.13 (s, 1H), 8.22 (dd, *J* = 6.88, 2.60 Hz, 1H), 8.34 (t, *J* = 2.12 Hz, 1H), 8.91 (d, *J* = 2.16 Hz, 1H), 9.00 (d, *J* = 1.96 Hz, 1H), 9.69 (s, 1H).	1-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-yl]-piperidin-4-ol **(Intermediate 78)**
118	 ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(hydroxymethyl)piperidin-1-yl]pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES): 484.2 (M-1) for $C_{24}H_{25}ClFN_5O_3$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.10-1.13 (m, 1H), 1.36 (t, *J* = 7.12 Hz, 3H), 1.40 (m, 1H), 1.52-1.69 (m, 3H), 2.60 (t, 1H), 2.76 (t, *J* = 10.76 Hz, 1H), 3.13 (dd, *J* = 10.38, 7.44 Hz, 1H), 3.21 (dd, *J* = 10.56, 5.32 Hz, 1H), 3.58 (d, *J* = 12.56 Hz, 1H), 3.74 (d, *J* = 11.48 Hz, 1H), 4.37 (q, *J* = 7.04 Hz, 2H), 7.32 (t, *J* = 9.12 Hz, 1H), 7.66 (ddd, *J* = 9.10, 4.22, 2.76 Hz, 1H), 8.12 (s, 1H), 8.17 (dd, *J* = 6.86, 2.64 Hz, 1H), 8.31-8.33 (m, 1H), 8.89 (d, *J* = 2.12 Hz, 1H), 8.99 (d, *J* = 1.96 Hz, 1H), 9.69 (s, 1H).	{1-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-yl]-piperidin-3-yl}-methanol **(Intermediate 79)**

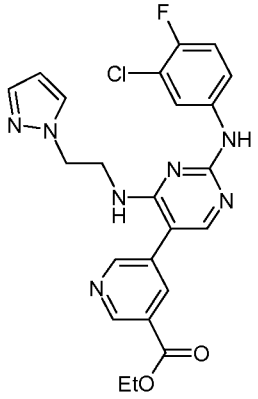
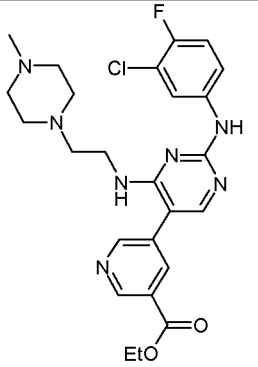
Ex	Compound	Data	SM
119	 ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(4-morpholin-4-ylpiperidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES): 541 (M+1) for $C_{27}H_{30}ClFN_6O_3$. ^{1}H NMR (400 MHz $CDCl_3$): δ 1.45 (t, *J* = 7.12 Hz, 3H), 1.9 (m, 2H), 2.40 (br s, 1H), 2.53 (br s, 4H), 2.80 (m, 2H), 3.71 (br s, 4H), 3.85 (d, *J* = 13.04 Hz, 2H), 4.46 (q, *J* = 7.12 Hz, 2H), 6.90 (s, 1H), 7.10 (t, *J* = 8.80 Hz, 1H), 7.27 (m, 1H), 7.98 (s, 1H), 8.06 (d, *J* = 3.96 Hz, 1H), 8.35 (t, *J* = 2.12 Hz, 1H), 8.84 (d, *J* = 2.24 Hz, 1H), 9.16 (d, *J* = 1.96 Hz, 1H).	[5-Bromo-4-(4-morpholin-4-yl-piperidin-1-yl)-pyrimidin-2-yl]-(3-chloro-4-fluoro-phenyl)-amine **(Intermediate 80)**
120	 ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(methylcarbamoyl)piperidin-1-yl]pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES):513 (M+1) for $C_{25}H_{26}ClFN_6O_3$ ^{1}H NMR (400 MHz DMSO-d_6): δ 1.35 (t, *J* = 7.12 Hz, 3H), 1.5 (m, 4H), 2.26 (m, 1H), 2.52 (d, *J* = 4.56Hz, 3H), 2.79 (t, *J* = 11.32 Hz, 2H), 3.84 (d, *J* = 13.04 Hz, 2H), 4.36 (q, *J* = 7.08 Hz, 2H), 7.33 (t, *J* = 9.08 Hz, 1H) 7.6 (ddd, *J* = 9.06, 4.22, 2.68 Hz, 1H), 7.70 (q, *J* = 4.24 Hz, 1H), 8.1 (s, 1H), 8.21 (dd, *J* = 6.92, 2.64 Hz, 1H), 8.34 (t, *J* = 2.16 Hz, 1H), 8.91 (d, *J* = 2.2 Hz, 1H), 9.0 (d, *J* = 2 Hz, 1H), 9.71 (s, 1H).	1-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-yl]-piperidine-4-carboxylic acid methylamide **(Intermediate 81)**

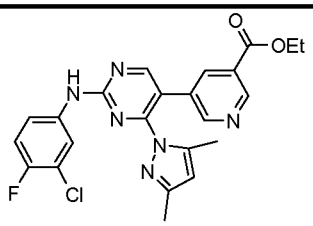
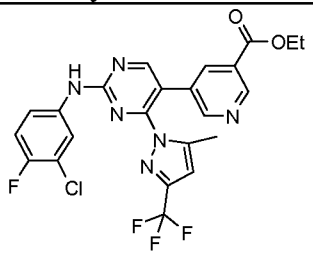
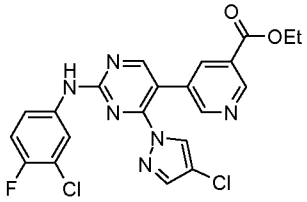
Ex	Compound	Data	SM
121	 ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(4-fluoropiperidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES): 474 (M+1) for $C_{23}H_{22}ClF_2N_5O_2$. ^{1}H NMR (400 MHz MeOD): δ 1.43 (t, *J* = 7.0 Hz, 3H), 1.77 (m, 2H), 1.9 (m, 2H), 3.3 (m, 2H), 3.45 (m, 2H), 4.45 (q, *J* = 7.16 Hz, 2H), 7.17 (t, *J* = 8.96 Hz, 1H), 7.49 (ddd, *J* = 8.96, 4.08, 2.68 Hz, 1H), 8.07 (s, 1H), 8.11 (dd, *J* = 6.76, 2.64 Hz, 1H), 8.49 (t, *J* = 2.08 Hz, 1H) 8.87 (d, *J* = 2.16 Hz, 1H), 9.06 (d, *J* = 1.92 Hz, 1H).	[5-Bromo-4-(4-fluoro-piperidin-1-yl)-pyrimidin-2-yl]-(3-chloro-4-fluoro-phenyl)-amine **(Intermediate 82)**
122	 ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(4-methoxypiperidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES): 486 (M+1) for $C_{24}H_{25}ClFN_5O_3$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.32-1.42 (m, 5H), 1.77-1.79 (m, 2H), 2.99 (t, *J* = 9.88 Hz, 2H), 3.2 (s, 3H), 3.37 (m, 1H), 3.47 (m, 2H), 4.36 (q, *J* = 6.96 Hz, 2H), 7.33 (t, *J* = 9.12 Hz, 1H), 7.58-7.62 (m, 1H), 8.14 (s, 1H), 8.2 (dd, *J* = 6.9, 2.52 Hz, 1H), 8.35 (t, *J* = 2 Hz, 1H), 8.91 (d, *J* = 2.12 Hz, 1H), 9 (d, *J* = 1.84 Hz, 1H), 9.7 (s, 1H).	[5-Bromo-4-(4-methoxy-piperidin-1-yl)-pyrimidin-2-yl]-(3-chloro-4-fluoro-phenyl)-amine **(Intermediate 83)**
123	 ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(3-hydroxypyrrolidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES): 458.2 (M+1) for $C_{22}H_{21}ClFN_5O_3$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.34 (t, *J* = 4.60 Hz, 3H), 1.74 (m, 1H), 1.81 (m, 1H), 2.89 (br s, 1H), 3.20 (br s, 2H), 3.41 (br s, 1H), 4.19 (br s, 1H), 4.35 (q, *J* = 7.04 Hz, 2H), 4.89 (d, *J* = 3.36 Hz, 1H), 7.32 (t, *J* = 9.12 Hz, 1H), 7.65 (ddd, *J* = 9.08, 4.22, 2.68 Hz, 1H), 7.95 (s, 1H), 8.13 (br s, 1H), 8.25 (dd, *J* = 6.94, 2.60 Hz, 1H), 8.76 (br s, 1H), 9.01 (d, *J* = 2.00 Hz, 1H), 9.56 (s, 1H).	1-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-yl]-pyrrolidin-3-ol **(Intermediate 84)**

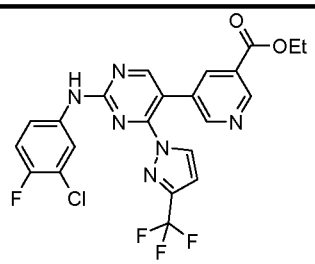
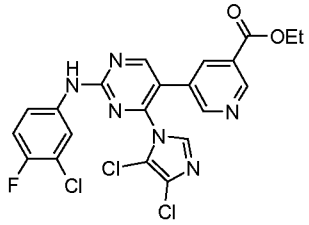
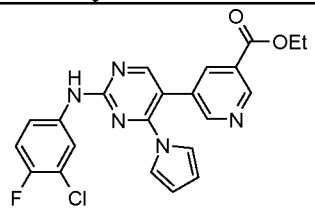
Ex	Compound	Data	SM
124	 ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(2-methylpyrrolidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES):456.2 (M) for $C_{23}H_{23}ClFN_5O_2$. ^{1}H NMR (400 MHz MeOD): δ 1.34 (d, *J* = 6.20 Hz, 3H), 1.43 (t, *J* = 7.16 Hz, 3H), 1.62-1.66 (m, 2H), 1.9-1.94 (m, 1H), 2.1-2.14 (m, 1H), 2.8-2.97 (m, 1H), 2.98-3.1 (m, 1H), 4.41-4.48 (s, 1H), 4.45 (q, *J* = 7.12 Hz, 2H), 7.24 (t, *J* = 8.96 Hz, 1H), 7.46 (ddd, *J* = 8.96, 4.06, 2.68 Hz, 1H), 7.88 (s, 1H), 8.09 (dd, *J* = 6.70, 2.68 Hz, 1H), 8.35 (t, *J* = 2.00 Hz, 1H), 8.77 (d, *J* = 1.68 Hz, 1H), 9.12 (d, *J* = 1.56 Hz, 1H).	[5-Bromo-4-(2-methyl-pyrrolidin-1-yl)-pyrimidin-2-yl]-(3-chloro-4-fluoro-phenyl)-amine **(Intermediate 85)**
125	 ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(2,5-dimethylpyrrolidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES): 470 (M+1) for $C_{24}H_{25}ClFN_5O_2$. ^{1}H NMR (400 MHz DMSO-d_6): δ 0.99 (d, *J* = 6.20 Hz, 6H), 1.34 (t, *J* = 7.08 Hz, 3H), 1.62 (br s, 2H), 1.95 (br s, 2H), 3.96 (br s, 2H), 4.36 (q, *J* = 7.08 Hz, 2H), 7.31 (t, *J* = 9.12 Hz, 1H), 7.56 (dt, *J* = 8.57, 4.00 Hz, 1H), 7.82 (s, 1H), 8.21 (t, *J* = 2.04 Hz, 1H), 8.28 (dd, *J* = 6.88, 2.52 Hz, 1H), 8.80 (d, *J* = 2.12 Hz, 1H), 9.03 (d, *J* = 1.92 Hz, 1H), 9.51 (s, 1H).	[5-Bromo-4-(2,5-dimethyl-pyrrolidin-1-yl)-pyrimidin-2-yl]-(3-chloro-4-fluoro-phenyl)-amine **(Intermediate 86)**

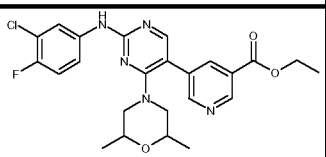
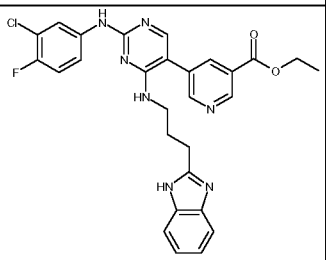
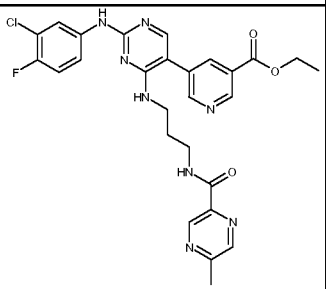
Ex	Compound	Data	SM
126	 ethyl 5-[4-(azetidin-1-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES): 428 (M+1) for $C_{21}H_{19}ClFN_5O_2$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.35 (t, J = 7.04 Hz, 3H), 2.13-2.21 (m, 2H), 3.76 (br s, 4H), 4.37 (q, J = 7.04 Hz, 2H), 7.31 (t, J = 9.12 Hz, 1H), 7.65 (ddd, J = 9.02, 4.26, 2.64 Hz, 1H), 7.98 (s, 1H), 8.16 (t, J = 2.08 Hz, 1H), 8.25 (dd, J = 6.94, 2.60 Hz, 1H), 8.79 (d, J = 2.16 Hz, 1H), 9.02 (d, J = 1.96 Hz, 1H), 9.61 (s, 1H).	(4-Azetidin-1-yl-5-bromo-pyrimidin-2-yl)-(3-chloro-4-fluoro-phenyl)-amine **(Intermediate 87)**
127	 ethyl 5-[4-(azepan-1-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES): 470 (M+1) for $C_{24}H_{25}ClFN_5O_2$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.34 (t, J = 7.04 Hz, 3H), 1.41 (m, 4H), 1.60 (m, 4H), 3.30 (m, 4H), 4.36 (q, J = 7.08 Hz, 2H), 7.32 (t, J = 9.12 Hz, 1H), 7.54-7.57 (m, 1H), 7.91 (s, 1H), 8.15 (t, J = 2.12 Hz, 1H), 8.26 (dd, J = 6.88, 2.44 Hz, 1H), 8.78 (d, J = 2.16 Hz, 1H), 9.00 (d, J = 1.96 Hz, 1H), 9.57 (s, 1H).	(4-Azepan-1-yl-5-bromo-pyrimidin-2-yl)-(3-chloro-4-fluoro-phenyl)-amine **(Intermediate 88)**
128	 ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[(*trans*-4-hydroxycyclohexyl)amino]pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES): 486 (M+1) for $C_{24}H_{25}ClFN_5O_3$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (m, 4H), 1.33 (t, J = 7.00 Hz, 3H), 1.84 (m, 4H), 3.98 (s, 1H), 4.36 (q, J = 7.04 Hz, 2H), 4.55 (d, J = 3.28 Hz, 1H), 6.58 (d, J = 7.84 Hz, 1H), 7.29 (t, J = 9.16 Hz, 1H), 7.54 (dd, J = 5.60, 2.52 Hz, 1H), 7.83 (s, 1H), 8.19 (d, J = 1.92 Hz, 1H), 8.28 (dd, J = 9.30, 4.52 Hz, 1H), 8.76 (d, J = 1.88 Hz, 1H), 9.02 (d, J = 1.76 Hz, 1H), 9.49 (s, 1H).	*Trans*-4-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-ylamino]-cyclohexanol **(Intermediate 89)**

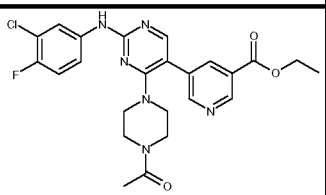
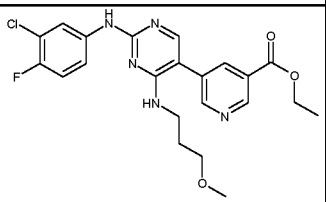
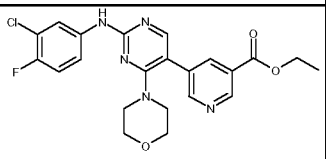
Ex	Compound	Data	SM
129	 ethyl 5-[4-(4-acetamidopiperidin-1-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl]pyridine-3-carboxylate	MS(ES): 513 (M+1) for $C_{25}H_{26}ClFN_6O_3$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.29 (m, 2H), 1.35 (t, J = 7.08 Hz, 3H), 1.66 (m, 2H), 1.74 (s, 3H), 2.90 (m, 2H), 3.60 (m, 2H), 3.70 (br s, 1H), 4.37 (q, J = 7.08 Hz, 2H), 7.34 (t, J = 9.12 Hz, 1H), 7.59-7.62 (m, 1H), 7.81 (d, J = 7.60 Hz, 1H), 8.13 (s, 1H), 8.21 (dd, J = 6.90, 2.64 Hz, 1H), 8.32 (t, J = 2.12 Hz, 1H), 8.91 (d, J = 2.20 Hz, 1H), 9.00 (d, J = 2.00 Hz, 1H), 9.72 (s, 1H).	N-{1-[5-Bromo-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-4-yl]-piperidin-4-yl}-acetamide **(Intermediate 90)**
130	 ethyl 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-imidazol-1-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylate	MS(ES): 482 (M+1) for $C_{23}H_{21}ClFN_7O_2$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.36 (t, J = 7.08 Hz, 3H), 3.65 (q, J = 5.72 Hz, 2H), 4.22 (t, J = 5.88 Hz, 2H), 4.39 (q, J = 6.96 Hz, 2H), 6.87 (s, 1H), 7.00 (t, J = 5.08 Hz, 1H), 7.14 (s, 1H), 7.32 (t, J = 9.08 Hz, 1H), 7.59 (s, 1H), 7.61-7.64 (m, 1H), 7.89 (s, 1H), 8.14-8.17 (m, 2H), 8.31 (s, 1H), 8.72 (d, J = 1.76 Hz, 1H), 9.05 (s, 1H), 9.50 (s, 1H).	5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-[2-(1*H*-imidazol-1-yl)ethyl]pyrimidine-2,4-diamine **(Intermediate 64)**

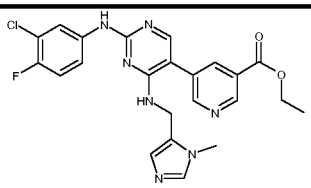
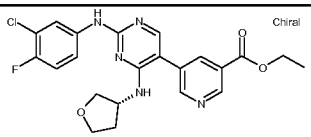
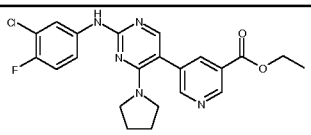
Ex	Compound	Data	SM
131	 ethyl 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-pyrazol-1-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylate	MS(ES): 482 (M+1) for $C_{23}H_{21}ClFN_7O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.34 (t, *J* = 7.04 Hz, 3H), 3.72 (q, *J* = 5.80 Hz, 2H), 4.35-4.40 (m, 4H), 6.22 (t, *J* = 2.08 Hz, 1H), 6.96 (t, *J* = 5.36 Hz, 1H), 7.31 (t, *J* = 9.12 Hz, 1H), 7.43 (t, *J* = 1.28 Hz, 1H), 7.68-7.72 (m, 2H), 7.88 (s, 1H), 8.13 (dd, *J* = 2.56, 6.86 Hz, 1H), 8.17 (t, *J* = 2.08 Hz, 1H), 8.72 (d, *J* = 2.16 Hz, 1H), 9.03 (d, *J* = 1.92 Hz, 1H), 9.51 (s, 1H).	5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-[2-(1*H*-pyrazol-1-yl)ethyl]pyrimidine-2,4-diamine **(Intermediate 91)**
132	 ethyl 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(4-methylpiperazin-1-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylate	MS(ES): 514 (M+1) for $C_{25}H_{29}ClFN_7O_2$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.34 (t, *J* = 7.08 Hz, 3H), 2.14 (s, 3H), 2.30-2.50 (m, 8H), 3.40 (m, 2H), 3.50 (m, 2H), 4.38 (q, *J* = 7.12 Hz, 2H), 6.77 (m, 1H), 7.29 (t, *J* = 9.08 Hz, 1H), 7.65 (ddd, *J* = 2.64, 4.24, 9.09 Hz, 1H), 7.88 (s, 1H), 8.19 (dd, *J* = 2.60, 6.90 Hz, 1H), 8.23-8.24 (m, 1H), 8.81 (d, *J* = 2.20 Hz, 1H), 9.06 (d, *J* = 2.00 Hz, 1H), 9.48 (s, 1H).	5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-[2-(4-methylpiperazin-1-yl)ethyl]pyrimidine-2,4-diamine **(Intermediate 92)**

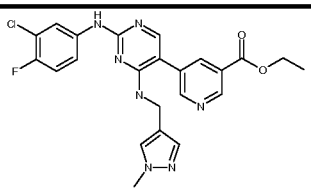
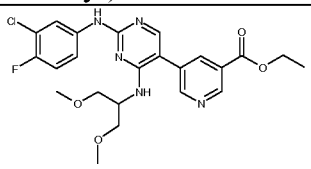
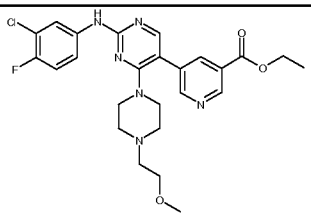
Ex	Compound	Data	SM
133	 ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 467 (M+1) for $C_{23}H_{20}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (t, *J* = 7.08 Hz, 3H), 1.91 (s, 3H), 2.37 (s, 3H), 4.33 (q, *J* = 7.12 Hz, 2H), 6.09 (s, 1H), 7.41 (t, *J* = 9.08 Hz, 1H), 7.62-7.66 (m, 1H), 7.86 (t, *J* = 2.12 Hz, 1H), 8.09 (dd, *J* = 2.56, 6.68 Hz, 1H), 8.49 (d, *J* = 2.24 Hz, 1H), 8.86 (s, 1H), 8.95 (d, *J* = 1.96 Hz, 1H), 10.30 (s, 1H).	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyrimidin-2-amine **(Intermediate 112)**
134	 ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 521 (M+1) for $C_{23}H_{17}ClF_4N_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (t, *J* = 7.20 Hz, 3H), 2.43 (s, 3H), 4.31 (q, *J* = 8.40 Hz, 2H), 6.79 (s, 1H), 7.43 (t, *J* = 8.80 Hz, 1H), 7.65-7.69 (m, 1H), 7.79-7.80 (m, 1H), 8.07-8.08 (m, 1H), 8.61 (d, *J* = 2.40 Hz, 1H), 8.98-9.02 (m, 2H), 10.51 (s, 1H).	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **(Intermediate 113)**
135	 ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(4-chloro-1*H*-pyrazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 473 (M) and 475 (M+2) for $C_{21}H_{15}Cl_2FN_6O_2$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.32 (t, *J* = 7.02 Hz, 3H), 4.34 (q, *J* = 7.02 Hz, 2H), 7.43 (t, *J* = 8.88 Hz, 1H), 7.71-7.73 (m, 1H), 7.74 (s, 1H), 8.03 (d, *J* = 4.53 Hz, 1H), 8.11 (s, 1H), 8.59 (s, 1H), 8.66 (d, *J* = 1.98 Hz, 1H), 8.72 (s, 1H), 9.01 (d, *J* = 1.62 Hz, 1H).	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(4-chloro-1*H*-pyrazol-1-yl)pyrimidin-2-amine **(Intermediate 114)**

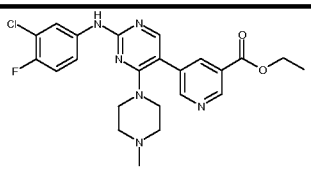
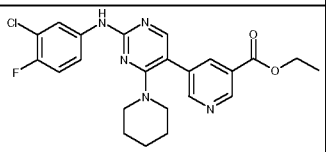
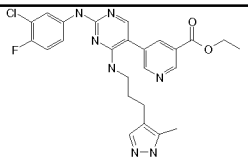
Ex	Compound	Data	SM
136	 ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 507 (M+1) for $C_{22}H_{15}ClF_4N_6O_2$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.30 (t, *J* = 7.0 Hz, 3H), 4.33 (q, *J* = 6.92 Hz, 2H), 7.05 (s, 1H), 7.43 (t, *J* = 6.92 Hz 1H), 7.71-7.74 (m, 1H), 8.03 (s, 1H), 8.03-8.07(m, 1H), 8.55 (s, 1H), 8.68 (m, 1H), 8.85 (s, 1H), 9.02 (s, 1H), 10.48 (s, 1H).	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **(Intermediate 115)**
137	 ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(4,5-dichloro-1*H*-imidazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 507 (M) and 509 (M+2) for $C_{21}H_{14}Cl_3FN_6O$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.32 (t, *J* = 7.08 Hz, 3H), 4.33 (q, *J* = 7.12 Hz, 2H), 7.43 (t, *J* = 9.08 Hz, 1H), 7.69 (ddd, *J* = 9.08, 4.24, 2.76 Hz, 1H), 7.95 (m, 1H), 8.05 (d, *J* = 4.28 Hz, 1H), 8.12 (s, 1H), 8.67 (d, *J* = 2.16 Hz, 1H), 9.04 (d, *J* = 1.92 Hz, 1H), 9.07 (s, 1H).	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(4,5-dichloro-1*H*-imidazol-1-yl)pyrimidin-2-amine **(Intermediate 116)**
138	 ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-pyrrol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 438 (M+1) for $C_{22}H_{17}ClFN_5O_2$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.31 (t, *J* = 6.96 Hz, 3H), 4.33 (q, *J* = 7.08 Hz, 2H), 6.19 (s, 2H), 6.90 (s, 2H), 7.40 (t, 1H), 7.69-7.73 (m, 1H), 8.10-8.14 (m, 2H), 8.64-8.66 (m, 2H), 9.04 (s, 1H), 10.25 (s, 1H).	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(1*H*-pyrrol-1-yl)pyrimidin-2-amine **(Intermediate 117)**

Ex	Compound	Data	SM
139	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(2,6-dimethylmorpholino)pyrimidin-5-yl)nicotinate	MS(ES): 486 (M+1) for $C_{24}H_{25}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 0.96 (d, J=6.03 Hz, 6 H) 1.34 (t, J=7.06 Hz, 3 H) 3.25 - 3.41 (m, 2 H) 3.40 - 3.70 (m, 4 H) 4.37 (q, J=7.10 Hz, 2 H) 7.33 (t, J=9.14 Hz, 1 H) 7.54 (d, J=13.00 Hz, 1 H) 8.05 - 8.28 (m, 2 H) 8.34 (t, J=2.17 Hz, 1 H) 8.91 (d, J=2.26 Hz, 1 H) 9.01 (d, J=1.88 Hz, 1 H) 9.75 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(2,6-dimethylmorpholino)pyrimidin-2-amine **(Intermediate 95)**
140	 ethyl 5-(4-(3-(1H-benzo[d]imidazol-2-yl)propylamino)-2-(3-chloro-4-fluorophenylamino)pyrimidin-5-yl)nicotinate	MS(ES): (M+1) for $C_{28}H_{25}ClFN_7O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.30 (t, J=7.16 Hz, 3 H) 1.98 - 2.19 (m, J=1.51 Hz, 2 H) 2.76 - 2.97 (m, 2 H) 3.37 - 3.57 (m, 2 H) 4.34 (q, J=7.03 Hz, 2 H) 6.95 - 7.18 (m, 3 H) 7.26 (t, J=9.14 Hz, 1 H) 7.30 - 7.49 (m, 2 H) 7.51 - 7.71 (m, 1 H) 7.86 (s, 1 H) 8.10 - 8.36 (m, 2 H) 8.80 (d, J=2.07 Hz, 1 H) 9.03 (d, J=2.07 Hz, 1 H) 9.49 (s, 1 H) 12.15 (s, 1 H)	N^4-(3-(1*H*-benzo[d]imidazol-2-yl)propyl)-5-bromo-N^2-(3-chloro-4-fluorophenyl)pyrimidine-2,4-diamine **(Intermediate 93)**
141	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(5-methylpyrazine-2-carboxamido)propylamino)pyrimidin-5-yl)nicotinate	MS(ES): 565 (M+1) for $C_{27}H_{26}ClFN_8O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.32 (t, J=7.06 Hz, 3 H) 1.74 - 1.93 (m, 2 H) 2.56 (s, 3 H) 3.32 - 3.61 (m, 4 H) 4.35 (q, J=7.10 Hz, 2 H) 7.01 (t, J=5.18 Hz, 1 H) 7.28 (t, J=9.14 Hz, 1 H) 7.50 - 7.72 (m, 1 H) 7.86 (s, 1 H) 8.10 - 8.38 (m, 2 H) 8.54 (s, 1 H) 8.81 (d, J=2.07 Hz, 1 H) 8.91 (t, J=6.03 Hz, 1 H) 8.98 (d, J=1.13 Hz, 1 H) 9.05 (d, J=2.07 Hz, 1 H) 9.48 (s, 1 H)	*N*-(3-(5-bromo-2-(3-chloro-4-fluorophenylamino)pyrimidin-4-ylamino)propyl)-5-methylpyrazine-2-carboxamide **(Intermediate 102)**

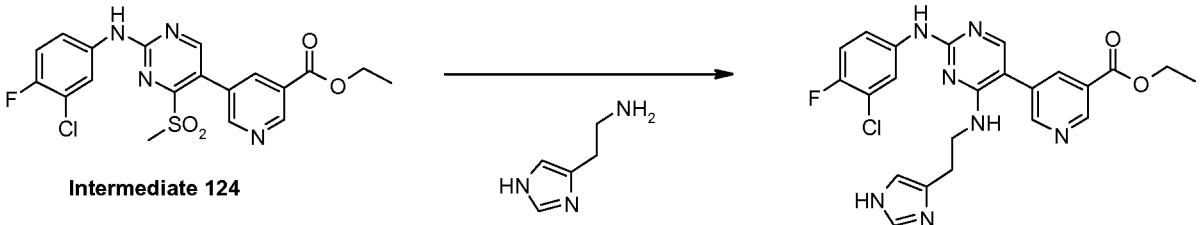
Ex	Compound	Data	SM
142	 ethyl 5-(4-(4-acetylpiperazin-1-yl)-2-(3-chloro-4-fluorophenylamino)pyrimidin-5-yl)nicotinate	MS(ES): 499 (M+1) for $C_{24}H_{24}ClFN_6O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.33 (t, J=7.06 Hz, 3 H) 1.95 (s, 3 H) 3.24 (d, J=10.93 Hz, 4 H) 3.42 (d, J=11.49 Hz, 4 H) 4.37 (q, J=6.97 Hz, 2 H) 7.34 (t, J=9.14 Hz, 1 H) 7.49 - 7.79 (m, 1 H) 7.99 - 8.28 (m, 2 H) 8.28 - 8.46 (m, 1 H) 8.92 (d, J=2.07 Hz, 1 H) 9.01 (d, J=1.88 Hz, 1 H) 9.75 (s, 1 H)	1-{4-[5-bromo-2-(3-chloro-4-fluorophenylamino)pyrimidin-4-yl]piperazin-1-yl}ethanone **(Intermediate 98)**
143	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)nicotinate	MS(ES): 460 (M+1) for $C_{22}H_{23}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.34 (t, J=7.06 Hz, 3 H) 1.67 - 1.88 (m, 2 H) 3.18 (s, 3 H) 3.25 - 3.50 (m, 4 H) 4.38 (q, J=7.16 Hz, 2 H) 7.39 (t, J=9.04 Hz, 1 H) 7.47 - 7.63 (m, 1 H) 7.73 (s, 1 H) 7.89 (s, 1 H) 8.07 (d, J=4.90 Hz, 1 H) 8.25 (t, J=2.07 Hz, 1 H) 8.80 (d, J=2.26 Hz, 1 H) 9.11 (d, J=1.88 Hz, 1 H) 9.98 (s, 1 H)	5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)pyrimidine-2,4-diamine **(Intermediate 119)**
144	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)nicotinate	MS(ES): 458 (M+1) for $C_{22}H_{21}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.35 (t, J=7.16 Hz, 3 H) 3.06 - 3.41 (m, 4 H) 3.45 - 3.69 (m, 4 H) 4.31 - 4.42 (q, 2 H) 7.36 (t, J=9.14 Hz, 1 H) 7.48 - 7.70 (m, 1 H) 8.08 (dd, J=6.88, 2.54 Hz, 1 H) 8.17 (s, 1 H) 8.38 (t, J=1.98 Hz, 1 H) 8.92 (d, J=2.07 Hz, 1 H) 9.02 (d, J=1.88 Hz, 1 H) 9.88 (s, 1 H)	5-Bromo-N-(3-chloro-4-fluorophenyl)-4-morpholin-4-ylpyrimidin-2-amine **(Intermediate 111)**

Ex	Compound	Data	SM
145	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-((1-methyl-1H-imidazol-5-yl)methylamino)pyrimidin-5-yl)nicotinate	MS(ES): 482 (M+1) for $C_{23}H_{21}ClFN_7O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.33 (t, J=7.06 Hz, 3 H) 3.59 (s, 3 H) 4.36 (q, J=7.16 Hz, 2 H) 4.52 (d, J=5.09 Hz, 2 H) 6.81 (s, 1 H) 7.20 - 7.40 (m, 2 H) 7.51 (s, 1 H) 7.56 - 7.73 (m, 1 H) 7.90 (s, 1 H) 8.13 (dd, J=6.88, 2.73 Hz, 1 H) 8.22 (t, J=2.07 Hz, 1 H) 8.78 (d, J=2.07 Hz, 1 H) 9.04 (d, J=2.07 Hz, 1 H) 9.49 (s, 1 H)	5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-((1-methyl-1*H*-imidazol-5-yl)methyl)pyrimidine-2,4-diamine **(Intermediate 105)**
146	 (R)-ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(tetrahydrofuran-3-ylamino)pyrimidin-5-yl)nicotinate	MS(ES): 487 (M+1) for $C_{24}H_{24}ClFN_4O_4$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.33 (t, J=7.06 Hz, 3 H) 1.78 - 2.05 (m, 1 H) 2.03 - 2.34 (m, 1 H) 3.59 (dd, J=8.76, 4.43 Hz, 1 H) 3.64 - 3.87 (m, 2 H) 3.93 (dd, J=8.85, 6.22 Hz, 1 H) 4.37 (q, J=7.10 Hz, 2 H) 4.51 - 4.77 (m, 1 H) 6.93 (d, J=6.03 Hz, 1 H) 7.32 (t, J=9.14 Hz, 1 H) 7.47 - 7.70 (m, 1 H) 7.88 (s, 1 H) 8.11 - 8.37 (m, 2 H) 8.78 (d, J=2.26 Hz, 1 H) 9.03 (d, J=2.07 Hz, 1 H) 9.53 (s, 1 H)	(R)-5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(tetrahydrofuran-3-yl)pyrimidine-2,4-diamine **(Intermediate 103)**
147	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(pyrrolidin-1-yl)pyrimidin-5-yl)nicotinate	MS(ES): 442 (M+1) for $C_{22}H_{21}ClFN_5O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.34 (t, J=7.06 Hz, 3 H) 1.65 - 1.89 (m, 4 H) 2.99 - 3.26 (m, 4 H) 4.36 (q, J=7.10 Hz, 2 H) 7.31 (t, J=9.14 Hz, 1 H) 7.54 - 7.76 (m, 1 H) 7.94 (s, 1 H) 8.14 (t, J=2.07 Hz, 1 H) 8.24 (dd, J=6.88, 2.54 Hz, 1 H) 8.76 (d, J=2.07 Hz, 1 H) 9.00 (d, J=1.88 Hz, 1 H) 9.55 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(pyrrolidin-1-yl)pyrimidin-2-amine **(Intermediate 104)**

Ex	Compound	Data	SM
148	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-((1-methyl-1H-pyrazol-4-yl)methylamino)pyrimidin-5-yl)nicotinate	MS(ES): 482 (M+1) for $C_{23}H_{21}ClFN_7O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.34 (t, J=7.06 Hz, 3 H) 3.74 (s, 3 H) 4.19 - 4.52 (m, 4 H) 7.14 - 7.42 (m, 3 H) 7.54 (s, 1 H) 7.57 - 7.73 (m, 1 H) 7.87 (s, 1 H) 8.07 - 8.31 (m, 2 H) 8.78 (d, J=2.26 Hz, 1 H) 9.04 (d, J=1.88 Hz, 1 H) 9.47 (s, 1 H)	5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-((1-methyl-1H-pyrazol-4-yl)methyl)pyrimidine-2,4-diamine **(Intermediate 106)**
149	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(1,3-dimethoxypropan-2-ylamino)pyrimidin-5-yl)nicotinate	MS(ES): 490 (M+1) for $C_{23}H_{25}ClFN_5O_4$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.23 - 1.46 (m, 3 H) 3.25 (s, 6 H) 3.35 - 3.55 (m, 4 H) 4.36 (q, J=7.10 Hz, 2 H) 4.49 - 4.78 (m, 1 H) 6.55 (d, J=8.48 Hz, 1 H) 7.15 - 7.41 (m, J=9.14, 9.14 Hz, 1 H) 7.50 - 7.71 (m, 1 H) 7.82 - 7.96 (m, 1 H) 8.16 (dd, J=6.88, 2.54 Hz, 1 H) 8.23 (t, J=2.07 Hz, 1 H) 8.78 (d, J=2.07 Hz, 1 H) 9.04 (d, J=2.07 Hz, 1 H) 9.49 (s, 1 H)	5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(1,3-dimethoxypropan-2-yl)pyrimidine-2,4-diamine **(Intermediate 107)**
150	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(4-(2-methoxyethyl)piperazin-1-yl)pyrimidin-5-yl)nicotinate	MS(ES): 515 (M+1) for $C_{25}H_{28}ClFN_6O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.35 (t, J=7.06 Hz, 3 H) 2.29 - 2.45 (m, 6 H) 3.08 - 3.26 (m, 7 H) 3.39 (t, J=5.75 Hz, 2 H) 4.37 (q, J=7.03 Hz, 2 H) 7.33 (t, J=9.14 Hz, 1 H) 7.49 - 7.78 (m, 1 H) 8.06 - 8.28 (m, 2 H) 8.36 (t, J=2.07 Hz, 1 H) 8.91 (d, J=2.26 Hz, 1 H) 9.00 (d, J=1.88 Hz, 1 H) 9.72 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[4-(2-methoxyethyl)piperazin-1-yl]pyrimidin-2-amine **(Intermediate 108)**

Ex	Compound	Data	SM
151	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(4-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinate	MS(ES): 471 (M+1) for $C_{23}H_{24}ClFN_6O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.35 (t, J=7.06 Hz, 3 H) 2.14 (s, 3 H) 2.19 - 2.37 (m, 4 H) 3.12 - 3.26 (m, 4 H) 4.37 (q, J=6.97 Hz, 2 H) 7.33 (t, J=9.14 Hz, 1 H) 7.52 - 7.73 (m, 1 H) 8.05 - 8.27 (m, 2 H) 8.29 - 8.49 (m, 1 H) 8.92 (d, J=1.88 Hz, 1 H) 9.00 (d, J=1.51 Hz, 1 H) 9.73 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(4-methylpiperazin-1-yl)pyrimidin-2-amine **(Intermediate 109)**
152	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(piperidin-1-yl)pyrimidin-5-yl)nicotinate	MS(ES): 456 (M+1) for $C_{23}H_{23}ClFN_5O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.34 (t, J=6.97 Hz, 3 H) 1.40 - 1.65 (m, 6 H) 3.10 - 3.27 (m, 4 H) 4.36 (q, J=7.16 Hz, 2 H) 7.33 (t, J=9.14 Hz, 1 H) 7.50 - 7.78 (m, 1 H) 8.13 (s, 1 H) 8.22 (dd, J=6.88, 2.54 Hz, 1 H) 8.35 (t, J=1.98 Hz, 1 H) 8.91 (d, J=2.07 Hz, 1 H) 8.99 (d, J=1.88 Hz, 1 H) 9.68 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(piperidin-1-yl)pyrimidin-2-amine **(Intermediate 100)**
153	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(5-methyl-1H-pyrazol-4-yl)propylamino)pyrimidin-5-yl)nicotinate	MS(ES): 510 (M+1) for $C_{25}H_{25}ClFN_7O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.26 - 1.42 (m, 3 H) 1.67 - 1.89 (m, 2 H) 2.08 (br. s., 3 H) 2.40 (t, *J*=7.54 Hz, 2 H) 3.37 - 3.48 (m, 2 H) 4.36 (q, *J*=7.10 Hz, 2 H) 7.00 (br. s., 1 H) 7.30 (t, *J*=9.14 Hz, 1 H) 7.60 (dd, *J*=11.77, 4.05 Hz, 1 H) 7.85 (s, 1 H) 8.13 - 8.38 (m, 2 H) 8.79 (t, *J*=1.98 Hz, 1 H) 9.05 (d, *J*=1.88 Hz, 1 H) 9.49 (s, 1 H)	5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-(5-methyl-1*H*-pyrazol-4-yl)propyl)pyrimidine-2,4-diamine **(Intermediate 99)**

Example 154: Ethyl 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-imidazol-4-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylate

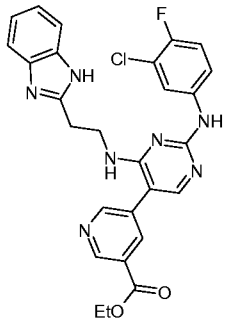
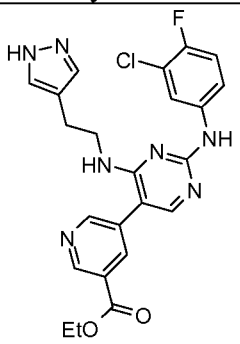


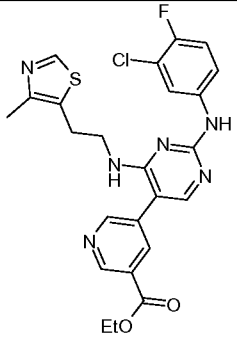
Ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}pyridine-3-carboxylate (**Intermediate 124,** 200 mg, 0.44 mmol) was suspended in NMP (1 mL), treated with N,N-diisopropylethylamine (1 eq) and the 2-(1*H*-imidazol-4-yl)ethanamine (49 mg, 0.44 mmol). The mixture was heated at 90 °C for 30 min in a sealed tube. The reaction mixture was added to water and stirred for 15 min. The precipitated solid was filtered, washed with water and dried to afford the crude product. It was further purified by flash chromatography (chloroform:methanol (9:1)) to provide the title compound (100 mg).

MS (ES) 482 (M+1) for $C_{23}H_{21}ClFN_7O_2$.

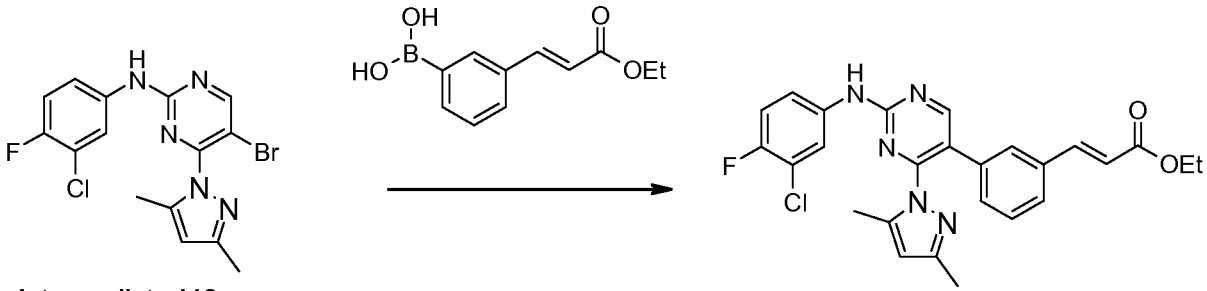
^{1}H NMR 300 MHz, DMSO-d_6: δ 1.34 (t, *J* = 6.96 Hz, 3H), 3.16 (br s, 2H), 3.58 (br s, 2H), 4.36 (q, *J* = 7.68 Hz, 2H), 6.82 (s, 1H), 7.09 (br s, 1H), 7.29 (t, *J* = 7.95 Hz, 1H), 7.51 (s, 1H), 7.7 (br s, 1H), 7.86 (s, 1H), 8.16 (br s, 1H), 8.21 (s, 1H), 8.76 (s, 1H), 9.04 (s, 1H), 9.47 (s, 1H), 11.8 (br s, 1H).

The following examples were prepared using the general method described above for **Example 154** using ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}pyridine-3-carboxylate **Intermediate 124**, N,N-diisopropylethylamine and the starting material (SM) indicated.

Ex	Compound	Data	SM
155	 ethyl 5-(4-{[2-(1*H*-benzimidazol-2-yl)ethyl]amino}-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl)pyridine-3-carboxylate	MS(ES): 532 (M+1) for $C_{27}H_{23}ClFN_7O_2$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.28 (t, *J* = 7.11 Hz, 3H), 3.12-3.16 (m, 2H), 3.82-3.84 (m, 2H), 4.30 (q, *J* = 7.20 Hz, 2H), 7.09-7.12 (m, 2H), 7.26 (t, *J* = 9.00 Hz, 2H), 7.44 (br s, 2H), 7.71 (br s, 1H), 7.89 (s, 1H), 8.16-8.18 (m, 1H), 8.21 (s, 1H), 8.80 (br s, 1H), 9.10 (br s, 1H), 9.52 (br s, 1H), 12.26 (br s, 1H).	2-(1*H*-benzimidazol-2-yl)ethanamine
156	 ethyl 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-pyrazol-4-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylate	MS(ES): 482 (M+1) for $C_{23}H_{21}ClFN_7O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.35 (t, *J* = 7.08 Hz, 3H), 2.73 (t, *J* = 7.12 Hz, 2H), 4.38 (q, *J* = 7.12 Hz, 2H), 7.00 (br s, 1H), 7.25 (t, *J* = 9.08 Hz, 1H), 7.30 (br s, 1H), 7.50 (br s, 1H), 7.64 (m, 1H), 7.85 (s, 1H), 8.18 (dd, *J* = 2.72, 6.78 Hz, 2H), 8.75 (d, *J* = 2.04 Hz, 1H), 9.02 (d, *J* = -13.96 Hz, 1H), 9.47 (s, 1H), 12.56 (br s, 1H).	2-(1*H*-pyrazol-4-yl)ethanamine

Ex	Compound	Data	SM
157	 ethyl 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(4-methyl-1,3-thiazol-5-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylate	MS(ES): 513 (M+1) for $C_{24}H_{22}ClFN_6O_2S$. ^{1}H NMR (400 MHz,DMSO-d_6): δ 1.34 (t, *J* = 7.08 Hz, 3H), 2.25 (s, 3H), 3.06 (t, *J* = 6.92 Hz, 2H), 3.56 (q, *J* = 6.72 Hz, 2H), 4.38 (q, *J* = 7.12 Hz, 2H), 7.04 (t, *J* = 5.80 Hz, 1H), 7.29 (t, *J* = 9.12 Hz, 1H), 7.65 (ddd, *J* = 2.72, 4.20, 9.09 Hz, 1H), 7.88 (s, 1H), 8.15 (dd, *J* = 2.64, 6.90 Hz, 1H), 8.19 (t, *J* = 2.12 Hz, 1H), 8.75 (d, *J* = 2.24 Hz, 1H), 8.81 (s, 1H), 9.05 (d, *J* = 2.00 Hz, 1H), 9.49 (s, 1H).	2-(4-methyl-1,3-thiazol-5-yl)ethanamine

Example 158: ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoate



Intermediate 112

Example 158

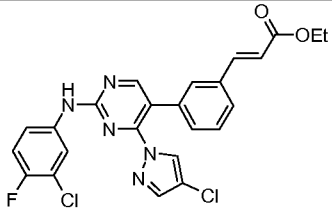
A suspension of 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyrimidin-2-amine (**Intermediate 112**, 1 eq, 3.5 mmol), {3-[(1*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]phenyl}boronic acid (1.1 eq, 3.95 mmol), [1,1′-bis (diphenylphosphino) ferrocene] dichloropalladium(II) complex with CH_2Cl_2 (10 mol %) and sodium carbonate (1 eq, 3.5 mmol) in acetonitrile/water (20 mL : 5 mL) was degassed and heated to 90 °C for 15-20 min in an oil bath under inert atmosphere. Completion of the reaction was monitored by TLC. The solvent was

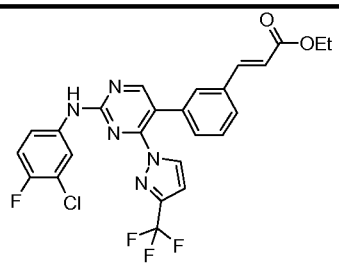
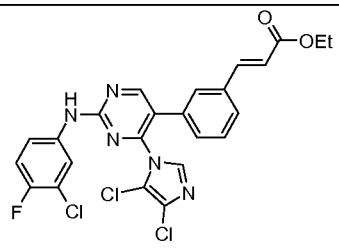
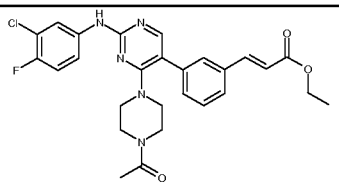
removed under vacuum and the crude mixture was taken up in $CHCl_3$ (30 mL). It was then washed with water, brine, dried over sodium sulfate, filtered and concentrated. The crude material was purified by silica gel column chromatography using chloroform-methanol as an eluent to provide the title compound (620 mg, 63%).

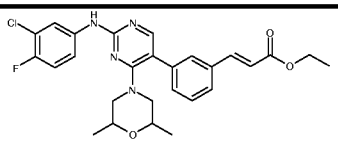
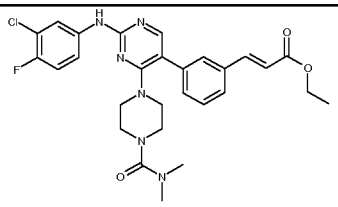
MS(ES): 492 (M+1) for $C_{26}H_{23}ClFN_5O_2$.

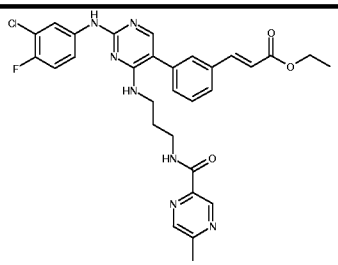
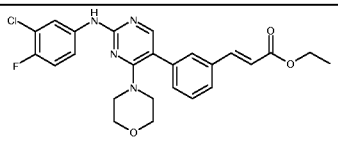
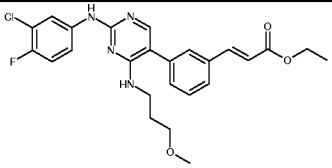
^{1}H NMR 400 MHz, DMSO-d_6 : δ 1.25 (dt, J = 1.28, 7.06 Hz, 3H), 2.02 (s, 3H), 2.13 (s, 3H), 4.18 (dq, J = 1.12, 7.14 Hz, 2H), 6.03 (s, 1H), 6.54 (dd, J = 1.24, 16.02 Hz, 1H), 7.01 (d, J = 7.24 Hz, 1H), 7.34 (t, J = 7.76 Hz, 1H), 7.37-7.42 (m, 2H), 7.56-7.60 (m, 2H), 7.63-7.67 (m, 1H), 8.10 (d, J = 6.76 Hz, 1H), 8.87 (d, J = 1.36 Hz, 1H), 10.30 (s, 1H).

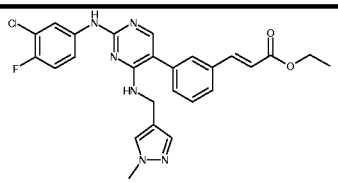
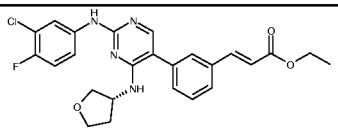
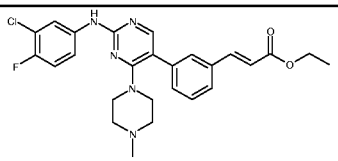
The following examples were prepared following the general procedure described above for **Example 158** using {3-[(1*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]phenyl}boronic acid, [1,1′-bis (diphenylphosphino) ferrocene] dichloropalladium(II), sodium carbonate and the starting material (SM) listed.

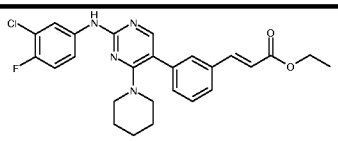
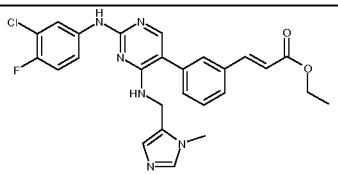
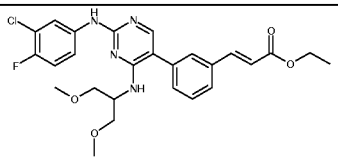
Ex	Compound	Data	SM
159	 ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(4-chloro-1*H*-pyrazol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES) : 498 (M+1) and 500 (M+2) for $C_{24}H_{18}Cl_2FN_5O_2$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.25 (t, J = 7.02 Hz, 3H), 4.18 (q, J = 7.02 Hz, 2H), 6.62 (d, J = 16.05 Hz, 1H), 7.15 (d, J = 7.68 Hz, 1H), 7.34-7.44 (m, 2H), 7.59-7.64 (m, 3H), 7.71-7.74 (m, 2H), 8.05 (dd, J = 2.19, 6.63 Hz, 1H), 8.47 (s, 1H), 8.71 (s, 1H), 10.30 (s, 1H).	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(4-chloro-1*H*-pyrazol-1-yl)pyrimidin-2-amine **(Intermediate 114)**

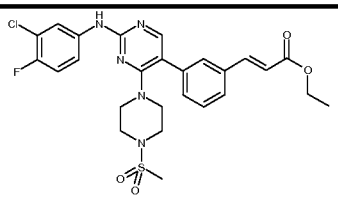
Ex	Compound	Data	SM
160	 ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 532 (M+1) for $C_{25}H_{18}ClF_4N_5O_2$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.25 (t, *J* = 7.12 Hz, 3H), 4.18 (q, *J* = 7.04 Hz, 2H), 6.59 (d, *J* = 16.0 Hz, 1H), 7.00 (d, *J* = 2.44 Hz, 1H), 7.13 (d, *J* = 7.64 Hz, 1H), 7.35-7.43 (m, 2H), 7.62 (s, 2H), 7.68-7.72 (m, 2H), 8.12 (dd, *J* = 6.68, 2.44 Hz, 1H), 8.35 (s, 1H), 8.83 (s, 1H), 10.44 (s, 1H).	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **(Intermediate 115)**
161	 ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(4,5-dichloro-1*H*-imidazol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES) : 532 (M+1) and 534 (M+3) for $C_{24}H_{17}Cl_3FN_5O_2$. ^{1}H NMR (400 MHz DMSO-d_6): δ1.24 (m, 3H), 4.19 (q, *J* = 7.12 Hz, 2H), 6.63 (d, *J* = 16.04 Hz, 1H), 7.10 (d, *J* = 7.76 Hz, 1H), 7.41 (t, *J* = 7.80 Hz, 2H), 7.61 (d, *J* = 15.96 Hz, 1H), 7.61 (s, 1H), 7.66 (m, 2H), 8.05 (m, 2H), 8.98 (d, *J* = 0.88 Hz, 1H), 10.55 (s, 1H).	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(4,5-dichloro-1*H*-imidazol-1-yl)pyrimidin-2-amine **(Intermediate 116)**
162	 (E)-ethyl 3-(3-(4-(4-acetylpiperazin-1-yl)-2-(3-chloro-4-fluorophenylamino)pyrimidin-5-yl)phenyl)acrylate	MS(ES): 524 (M+1) for $C_{27}H_{27}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.25 (t, J=7.06 Hz, 3 H) 1.95 (s, 3 H) 3.10 - 3.57 (m, 8 H) 4.19 (q, J=6.97 Hz, 2 H) 6.72 (d, J=16.01 Hz, 1 H) 7.33 (t, J=9.04 Hz, 1 H) 7.42 - 7.58 (m, 2 H) 7.57 - 7.77 (m, 3 H) 7.81 (s, 1 H) 7.99 - 8.28 (m, 2 H) 9.64 (s, 1 H)	1-{4-[5-bromo-2-(3-chloro-4-fluorophenylamino)pyrimidin-4-yl]piperazin-1-yl}ethanone **(Intermediate 98)**

Ex	Compound	Data	SM
163	 (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(2,6-dimethylmorpholino)pyrimidin-5-yl)phenyl)acrylate	MS(ES): 511 (M+1) for $C_{27}H_{28}ClFN_4O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 0.93 (d, J=6.03 Hz, 6 H) 1.25 (t, J=7.16 Hz, 3 H) 2.31 - 2.45 (m, 2 H) 3.42 - 3.71 (m, 4 H) 4.19 (q, J=7.16 Hz, 2 H) 6.72 (d, J=16.01 Hz, 1 H) 7.32 (t, J=9.14 Hz, 1 H) 7.40 - 7.62 (m, 3 H) 7.61 - 7.88 (m, 3 H) 8.06 (s, 1 H) 8.23 (dd, J=6.97, 2.45 Hz, 1 H) 9.63 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(2,6-dimethylmorpholino)pyrimidin-2-amine **(Intermediate 95)**
164	 (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(4-(dimethylcarbamoyl)piperazin-1-yl)pyrimidin-5-yl)phenyl)acrylate	MS(ES): 553 (M+1) for $C_{28}H_{30}ClFN_6O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.25 (t, J=7.06 Hz, 3 H) 2.70 (s, 6 H) 2.96 - 3.15 (m, 4 H) 3.17 - 3.29 (m, 4 H) 4.19 (q, J=6.97 Hz, 2 H) 6.72 (d, J=16.20 Hz, 1 H) 7.33 (t, J=9.04 Hz, 1 H) 7.42 - 7.57 (m, 2 H) 7.57 - 7.75 (m, 3 H) 7.80 (s, 1 H) 8.08 (s, 1 H) 8.14 (dd, J=6.88, 2.54 Hz, 1 H) 9.62 (s, 1 H)	4-(5-bromo-2-(3-chloro-4-fluorophenylamino)pyrimidin-4-yl)-*N,N*-dimethylpiperazine-1-carboxamide **(Intermediate 101)**

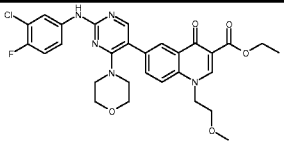
Ex	Compound	Data	SM
165	 (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(5-methylpyrazine-2-carboxamido)propylamino)pyrimidin-5-yl)phenyl)acrylate	MS(ES): 590 (M+1) for $C_{30}H_{29}ClFN_7O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.22 (t, J=7.16 Hz, 3 H) 1.69 - 1.97 (m, 2 H) 2.56 (s, 3 H) 3.33 - 3.61 (m, 4 H) 4.17 (q, J=7.10 Hz, 2 H) 6.71 (d, J=16.20 Hz, 1 H) 6.83 (t, J=5.37 Hz, 1 H) 7.27 (t, J=9.14 Hz, 1 H) 7.40 - 7.55 (m, 2 H) 7.56 - 7.63 (m, 1 H) 7.66 - 7.78 (m, 3 H) 7.81 (s, 1 H) 8.23 (dd, J=6.78, 2.26 Hz, 1 H) 8.55 (d, J=0.94 Hz, 1 H) 8.77 - 9.11 (m, 2 H) 9.40 (s, 1 H)	*N*-(3-(5-bromo-2-(3-chloro-4-fluorophenylamino)pyrimidin-4-ylamino)propyl)-5-methylpyrazine-2-carboxamide **(Intermediate 102)**
166	 (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)phenyl)acrylate	MS(ES): 483 (M+1) for $C_{25}H_{24}ClFN_4O_3$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.20 (t, J=7.16 Hz, 3 H) 3.10 - 3.30 (m, 4 H) 3.41 - 3.58 (m, 4 H) 4.14 (q, J=7.10 Hz, 2 H) 6.66 (d, J=16.20 Hz, 1 H) 7.28 (t, J=9.04 Hz, 1 H) 7.36 - 7.71 (m, 5 H) 7.76 (s, 1 H) 7.94 - 8.17 (m, 2 H) 9.64 (s, 1 H)	5-Bromo-N-(3-chloro-4-fluorophenyl)-4-morpholin-4-ylpyrimidin-2-amine **(Intermediate 111)**
167	 (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)phenyl)acrylate	MS(ES): 485 (M+1) for $C_{25}H_{26}ClFN_4O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.25 (t, J=7.06 Hz, 3 H) 1.60 - 1.96 (m, 2 H) 3.16 (s, 3 H) 3.25 - 3.52 (m, 4 H) 4.19 (q, J=7.16 Hz, 2 H) 6.71 (d, J=16.01 Hz, 1 H) 7.31 - 7.47 (m, 2 H) 7.48 - 7.61 (m, 2 H) 7.63 - 7.90 (m, 5 H) 8.05 (d, J=4.33 Hz, 1 H) 9.97 (s, 1 H)	5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)pyrimidine-2,4-diamine **(Intermediate 119)**

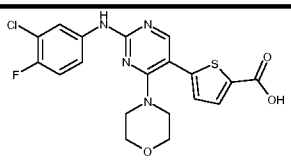
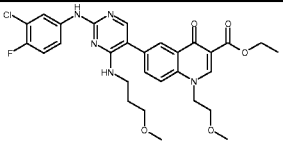
Ex	Compound	Data	SM
168	 (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-((1-methyl-1H-pyrazol-4-yl)methylamino)pyrimidin-5-yl)phenyl)acrylate	MS(ES): 507 (M+1) for $C_{26}H_{24}ClFN_6O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.25 (t, J=7.06 Hz, 3 H) 3.73 (s, 3 H) 4.19 (q, J=7.16 Hz, 2 H) 4.40 (d, J=5.65 Hz, 2 H) 6.69 (d, J=16.01 Hz, 1 H) 7.01 (t, J=5.65 Hz, 1 H) 7.17 - 7.38 (m, 2 H) 7.39 - 7.58 (m, 3 H) 7.59 - 7.78 (m, 4 H) 7.82 (s, 1 H) 8.18 (dd, J=6.88, 2.73 Hz, 1 H) 9.39 (s, 1 H)	5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-((1-methyl-1H-pyrazol-4-yl)methyl)pyrimidine-2,4-diamine **(Intermediate 106)**
169	 (R,E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(tetrahydrofuran-3-ylamino)pyrimidin-5-yl)phenyl)acrylate	MS(ES): 483 (M+1) for $C_{25}H_{24}ClFN_4O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.25 (t, J=7.06 Hz, 3 H) 1.83 - 2.04 (m, 1 H) 2.08 - 2.32 (m, 1 H) 3.50 - 4.02 (m, 4 H) 4.19 (q, J=7.10 Hz, 2 H) 4.48 - 4.78 (m, 1 H) 6.55 (d, J=6.22 Hz, 1 H) 6.69 (d, J=16.01 Hz, 1 H) 7.31 (t, J=9.14 Hz, 1 H) 7.37 - 7.53 (m, 2 H) 7.53 - 7.64 (m, 1 H) 7.63 - 7.79 (m, 3 H) 7.85 (s, 1 H) 8.25 (dd, J=6.88, 2.54 Hz, 1 H) 9.45 (s, 1 H)	(R)-5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(tetrahydrofuran-3-yl)pyrimidine-2,4-diamine **(Intermediate 103)**
170	 (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(4-methylpiperazin-1-yl)pyrimidin-5-yl)phenyl)acrylate	MS(ES): 496 (M+1) for $C_{26}H_{27}ClFN_5O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.25 (t, J=7.06 Hz, 3 H) 2.13 (s, 3 H) 2.19 - 2.41 (m, 4 H) 3.11 - 3.29 (m, 4 H) 4.19 (q, J=6.97 Hz, 2 H) 6.71 (d, J=16.01 Hz, 1 H) 7.32 (t, J=9.04 Hz, 1 H) 7.41 - 7.55 (m, 2 H) 7.54 - 7.75 (m, 3 H) 7.80 (s, 1 H) 8.06 (s, 1 H) 8.13 - 8.29 (m, 1 H) 9.61 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(4-methylpiperazin-1-yl)pyrimidin-2-amine **(Intermediate 109)**

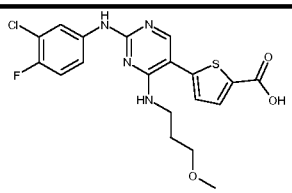
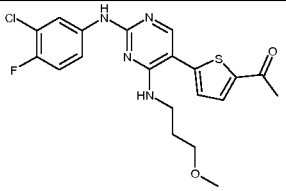
Ex	Compound	Data	SM
171	 (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(piperidin-1-yl)pyrimidin-5-yl)phenyl)acrylate	MS(ES): 481 (M+1) for $C_{26}H_{26}ClFN_4O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.25 (t, J=7.06 Hz, 3 H) 1.34 - 1.63 (m, 6 H) 3.15 - 3.24 (m, 4 H) 4.19 (q, J=6.97 Hz, 2 H) 6.71 (d, J=16.20 Hz, 1 H) 7.31 (t, J=9.14 Hz, 1 H) 7.40 - 7.52 (m, 2 H) 7.54 - 7.87 (m, 4 H) 8.02 (s, 1 H) 8.23 (dd, J=6.88, 2.54 Hz, 1 H) 9.56 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(piperidin-1-yl)pyrimidin-2-amine **(Intermediate 100)**
172	 (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-((1-methyl-1H-imidazol-5-yl)methylamino)pyrimidin-5-yl)phenyl)acrylate	MS(ES): 507 (M+1) for $C_{26}H_{24}ClFN_6O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) d ppm 1.25 (t, J=7.06 Hz, 3 H) 3.58 (s, 3 H) 4.19 (q, J=7.10 Hz, 2 H) 4.52 (s, 2 H) 6.69 (d, J=16.01 Hz, 1 H) 6.79 (s, 1 H) 7.03 (t, J=5.65 Hz, 1 H) 7.28 (t, J=9.14 Hz, 1 H) 7.36 - 7.55 (m, 3 H) 7.54 - 7.78 (m, 4 H) 7.85 (s, 1 H) 8.11 (dd, J=6.78, 2.64 Hz, 1 H) 9.39 (s, 1 H)	5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-((1-methyl-1*H*-imidazol-5-yl)methyl)pyrimidine-2,4-diamine **(Intermediate 105)**
173	 (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(1,3-dimethoxypropan-2-ylamino)pyrimidin-5-yl)phenyl)acrylate	MS(ES): 515 (M+1) for $C_{26}H_{28}ClFN_4O_4$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.25 (t, J=7.06 Hz, 3 H) 3.25 (s, 6 H) 3.37 - 3.62 (m, 4 H) 4.19 (q, J=6.97 Hz, 2 H) 4.38 - 4.76 (m, 1 H) 6.10 (d, J=8.29 Hz, 1 H) 6.68 (d, J=16.01 Hz, 1 H) 7.28 (t, J=9.14 Hz, 1 H) 7.37 - 7.56 (m, 2 H) 7.57 - 7.81 (m, 4 H) 7.88 (s, 1 H) 8.15 (dd, J=6.78, 2.64 Hz, 1 H) 9.43 (s, 1 H)	5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(1,3-dimethoxypropan-2-yl)pyrimidine-2,4-diamine **(Intermediate 107)**

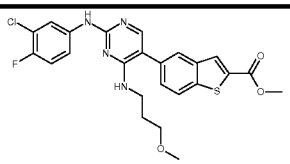
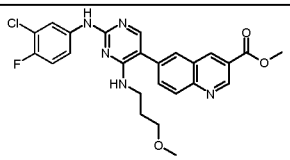
Ex	Compound	Data	SM
174	 (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-5-yl)phenyl)acrylate	MS(ES): 560 (M+1) for $C_{26}H_{27}ClFN_5O_4S$ ^{1}H NMR (300 MHz, DMSO-*d6*) δ ppm 1.25 (t, J=7.06 Hz, 3 H) 2.86 (s, 3 H) 2.99 - 3.18 (m, 4 H) 3.24 - 3.50 (m, 4 H) 4.19 (q, J=6.97 Hz, 2 H) 6.74 (d, J=16.01 Hz, 1 H) 7.36 (t, J=9.14 Hz, 1 H) 7.44 - 7.58 (m, 2 H) 7.57 - 7.79 (m, 3 H) 7.82 (s, 1 H) 7.99 - 8.20 (m, 2 H) 9.80 (s, 1 H)	5-Bromo-N-(3-chloro-4-fluorophenyl)-4-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-2-amine **(Intermediate 130)**

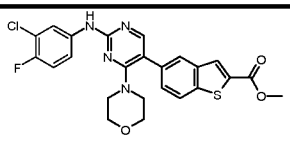
The following examples were prepared using the general method described above for **Example 1** using tris(dibenzyledeneacetone)-dipalladium(0), 2-dicyclohexyl phosphino-2',4',6'-triiso-propyl-1,1'-biphenyl, sodium carbonate and the starting materials (SM) indicated.

Ex	Compound	Data	SM
175	 ethyl 6-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate	MS(ES): 582 (M+1) for $C_{29}H_{29}ClFN_5O_5$ ^{1}H NMR (300 MHz, DMSO- *d6*) δ ppm 1.28 (t, J=7.06 Hz, 3 H) 3.08 - 3.28 (m, 7 H) 3.47 - 3.64 (m, 4 H) 3.69 (t, J=4.33 Hz, 2 H) 4.23 (q, J=7.10 Hz, 2 H) 4.59 (t, J=4.05 Hz, 2 H) 7.33 (t, J=9.14 Hz, 1 H) 7.55 - 7.74 (m, 1 H) 7.81 - 8.02 (m, 2 H) 8.05 - 8.26 (m, 2 H) 8.34 (d, J=1.32 Hz, 1 H) 8.58 (s, 1 H) 9.68 (s, 1 H)	Ethyl 1-(2-methoxyethyl)-4-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydroquinoline-3-carboxylate **(Intermediate 134)** and 5-Bromo-N-(3-chloro-4-fluorophenyl)-4-morpholin-4-ylpyrimidin-2-amine **(Intermediate 111)**

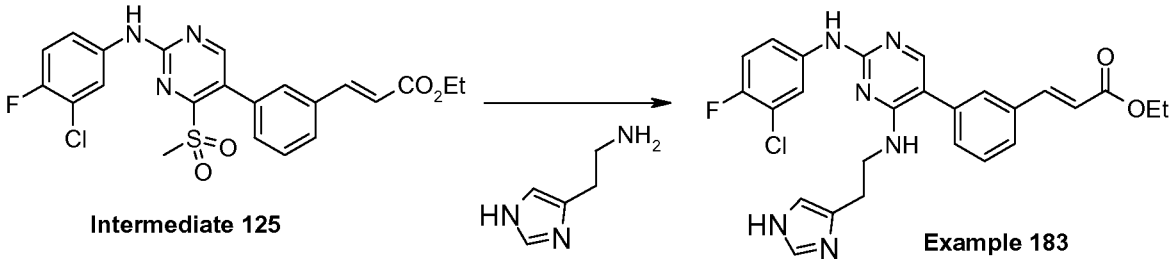
Ex	Compound	Data	SM
176	 5-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)thiophene-2-carboxylic acid	MS(ES): 435 (M+1) for $C_{19}H_{16}ClFN_4O_3S$ ^{1}H NMR (300 MHz, DMSO- *d*6) δ ppm 3.14 - 3.37 (m, 4 H) 3.75 - 3.98 (m, 4 H) 7.27 (d, J=3.77 Hz, 1 H) 7.34 (t, J=9.14 Hz, 1 H) 7.48 - 7.65 (m, 1 H) 7.69 (d, J=3.77 Hz, 1 H) 8.10 (dd, J=6.88, 2.54 Hz, 1 H) 8.21 (s, 1 H) 9.82 (s, 1 H) 13.10 (s, 1 H)	2-carboxythiophene-5-boronic acid and 5-Bromo-N-(3-chloro-4-fluorophenyl)-4-morpholin-4-ylpyrimidin-2-amine **(Intermediate 111)**
177	 ethyl 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate	MS(ES): 584 (M+1) for $C_{29}H_{31}ClFN_5O_5$ ^{1}H NMR (300 MHz, DMSO- *d*6) δ ppm 1.28 (t, J=7.06 Hz, 3 H) 1.65 - 1.94 (m, 2 H) 3.17 (s, 3 H) 3.24 (s, 3 H) 3.34 - 3.53 (m, 4 H) 3.57 - 3.83 (m, 2 H) 4.23 (q, J=7.16 Hz, 2 H) 4.60 (t, J=4.71 Hz, 2 H) 6.77 (t, J=5.18 Hz, 1 H) 7.29 (t, J=9.14 Hz, 1 H) 7.55 - 7.71 (m, 1 H) 7.70 - 7.80 (m, 1 H) 7.82 (s, 1 H) 7.93 (d, J=8.85 Hz, 1 H) 8.14 - 8.33 (m, 2 H) 8.59 (s, 1 H) 9.42 (s, 1 H)	Ethyl 1-(2-methoxyethyl)-4-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydroquinoline-3-carboxylate **(Intermediate 134)** and 5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)pyrimidine-2,4-diamine **(Intermediate 119)**

Ex	Compound	Data	SM
178	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)thiophene-2-carboxylic acid	MS(ES): 437 (M+1) for $C_{19}H_{18}ClFN_4O_3S$ ^{1}H NMR (300 MHz, DMSO- *d*6) δ ppm 1.71 - 1.94 (m, 2 H) 3.20 (s, 3 H) 3.32 - 3.58 (m, 4 H) 6.97 (t, J=5.09 Hz, 1 H) 7.20 (d, J=3.77 Hz, 1 H) 7.29 (t, J=9.04 Hz, 1 H) 7.50 - 7.69 (m, 1 H) 7.73 (d, J=3.96 Hz, 1 H) 7.97 (s, 1 H) 8.19 (dd, J=6.97, 2.64 Hz, 1 H) 9.56 (s, 1 H) 13.09 (s, 1 H)	2-carboxythiophene-5-boronic acid and 5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)pyrimidine-2,4-diamine **(Intermediate 119)**
179	 1-(5-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)thiophen-2-yl)ethanone	MS(ES): 435 (M+1) for $C_{20}H_{20}ClFN_4O_2S$ ^{1}H NMR (300 MHz, DMSO- *d*6) δ ppm 1.69 - 1.95 (m, 2 H) 2.55 (s, 3 H) 3.20 (s, 3 H) 3.29 - 3.58 (m, 4 H) 7.17 - 7.44 (m, 2 H) 7.45 - 7.70 (m, 2 H) 7.91 - 8.04 (m, 2 H) 8.09 (dd, J=6.88, 2.35 Hz, 1 H) 9.95 (s, 1 H)	5-acetyl-2-thiopheneboronic acid and 5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)pyrimidine-2,4-diamine **(Intermediate 119)**

Ex	Compound	Data	SM
180	 methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)benzo[b]thiophene-2-carboxylate	MS(ES): 501 (M+1) for $C_{24}H_{22}ClFN_4O_3S$ ^{1}H NMR (300 MHz, DMSO- *d*6) δ ppm 1.63 - 1.94 (m, 2 H) 3.15 (s, 3 H) 3.34 - 3.52 (m, 4 H) 3.90 (s, 3 H) 6.73 (t, J=5.27 Hz, 1 H) 7.28 (t, J=9.14 Hz, 1 H) 7.51 (dd, J=8.48, 1.70 Hz, 1 H) 7.57 - 7.72 (m, 1 H) 7.82 (s, 1 H) 8.01 (s, 1 H) 8.15 (d, J=8.48 Hz, 1 H) 8.20 - 8.35 (m, 2 H) 9.40 (s, 1 H)	methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-benzothiophene-2-carboxylate and 5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)pyrimidine-2,4-diamine **(Intermediate 119)**
181	 methyl 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)quinoline-3-carboxylate	MS(ES): 496 (M+1) for $C_{25}H_{23}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.80 (quin, *J*=6.45 Hz, 2 H) 3.16 (s, 3 H) 3.24 - 3.53 (m, 4 H) 3.98 (s, 3 H) 7.29 - 7.66 (m, 2 H) 7.83 - 8.09 (m, 3 H) 8.09 - 8.36 (m, 3 H) 9.09 (d, *J*=1.51 Hz, 1 H) 9.38 (d, *J*=2.07 Hz, 1 H) 10.38 (br. s., 1 H)	Methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline-3-carboxylate **(Intermediate 135)** and 5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)pyrimidine-2,4-diamine **(Intermediate 119)**

Ex	Compound	Data	SM
182	 methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)benzo[b]thiophene-2-carboxylate	MS(ES): 499 (M+1) for $C_{24}H_{20}ClFN_4O_3S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.14 - 3.29 (m, 4 H) 3.43 - 3.67 (m, 4 H) 3.91 (s, 3 H) 7.33 (t, *J*=9.14 Hz, 1 H) 7.55 - 7.77 (m, 2 H) 8.03 - 8.21 (m, 4 H) 8.26 (s, 1 H) 9.65 (s, 1 H)	methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-benzothiophene-2-carboxylate and 5-Bromo-N-(3-chloro-4-fluorophenyl)-4-morpholin-4-ylpyrimidin-2-amine **(Intermediate 111)**

Example 183: Ethyl (2*E*)-3-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-imidazol-4-yl)ethyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoate



Molecular Weight =475.93
Exact Mass =475

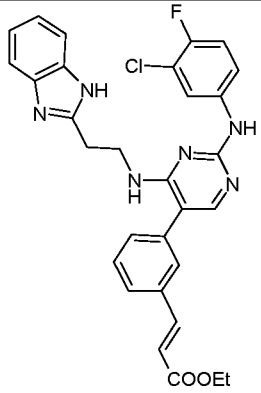
Molecular Weight =111.15
Exact Mass =111

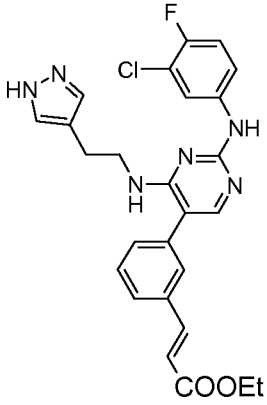
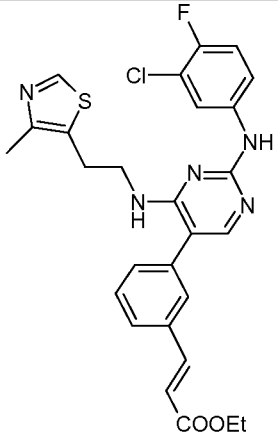
Molecular Weight =506.97
Exact Mass =506

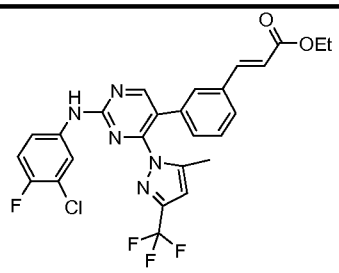
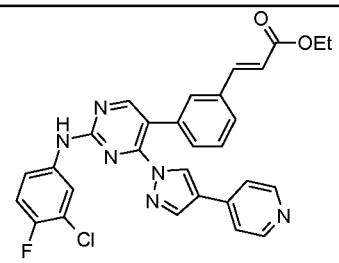
A solution of 2-(1*H*-imidazol-4-yl)ethanamine (46 mg, 0.4 mmol) in THF (1 mL) was added slowly by syringe to a stirred suspension of sodium hydride (60%, 16 mg, 0.4 mmol) in THF (1 ml) at 0 °C. After 30 min, ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}phenyl)prop-2-enoate (**Intermediate 125**, 200 mg, 0.4 mmol) in THF (2 mL) was added slowly by syringe to the stirred mixture while maintaining the temperature at 0 °C. The mixture was stirred under nitrogen for 2 h and poured into ice-water,

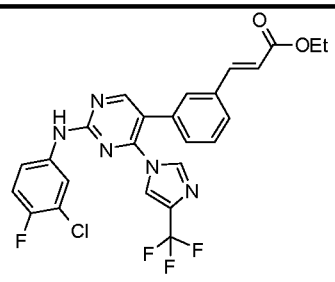
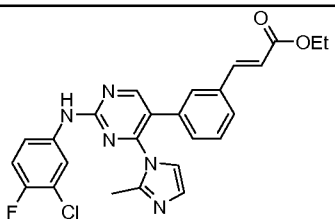
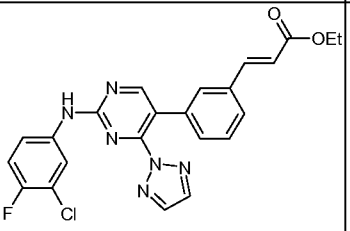
extracted with ethyl acetate (3 x 50 mL). The ethyl acetate layer was then washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography using 1% MeOH in $CHCl_3$ to yield the title compound (150 mg).
MS(ES): 506 (M+1) for $C_{26}H_{24}ClFN_6O_2$.
^{1}H NMR 400 MHz, DMSO-d_6: δ 1.26 (t, *J* = 7.08 Hz, 3H), 2.81-2.85 (m, 2H), 3.62-3.94 (m, 2H), 4.20 (q, *J* = 7.12 Hz, 2H), 6.68 (d, *J* = 16.08 Hz, 1H), 6.84 (br s, 1H), 6.93 (s, 1H), 7.26 (t, *J* = 9.12 Hz, 1H), 7.38 (d, *J* = 7.92 Hz, 1H), 7.48 (t, *J* = 7.64 Hz, 1H), 7.66-7.76 (m, 4H), 7.84 (s, 1H), 8.17 (dd, *J* = 2.64, 6.82 Hz, 1H), 9.41 (s, 1H), 12.50 (br s, 1H).

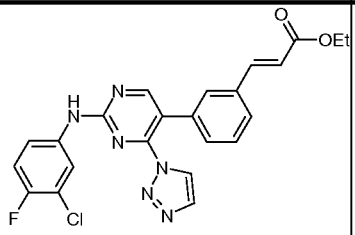
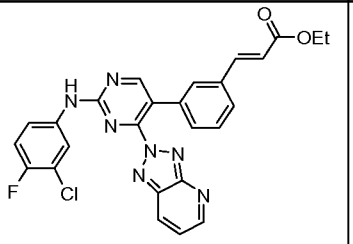
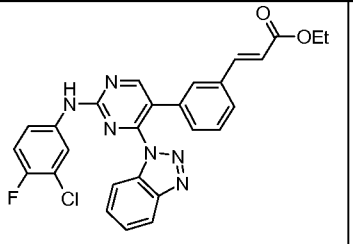
The following examples were prepared using the general method described above for **Example 183** using ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}phenyl)prop-2-enoate **Intermediate 125**, sodium hydride and the starting material (SM) indicated.

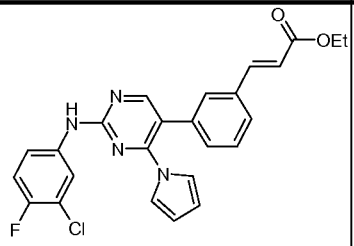
Ex	Compound	Data	SM
184	 ethyl (2*E*)-3-[3-(4-{[2-(1*H*-benzimidazol-2-yl)ethyl]amino}-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl)phenyl]prop-2-enoate	MS(ES): 557 (M+1) for $C_{30}H_{26}ClFN_6O_2$ ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.69 (t, *J* = Hz, 3H), 3.15-3.17 (m, 2H), 3.86-3.88 (m, 2H), 4.18 (q, *J* = 6.99 Hz, 2H), 6.67 (d, *J* = 15.81 Hz, 1H), 6.99 (br s, 1H), 7.11 (dd, *J* = 3.06, 5.81 Hz, 1H), 7.25 (t, *J* = 9.00 Hz, 1H), 7.38-7.43 (m, 4H), 7.60-7.70 (m, 4H), 7.85 (s, 1H), 8.18 (d, *J* = 4.83 Hz, 1H), 9.44 (s, 1H), 12.27 (br s, 1H).	2-(1*H*-benzimidazol-2-yl)ethanamine

Ex	Compound	Data	SM
185	 ethyl (2*E*)-3-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-pyrazol-4-yl)ethyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoate	MS(ES): 507 (M+1) for $C_{26}H_{24}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30-1.34 (m, 3H), 2.82 (m, 2H), 3.66 (m, 2H), 4.25 (m, 2H), 6.55 (d, *J* = 16.04 Hz, 1H), 7.10 (m, 1H), 7.30 (m, 1H), 7.4- 7.6 (m, 4H), 7.60 (m, 1H), 7.62-7.80 (m, 2H), 8.0-8.1 (m, 1H).	2-(1*H*-pyrazol-4-yl)ethanamine
186	 ethyl (2*E*)-3-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(4-methyl-1,3-thiazol-5-yl)ethyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoate	MS(ES): 538 (M+1) for $C_{27}H_{25}ClFN_5O_2S$. ^{1}H NMR (400 MHz,DMSO-d_6): δ 1.26 (t, *J* = 7.08 Hz, 3H), 2.23 (s, 3H), 3.07 (t, *J* = 6.64 Hz, 2H), 3.58-3.59 (m, 2H), 4.19 (q, *J* = 7.16 Hz, 2H), 6.68 (d, *J* = 16.04 Hz, 1H), 6.80 (br s, 1H), 7.28 (t, *J* = 9.08 Hz, 1H), 7.39 (d, *J* = 7.48 Hz, 1H), 7.49 (t, *J* = 7.76 Hz, 1H), 7.64 (br s, 2H), 7.69-7.72 (m, 2H), 7.84 (d, *J* = 1.52 Hz, 1H), 8.15 (dd, *J* = 2.48, 6.72 Hz, 1H), 8.80 (s, 1H), 9.41 (s, 1H).	2-(4-methyl-1,3-thiazol-5-yl)ethanamine

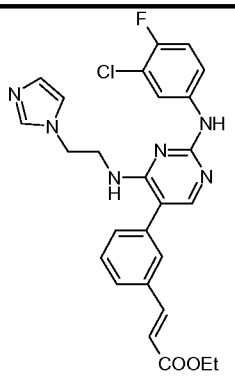
Ex	Compound	Data	SM
187	 ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES 546 (M+1) for $C_{26}H_{20}ClF_4N_5O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.25 (t, *J* = 7.08 Hz, 3H), 2.20 (s, 3H), 4.18 (q, *J* = 7.12 Hz, 2H), 6.55 (d, *J* = 16.04 Hz, 1H), 6.72 (s, 1H), 7.03 (d, *J* = 7.76 Hz, 1H), 7.35 (t, *J* = 7.76 Hz, 1H), 7.40 (br s, 1H), 7.41 (t, *J* = 9.12 Hz, 1H), 7.55 (d, *J* = 16.04 Hz, 1H), 7.63-7.67 (m, 2H), 8.08 (dd, *J* = 2.08, 6.64 Hz, 1H), 8.98 (s, 1H), 10.47 (br s, 1H).	(5-Methyl-3-trifluoromethyl-1*H*-pyrazole)
188	 ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyridin-4-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 541.2 (M+1) for $C_{29}H_{22}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.24 (t, *J* = 7.20 Hz, 3H), 4.17 (q, *J* = 7.20 Hz, 2H), 6.63 (d, *J* = 16.00 Hz, 1H), 7.19 (d, *J* = 6.00 Hz, 1H), 7.37 (t, *J* = 8.40 Hz, 1H), 7.44 (t, *J* = 9.20 Hz, 1H), 7.64 (d, *J* = 16.00 Hz, 1H), 7.61-7.85 (m, 4H), 8.16 (dd, *J* = 2.80, 6.80 Hz, 1H), 8.27 (s, 1H), 8.58 (d, *J* = 6.00 Hz, 1H), 8.76 (s, 1H), 9.00 (s, 1H), 10.36 (s, 1H).	4-(1H-Pyrazol-4-yl)-pyridine

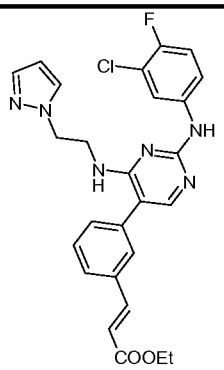
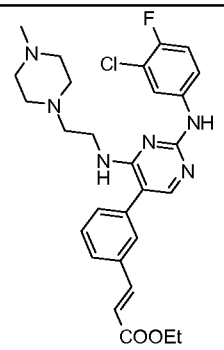
Ex	Compound	Data	SM
189	 ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(trifluoromethyl)-1*H*-imidazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 532.2 (M+1) for $C_{25}H_{18}ClF_4N_5O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.26 (t, *J* = 7.20 Hz, 3H), 4.20 (q, *J* = 7.20 Hz, 2H), 6.64 (d, *J* = 16.00 Hz, 1H), 7.27 (d, *J* = 7.60 Hz, 1H), 7.41-7.49 (m, 2H), 7.64 (d, *J* = 16.00 Hz, 1H), 7.69-7.73 (m, 2H), 7.76 (d, *J* = 7.60 Hz, 1H), 7.82 (s, 1H), 7.95 (s, 2H), 8.08 (dd, *J* = 2.40, 6.80 Hz, 1H), 8.83 (s, 1H).	4-Trifluoromethyl-1*H*-imidazole
190	 ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2-methyl-1*H*-imidazol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES) : 478 (M+1) for $C_{25}H_{21}ClFN_5O_2$. ^{1}H NMR (300 MHz DMSO-d_6): δ 1.25 (t, *J* = 7.11 Hz, 3H), 2.1 (s, 3H), 4.18 (q, *J* = 7.11 Hz, 2H), 6.59 (d, *J* = 16.02 Hz, 1H), 6.82 (s, 1H), 7.08 (br s, 2H), 7.35-7.43 (m, 2H), 7.52-7.55 (m, 2H), 7.65-7.68 (m, 2H), 8.17 (d, *J* = 4.89 Hz, 1H), 8.87 (s, 1H), 10.36 (s, 1H).	2-Methyl-1*H*-imidazole
191	 ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-1,2,3-triazol-2-yl)pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 465 (M+1) for $C_{23}H_{18}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.25 (t, *J* = 7.12 Hz, 3H), 4.18 (q, *J* = 7.12 Hz, 2H), 6.62 (d, *J* = 16.04 Hz, 1H), 6.99 (d, *J* = 7.72 Hz, 1H), 7.33 (t, *J* = 7.68 Hz, 1H), 7.40 (t, *J* = 9.08 Hz, 1H), 7.56 (s, 1H), 7.59 (d, *J* = 16.40 Hz, 1H), 7.65 (d, *J* = 7.76 Hz, 1H), 7.72-7.75 (m, 1H), 8.09 (s, 2H), 8.19 (dd, *J* = 2.36, 6.70 Hz, 1H), 8.87 (s, 1H), 10.50 (s, 1H).	1*H*-[1,2,3]Triazole

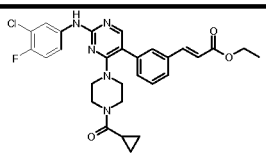
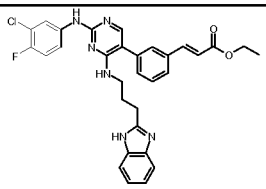
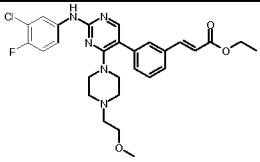
Ex	Compound	Data	SM
192	 ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-1,2,3-triazol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 465 (M+1) for $C_{23}H_{18}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.26 (t, *J* = 6.40 Hz, 3H), 4.19 (q, *J* = 7.20 Hz, 2H), 6.62 (d, *J* = 16.00 Hz, 1H), 7.10 (d, *J* = 7.20 Hz, 1H), 7.37 (t, *J* = 7.60 Hz, 1H), 7.42 (t, *J* = 9.60 Hz, 1H), 7.60 (d, *J* = 16.00 Hz, 1H), 7.61 (s, 1H), 7.68 (d, *J* = 7.60 Hz, 1H), 7.72-7.74 (m, 1H), 7.93 (s, 1H), 8.08 (d, *J* = 5.60 Hz, 1H), 8.52 (s, 1H), 8.91 (s, 1H), 10.50 (s, 1H).	1*H*-[1,2,3]Triazole
193	 ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-[1,2,3]triazolo[4,5-*b*]pyridin-2-yl)pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 518 (M+1) for $C_{26}H_{21}ClFN_7O_2$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.24 (t, J = 7.20 Hz, 3H), 4.16 (q, J = 7.20 Hz, 2H), 6.50 (d, J = 16.02 Hz, 1H), 6.90 (d, 1H), 7.25 (t, 1H), 7.41 (t, 1H), 7.56-7.63 (m, 3H), 7.70-7.80 (m, 1H), 8.15 (dd, 1H), 8.51 (dd, J = 1.47, 8.71 Hz, 1H), 8.90 (dd, J = 1.41, 4.03 Hz, 1H), 9.04 (s, 1H), 10.66 (s, 1H).	1*H*-[1,2,3]Triazolo[4,5-b]pyridine
194	 ethyl (2*E*)-3-(3-{4-(1*H*-benzotriazol-1-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 515.2 (M+1) for $C_{27}H_{20}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.25 (t, *J* = 7.28 Hz, 3H), 4.17 (q, *J* = 7.08 Hz, 2H), 6.58 (d, *J* = 16.04 Hz, 1H), 7.10 (d, *J* = 7.68 Hz, 1H), 7.30 (t, *J* = 7.44 Hz, 1H), 7.38-7.42 (m, 2H), 7.49-7.69 (m, 5H), 7.89-7.95 (m, 1H), 8.13-8.17 (m, 2H), 8.92 (s, 1H), 10.44 (s, 1H).	1*H*-Benzotriazole

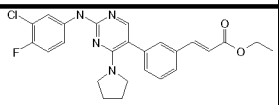
Ex	Compound	Data	SM
195	 ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-pyrrol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES) : 463 (M+1) for $C_{25}H_{20}ClFN_4O_2$. ^{1}H NMR (300 MHz DMSO-d_6): δ 1.24 (t, *J* = 7.05 Hz, 3H), 4.18 (q, *J* = 7.02 Hz, 2H), 6.16 (br s, 2H), 6.65 (d, *J* = 16.05 Hz, 1H), 6.91 (br s, 2H), 7.08 (br s, 2H), 7.27 (d, *J* = 7.62 Hz, 1H) 7.47-7.37 (m, 2H), 7.74-7.80 (m, 2H), 8.11 (d, *J* = 4.29 Hz, 1H), 8.58 (s, 1H), 10.16 (s, 1H).	1*H*-Pyrrole

The following examples were prepared using the general method described above for **Example 1** using {3-[(1*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]phenyl}boronic acid, tris(dibenzylideneacetone)dipalladium(0), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl, sodium carbonate and the starting material (SM) indicated.

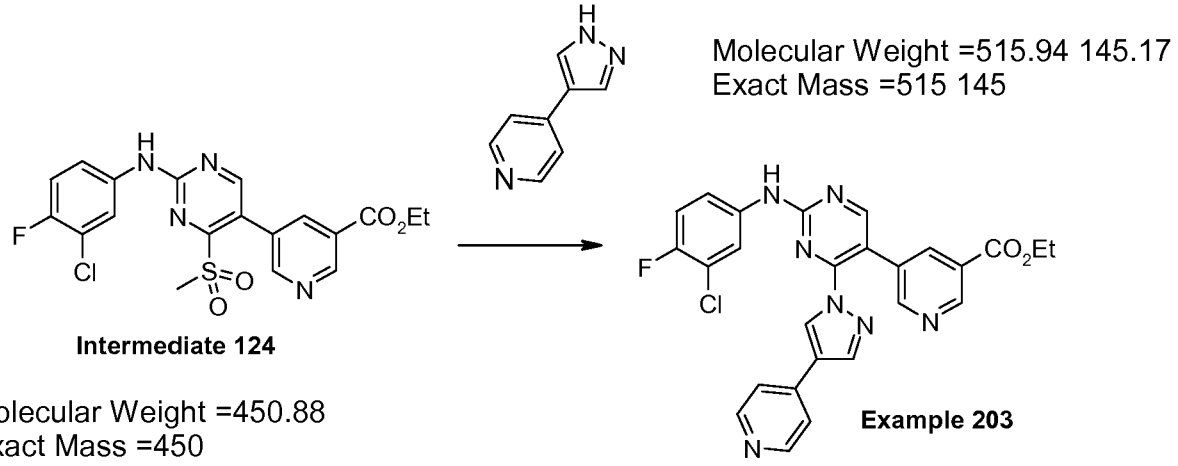
Ex	Compound	Data	SM
196	 ethyl (2*E*)-3-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-imidazol-1-yl)ethyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoate	MS(ES): 507 (M+1) for $C_{26}H_{24}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.27 (t, *J* = 7.08 Hz, 3H), 3.68 (q, *J* = 5.96 Hz, 2H), 4.18-4.24 (m, 4H), 6.68 (d, *J* = 16.04 Hz, 1H), 6.72 (t, *J* = 5.76 Hz, 1H), 6.89 (s, 1H), 7.15 (s, 1H), 7.28-7.35 (m, 2H), 7.47 (t, *J* = 7.68 Hz, 1H), 7.58-7.64 (m, 3H), 7.67 (d, *J* = 16.16 Hz, 1H), 7.71 (d, *J* = 7.68 Hz, 1H), 7.84 (s, 1H), 8.16 (dd, *J* = 2.48, 6.82 Hz, 1H), 9.40 (s, 1H).	5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-[2-(1*H*-imidazol-1-yl)ethyl]pyrimidine-2,4-diamine **(Intermediate 64)**

Ex	Compound	Data	SM
197	 ethyl (2*E*)-3-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-pyrazol-1-yl)ethyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoate	MS(ES): 507 (M+1) for $C_{26}H_{24}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.27 (t, *J* = 7.08 Hz, 3H), 3.76 (q, *J* = 5.72 Hz, 2H), 4.21 (q, *J* = 7.16 Hz, 2H), 4.38 (t, *J* = 6.00 Hz, 2H), 6.26 (t, *J* = 1.88 Hz, 1H), 6.66 (d, *J* = 16.04 Hz, 1H), 6.72 (t, *J* = 5.36 Hz, 1H), 7.30 (t, *J* = 9.12 Hz, 1H), 7.36 (d, *J* = 7.68 Hz, 1H), 7.45 (s, 1H), 7.49 (d, *J* = 7.68 Hz, 1H), 7.60 (s, 1H), 7.67 (d, *J* = 16.12 Hz, 1H), 7.69-7.72 (m, 3H), 7.85 (s, 1H), 8.15 (dd, *J* = 2.56, 6.88 Hz, 1H), 9.44 (s, 1H).	5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-[2-(1*H*-pyrazol-1-yl)ethyl]pyrimidine-2,4-diamine **(Intermediate 91)**
198	 ethyl (2*E*)-3-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(4-methylpiperazin-1-yl)ethyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoate	MS(ES): 539 (M+1) for $C_{28}H_{32}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.25 (t, *J* = 7.08 Hz, 3H), 2.11 (s, 3H), 2.20-2.40 (m, 8H), 3.30 (m, 2H), 3.45-3.49 (m, 2H), 4.19 (q, *J* = 7.12 Hz, 2H), 6.46 (t, *J* = 4.88 Hz, 1H), 6.70 (d, *J* = 16.00 Hz, 1H), 7.28 (t, *J* = 9.12 Hz, 1H), 7.45 (d, *J* = 7.64 Hz, 1H), 7.51 (t, *J* = 7.48 Hz, 1H), 7.64-7.66 (m, 1H), 7.67 (s, 1H), 7.71-7.74 (m, 2H), 7.85 (s, 1H), 8.19 (dd, *J* = 2.52, 6.90 Hz, 1H), 8.31 (s, 1H), 9.41 (s, 1H).	5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-[2-(4-methylpiperazin-1-yl)ethyl]pyrimidine-2,4-diamine **(Intermediate 92)**

Ex	Compound	Data	SM
199	 (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(4-(cyclopropanecarbonyl)piperazin-1-yl)pyrimidin-5-yl)phenyl)acrylate	MS(ES): 550 (M+1) for $C_{29}H_{29}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.56 - 0.78 (m, 4 H) 1.26 (t, *J*=7.06 Hz, 3 H) 1.76 - 2.06 (m, 1 H) 3.12 - 3.33 (m, 4 H) 3.38 - 3.81 (m, 4 H) 4.20 (q, *J*=7.10 Hz, 2 H) 6.74 (d, *J*=16.01 Hz, 1 H) 7.34 (t, *J*=9.14 Hz, 1 H) 7.42 - 7.60 (m, 2 H) 7.59 - 7.78 (m, 3 H) 7.82 (s, 1 H) 8.04 - 8.23 (m, 2 H) 9.65 (s, 1 H)	(4-(5-bromo-2-(3-chloro-4-fluorophenylamino)pyrimidin-4-yl)piperazin-1-yl)(cyclopropyl)methanone **(Intermediate 96)**
200	 (E)-ethyl 3-(3-(4-(3-(1*H*-benzo[d]imidazol-2-yl)propylamino)-2-(3-chloro-4-fluorophenylamino)pyrimidin-5-yl)phenyl)acrylate	MS(ES): 571 (M+1) for $C_{31}H_{28}ClFN_6O_2$	N^4-(3-(1*H*-benzo[d]imidazol-2-yl)propyl)-5-bromo-N^2-(3-chloro-4-fluorophenyl)pyrimidine-2,4-diamine **(Intermediate 93)**
201	 (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(4-(2-methoxyethyl)piperazin-1-yl)pyrimidin-5-yl)phenyl)acrylate	MS(ES): 540 (M+1) for $C_{28}H_{31}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.26 (t, 3 H) 2.30 - 2.47 (m, 6 H) 3.10 - 3.28 (m, 7 H) 3.39 (t, *J*=5.75 Hz, 2 H) 4.20 (q, *J*=7.10 Hz, 2 H) 6.72 (d, *J*=16.01 Hz, 1 H) 7.33 (t, *J*=9.14 Hz, 1 H) 7.42 - 7.55 (m, 2 H) 7.55 - 7.75 (m, 3 H) 7.81 (s, 1 H) 8.06 (s, 1 H) 8.19 (dd, *J*=6.88, 2.54 Hz, 1 H) 9.61 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[4-(2-methoxyethyl)piperazin-1-yl]pyrimidin-2-amine **(Intermediate 108)**

Ex	Compound	Data	SM
202	 (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(pyrrolidin-1-yl)pyrimidin-5-yl)phenyl)acrylate	MS(ES): 467 (M+1) for $C_{25}H_{24}ClFN_4O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.26 (t, *J*=7.06 Hz, 3 H) 1.76 (br. s., 4 H) 3.17 (br. s., 4 H) 4.19 (q, *J*=7.16 Hz, 2 H) 6.71 (d, *J*=16.01 Hz, 1 H) 7.20 - 7.39 (m, 2 H) 7.44 (t, *J*=7.91 Hz, 1 H) 7.55 - 7.81 (m, 4 H) 7.88 (s, 1 H) 8.26 (dd, *J*=6.97, 2.64 Hz, 1 H) 9.46 (s, 1 H)	5-bromo-N-(3-chloro-4-fluorophenyl)-4-(pyrrolidin-1-yl)pyrimidin-2-amine **(Intermediate 104)**

Example 203: Ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyridin-4-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

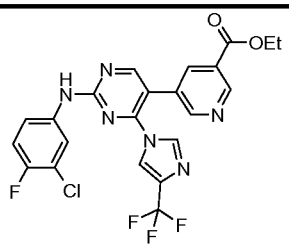
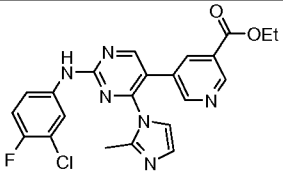


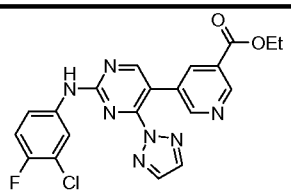
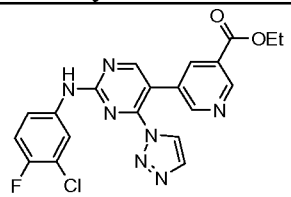
A solution of 4-(1*H*-pyrazol-4-yl)-pyridine (838 mg, 5.78 mmol) in DMF (2 mL) was added slowly to a suspension of sodium hydride (60%, 220 mg, 5.52 mmol) in DMF (2 mL). The reaction mixture was stirred for 25 min at room temperature. A solution of ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}pyridine-3-carboxylate (**Intermediate 124**, 1.18 g, 2.63 mmol) in DMF (1 mL) was added slowly to the reaction mixture and the mixture was stirred for 1 h. Water was added (~6 mL), and the solid formed was filtered, dried to yield the title compound (900 mg).

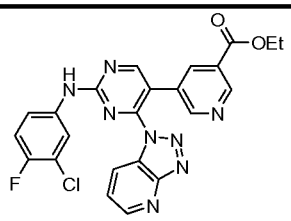
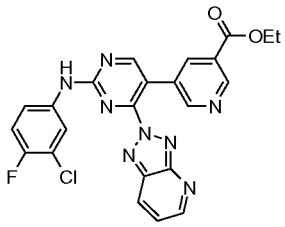
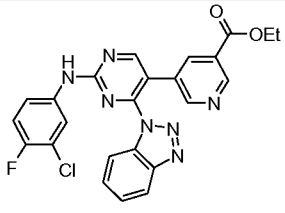
MS(ES): 516 (M+1) for $C_{26}H_{19}ClFN_7O_2$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (t, J = 7.20 Hz, 3H), 4.34 (q, J = 7.20 Hz, 2H), 7.46 (t, J = 8.80 Hz, 1H), 7.70-7.76 (m, 3H), 8.14-8.16 (m, 2H), 8.27 (s, 1H), 8.59 (s, 2H), 8.71 (s, 1H), 8.76 (s, 1H), 9.03 (s, 1H), 9.09 (s, 1H), 10.41 (s, 1H).

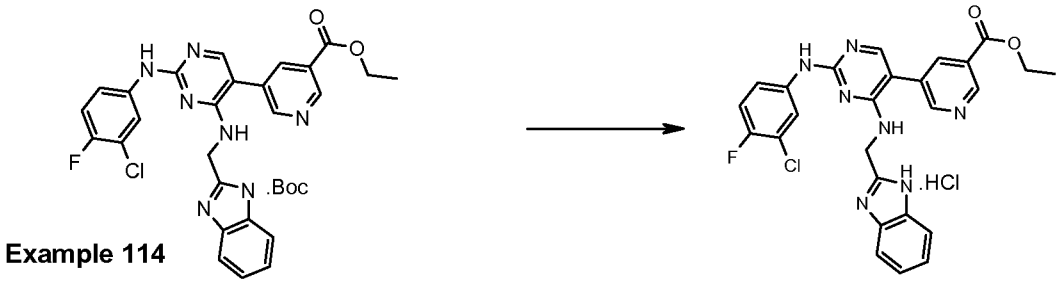
The following examples were prepared using the general method described above for **Example 203** using ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}pyridine-3-carboxylate (**Intermediate 124**), sodium hydride and the starting material (SM) indicated.

Ex	Compound	Data	SM
204	 ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(trifluoromethyl)-1*H*-imidazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 507 (M+1) for $C_{22}H_{15}ClF_4N_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (t, J = 7.12 Hz, 3H), 4.33 (q, J = 7.08 Hz, 2H), 7.42 (t, J = 9.12 Hz, 1H), 7.70 (ddd, J = 2.72, 4.14, 9.07 Hz, 1H), 7.92 (d, J = 1.24 Hz, 1H), 8.02 (s, 1H), 8.06 (dd, J = 2.52, 6.68 Hz, 1H), 8.11 (t, J = 2.12 Hz, 1H), 8.69 (d, J = 2.12 Hz, 1H), 8.91 (s, 1H), 9.07 (d, J = 1.88 Hz, 1H), 10.50 (s, 1H).	4-Trifluoromethyl-1*H*-imidazole
205	 ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2-methyl-1*H*-imidazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 453 (M+1) for $C_{22}H_{18}ClFN_6O_2$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.33 (t, J = 6.93 Hz, 3H), 2.20 (s, 3H), 4.3 (q, J = 6.66 Hz, 2H), 6.80 (s, 1H), 7.04 (s, 1H), 7.41 (t, J = 8.85 Hz, 1H), 7.66 (m, 1H), 7.98 (s, 1H), 8.06 (d, J = 4.36 Hz, 1H)), 8.52 (s, 1H), 8.90 (s, 1H), 8.97 (s, 1H), 10.42 (s, 1H).	2-Methyl-1*H*-imidazole

Ex	Compound	Data	SM
206	 ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-1,2,3-triazol-2-yl)pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 440 (M+1) for $C_{20}H_{15}ClFN_7O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (t, *J* = 7.20 Hz, 3H), 4.34 (q, *J* = 7.20 Hz, 2H), 7.43 (t, *J* = 9.20 Hz, 1H), 7.76-7.80 (m, 1H), 8.02 (t, *J* = 2.00 Hz, 1H), 8.12 (br s, 2H), 8.24 (d, *J* = 4.40 Hz, 1H), 8.62 (d, *J* = 2.00 Hz, 1H), 8.88 (s, 1H), 9.03 (d, *J* = 1.60 Hz, 1H), 10.59 (br s, 1H).	1*H*-[1,2,3]Triazole
207	 ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-1,2,3-triazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 440 (M+1) for $C_{20}H_{15}ClFN_7O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (t, *J* = 7.20 Hz, 3H), 4.35 (q, *J* = 7.20 Hz, 2H), 7.44 (t, *J* = 8.80 Hz, 1H), 7.72-7.76 (m, 1H), 7.96 (d, *J* = 1.16 Hz,1H), 8.06 (m, 1H), 8.08 (t, *J* = 2.12 Hz, 1H), 8.64-8.65 (m, 2H), 8.90 (s, 1H), 9.04 (d, *J* = 1.60 Hz, 1H), 10.54 (s, 1H).	1*H*-[1,2,3]Triazole

Ex	Compound	Data	SM
208	 ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-[1,2,3]triazolo[4,5-b]pyridin-1-yl)pyrimidin-5-yl}pyridine-3-carboxylate +  ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-[1,2,3]triazolo[4,5-b]pyridin-2-yl)pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 491 (M+1) for both isomers Mixture of regioisomers (3:2) ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.22 (t, J = 7.08 Hz, 3H), 1.29 (t, J = 7.04 Hz, 3H), 4.24-4.26 (m, 2H), 4.32 (q, J = 7.04 Hz, 2H), 7.44 (t, J = 9.04 Hz, 1H), 7.80-7.83 (m, 1H), 7.60-7.70 (m, 1H), 8.13 (dd, J = 2.28, 6.76 Hz, 1H), 8.23-8.25 (m, 1H), 8.50 (dd, J = 1.44, 8.76 Hz, 1H), 8.62 (d, J = 2.20 Hz, 1H), 8.77-8.86 (m, 2H), 9.00 (d, J = 1.92 Hz, 1H), 9.07 (s, 1H), 10.51 (br s, 1H), 10.76 (br s, 1H).	1*H*-[1,2,3]Triazolo[4,5-b]pyridine
209	 ethyl 5-{4-(1*H*-benzotriazol-1-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 490 (M+1) for $C_{24}H_{17}ClFN_7O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.19-1.30 (m, 3H), 4.23-4.33 (m, 2H), 7.43 (t, *J* = 9.08 Hz, 1H), 7.51-7.58 (m, 1H), 7.64-7.66 (m, 1H), 7.72-7.76 (m, 1H), 7.91-7.94 (m, 1H), 8.14-8.23 (m, 3H), 8.71 (s, 1H), 8.98 (s, 1H), 9.03-9.04 (m, 1H), 10.48 (s, 1H).	1*H*-Benzotriazole

Example 210: ethyl 5-[4-(1*H*-benzimidazol-2-ylmethylamino)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl]pyridine-3-carboxylate hydrochloride

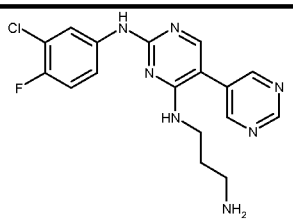


To a stirred solution of *tert*-butyl 2-[[[2-[(3-chloro-4-fluorophenyl)amino]-5-(5-ethoxycarbonylpyridin-3-yl)pyrimidin-4-yl]amino]methyl]benzimidazole-1-carboxylate (**Example 114**, 500mg, 0.81mmol) in 1,4- dioxane (10 mL) under nitrogen atmosphere was added 4N hydrochloric acid in 1,4–dioxane (10mL) dropwise. The reaction mixture was stirred at room temperature for 24 h, then concentrated to give ethyl 5-[4-(1*H*-benzimidazol-2-ylmethylamino)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl]pyridine-3-carboxylate hydrochloride as a white solid in 37 % yield (150 mg, 0.29 mmol).

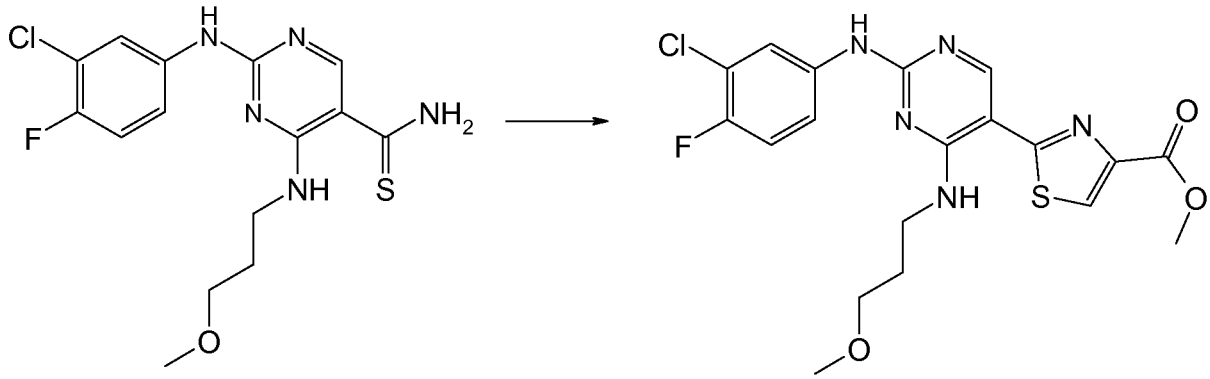
MS(ES):518.2 (M+1) for $C_{26}H_{21}ClFN_7O_2$.

^{1}H NMR (400 MHz) DMSO-d_6: δ 1.35 (t, *J* = 7.08 Hz, 3H), 4.40 (q, *J* = 2.88 Hz, 2H), 4.98 (d, *J* = 5.16 Hz, 2H), 7.12 (t, *J* = 0.00 Hz, 1H), 7.45 (br 1H), 7.52 (dd, *J* = 6.12, 3.20 Hz, 1H), 7.60 (s 7.77 (dd, *J* = 6.16, 3.12 Hz, 2H), 8.09 (s, 1H), 8.49 (t, *J* = 2.08 Hz, 1H), 9.03 (d, *J* = 2.20 Hz, 1H), 9.13 (d, *J* = 2.00 Hz, 1H), 10.00 (br s, 1H).

The following examples were prepared by the general method described above for **Example 210** using 4N hydrochloric acid in dioxane and the starting material (SM) indicated.

Ex	Compound	Data	SM
211	 N^4-(3-aminopropyl)-N^2-(3-chloro-4-fluorophenyl)-5,5'-bipyrimidine-2,4-diamine	MS(ES): 374 (M+1) for $C_{17}H_{17}ClFN_7$ ^{1}H NMR (300 MHz, DMSO- *d6*) δ ppm 3.14 - 3.37 (m, 4 H) 3.75 - 3.98 (m, 4 H) 7.27 (d, J=3.77 Hz, 1 H) 7.34 (t, J=9.14 Hz, 1 H) 7.48 - 7.65 (m, 1 H) 7.69 (d, J=3.77 Hz, 1 H) 8.10 (dd, J=6.88, 2.54 Hz, 1 H) 8.21 (s, 1 H) 9.82 (s, 1 H) 13.10 (s, 1 H)	*tert*-butyl 3-(2-(3-chloro-4-fluorophenylamino)-5,5'-bipyrimidin-4-ylamino)propylcarbamate **(Example 74)**

Example 212: Methyl 2-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)thiazole-4-carboxylate



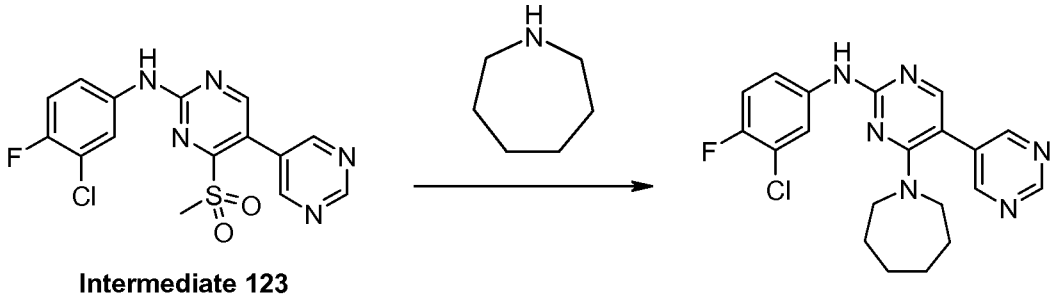
Intermediate 128 Example 212

A stirred suspension of 2-(3-chloro-4-fluorophenylamino)-4-(3-methoxy propylamino)pyrimidine-5-carbothioamide (**Intermediate 128**, 171 mg, 0.46 mmol) and methyl 3-bromo-2-oxopropanoate (84 mg, 0.46 mmol) in ethanol (2 mL) was purged with a stream of nitrogen and then placed under an atmosphere of nitrogen. This was heated to 80 degrees C for several days, with ethanol replaced as necessary. The reaction mixture was allowed to cool to room temperature. The mixture was diluted with dimethylsulfoxide (5 mL). The title compound was isolated (80 mg, 38%) via reverse-phase chromatography (acetonitrile/water/ammonium acetate).

MS: ES+ 452 for $C_{19}H_{19}ClFN_5O_3S$.

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.89 (quin, J=6.45 Hz, 2 H) 3.27 (s, 3 H) 3.51 (t, J=6.12 Hz, 2 H) 3.63 (q, J=6.40 Hz, 2 H) 3.87 (s, 3 H) 7.33 (t, J=9.04 Hz, 1 H) 7.57 - 7.71 (m, 1 H) 8.24 (dd, J=6.88, 2.35 Hz, 1 H) 8.45 (s, 1 H) 8.60 (s, 1 H) 9.37 (t, J=5.09 Hz, 1 H) 9.88 (s, 1 H).

Example 213: 4-(azepan-1-yl)-N-(3-chloro-4-fluorophenyl)-5-pyrimidin-5-ylpyrimidin-2-amine



Intermediate 123

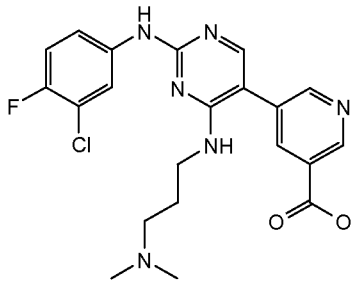
Example 213

N-(3-Chloro-4-fluorophenyl)-4-methylsulfonyl-5-pyrimidin-5-ylpyrimidin-2-amine (**Intermediate 123**, 0.21 mmol, 80 mg) was suspended in NMP (1 mL), then treated with N,N-diisopropylethylamine (0.25 mmol , 32 mg) and hexamethyleneimine (2.63 mmol). The mixture was heated at 90 °C for 30 min in a sealed tube. The reaction mixture was added to water and stirred for 15 min. The precipitated solid was filtered, washed with water and dried to afford the crude product which was further purified by flash chromatography to yield 18 mg of the title compound (0.045 mmol, 21%).

MS(ES):399 (M+1) for $C_{20}H_{20}ClFN_6$.

^{1}H NMR 400 MHz DMSO-d_6 : δ 1.41 (br s, 4H), 1.62 (br s, 4H), 3.31 (br s, 4H), 7.32 (t, J = 9.12 Hz, 1H), 7.56 (ddd, J = 9.00, 4.06, 2.76 Hz, 1H), 7.93 (s, 1H), 8.26 (dd, J = 6.90, 2.52 Hz, 1H), 8.80 (s, 2H), 9.10 (s, 1H), 9.57 (s, 1H).

Example 214: 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino)propylamino)pyrimidin-5-yl)nicotinic acid

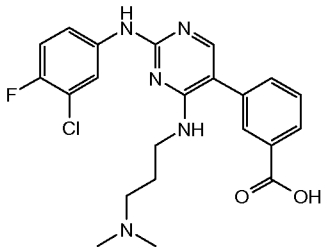
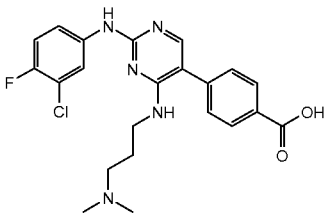
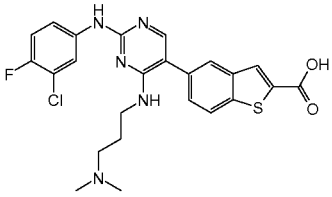


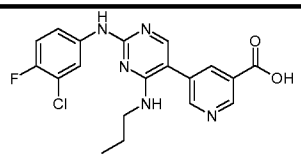
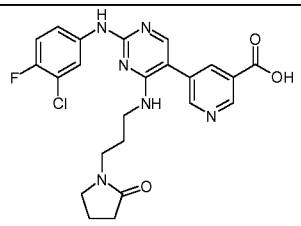
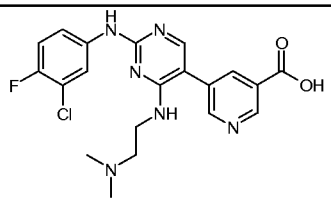
A solution of ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino) propylamino)pyrimidin-5-yl) nicotinate (**Example 5**, 50 mg, 0.09 mmol) in methanol (0.3 ml) was stirred under ambient conditions; if solubility was less than complete to the naked eye then small volumes of THF were added as necessary. Sodium hydroxide (aqueous, 1 N, 0.341 ml) was added to the solution, which was stirred under ambient conditions until high or complete conversion was indicated by LCMS or TLC. Careful acidification with 1 N HCl (aq) was followed by an aqueous workup, using methylene chloride and methanol (9:1) as the organic phase to extract the water layer (4 x 25 ml). The organic extracts were combined, dried over sodium sulfate, and concentrated, affording product of high purity (15 mg) which was characterized by LCMS and ^{1}H NMR.

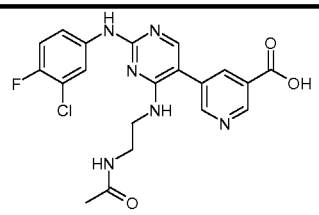
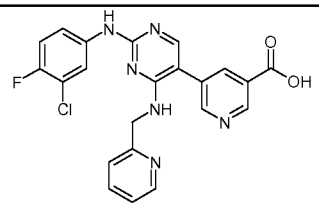
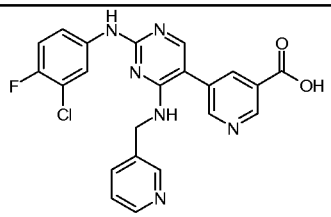
MS: ES+ 445 for $C_{21}H_{22}ClFN_6O_2$

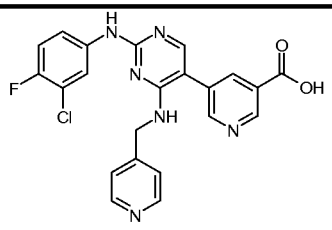
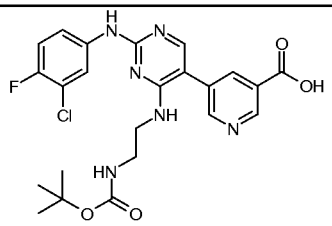
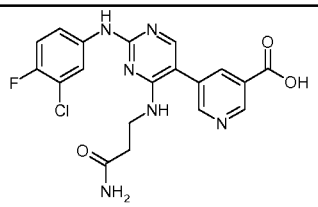
^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.85 - 2.01 (m, 2 H) 2.60 (s, 6 H) 2.93 (t, *J*=7.06 Hz, 2 H) 3.36 - 3.52 (m, 2 H) 7.14 (t, *J*=5.18 Hz, 1 H) 7.32 (t, *J*=9.14 Hz, 1 H) 7.58 - 7.67 (m, 1 H) 7.85 (s, 1 H) 8.17 (t, *J*=2.07 Hz, 1 H) 8.21 (dd, *J*=6.97, 2.64 Hz, 1 H) 8.69 (d, *J*=2.07 Hz, 1 H) 8.88 (d, *J*=1.51 Hz, 1 H) 9.50 (s, 1 H)

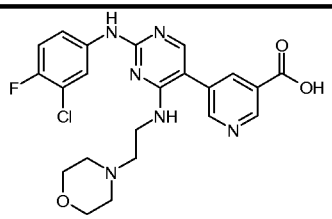
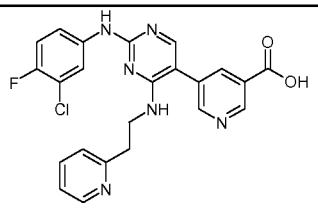
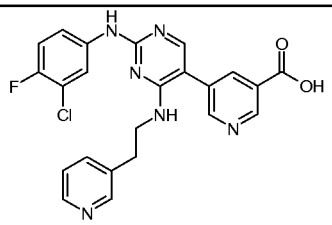
The following examples were prepared using the general method described above for **Example 214** using 1N sodium hydroxide and the starting material (SM) indicated.

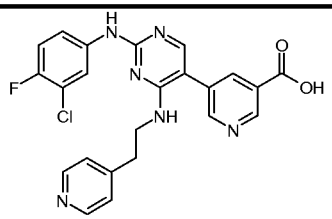
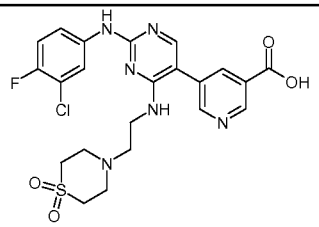
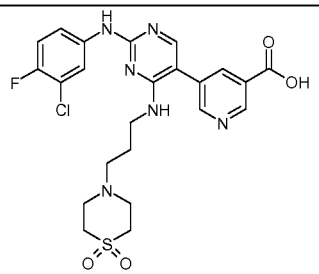
Ex	Compound	Data	SM
215	 3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[3-(dimethylamino) propyl]amino} pyrimidin-5-yl)benzoic acid	MS: ES+ 444 for $C_{22}H_{23}ClFN_5O_2$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.89 - 2.05 (m, 2 H) 2.69 (d, *J*=4.71 Hz, 6 H) 2.93 - 3.06 (m, 2 H) 3.36 - 3.48 (m, 2 H) 7.40 - 7.75 (m, 4 H) 7.83 - 8.26 (m, 5 H) 10.69 (d, *J*=83.08 Hz, 2 H) 13.17 (s, 1 H)	methyl 3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino) propylamino) pyrimidin-5-yl)benzoate **(Example 2)**
216	 4-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[3-(dimethylamino) propyl]amino} pyrimidin-5-yl)benzoic acid	MS: ES+ 444 for $C_{22}H_{23}ClFN_5O_2$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.89 - 2.03 (m, 2 H) 2.69 (s, 6 H) 2.97 - 3.08 (m, 2 H) 3.40 - 3.51 (m, 2 H) 6.92 (t, *J*=5.56 Hz, 1 H) 7.33 (t, *J*=9.14 Hz, 1 H) 7.53 (d, *J*=8.48 Hz, 2 H) 7.59 - 7.69 (m, 1 H) 7.86 (s, 1 H) 8.00 (d, *J*=8.48 Hz, 2 H) 8.19 (dd, *J*=6.97, 2.64 Hz, 1 H) 9.51 (s, 1 H)	Ethyl 4-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino) propylamino) pyrimidin-5-yl) benzoate **(Example 6)**
217	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino) propylamino) pyrimidin-5-yl)benzo[b] thiophene-2-carboxylic acid	MS: ES+ 500 for $C_{24}H_{23}ClFN_5O_2S$ ^{1}H NMR (300 MHz, DMSO-d_6) d ppm 1.66 (dq, *J*=6.59, 6.41 Hz, 2 H) 1.90 (s, 6 H) 2.27 (t, *J*=6.22 Hz, 2 H) 3.40 - 3.48 (m, 2 H) 7.16 - 7.34 (m, 3 H) 7.54 (s, 1 H) 7.59 - 7.69 (m, 1 H) 7.72 - 7.81 (m, 2 H) 7.91 (d, *J*=8.29 Hz, 1 H) 8.26 (dd, *J*=6.88, 2.54 Hz, 1 H) 9.35 (s, 1 H)	Methyl 5-{2-(3-chloro-4-fluorophenylamino)-4-[3-(dimethylamino) propylamino] pyrimidin-5-yl} benzo[b]thiophene-2-carboxylate **(Example 22)**

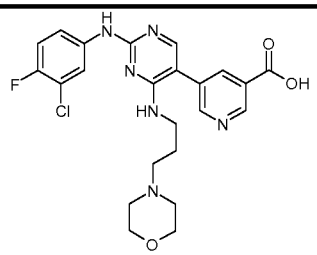
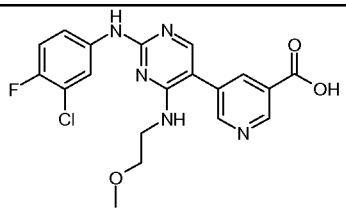
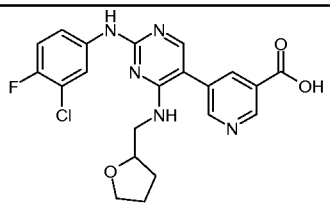
Ex	Compound	Data	SM
218	 5-[2-(3-Chloro-4-fluoro-phenylamino)-4-propylamino-pyrimidin-5-yl]-nicotinic acid	MS(ES): 402 (M+1) for $C_{19}H_{17}ClFN_5O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.87 (t, *J* = 7.44 Hz, 3H), 1.56 (q, *J* = 7.36 Hz, 2H), 3.31 (q, *J* = 6.12 Hz, 3H), 7.43-7.50 (m, 2H), 7.92 (s, 1H), 8.05 (dd, *J* = 6.74, 2.36 Hz, 1H), 8.25 (t, *J* = 2.12 Hz, 2H), 8.78 (d, *J* = 2.2 Hz, 1H), 9.12 (d, *J* = 1.96 Hz, 1H), 10.56 (br s, 1H).	5-[2-(3-Chloro-4-fluoro-phenylamino)-4-propylamino-pyrimidin-5-yl]-nicotinic acid ethyl ester **(Example 90)**
219	 5-{2-(3-Chloro-4-fluoro-phenylamino)-4-[3-(2-oxo-pyrrolidin-1-yl)-propylamino]-pyrimidin-5-yl}-nicotinic acid	MS(ES):485 (M+1) for $C_{23}H_{22}ClFN_6O_3$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.74 (t, *J* = 6.88 Hz, 2H), 1.86 (m, 2H), 2.15 (t, *J* = 8.04 Hz, 2H), 3.19-3.32 (m, 6H), 6.91 (br s, 1H), 7.32 (t, *J* = 9.16 Hz, 1H), 7.63 (m, 1H), 7.84 (s, 1H), 8.19 (s, 1H), 8.76 (s, 1H), 9.02 (s, 1H), 9.48 (s, 1H).	5-{2-(3-Chloro-4-fluoro-phenylamino)-4-[3-(2-oxo-pyrrolidin-1-yl)-propylamino]-pyrimidin-5-yl}-nicotinic acid ethyl ester **(Example 91)**
220	 5-[2-(3-Chloro-4-fluoro-phenylamino)-4-(2-dimethylamino-ethylamino)-pyrimidin-5-yl]-nicotinic acid	MS(ES):431 (M+1) for $C_{20}H_{20}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.77 (s, 6H), 3.28-3.32 (m, 2H), 3.67 (br s, 2H), 7.07 (t, *J* = 4.8 Hz, 1H), 7.34 (t, *J* = 9.04 Hz, 1H), 7.65 (m, 1H), 7.92 (s, 1H), 8.09 (dd, *J* = 6.7, 2.48 Hz, 1H), 8.23 (br s, 1H), 8.82 (d, *J* = 1.96 Hz, 1H), 9.03 (d, *J* = 1.72 Hz, 1H), 9.55 (s, 1H).	5-[2-(3-Chloro-4-fluoro-phenylamino)-4-(2-dimethylamino-ethylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester **(Example 93)**

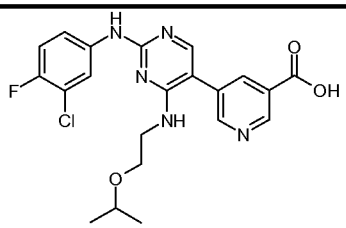
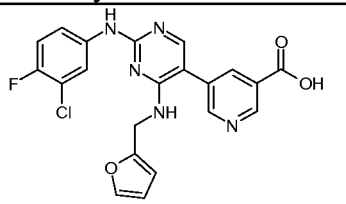
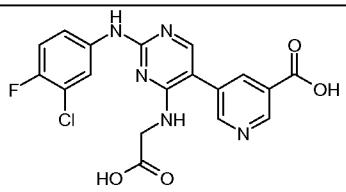
Ex	Compound	Data	SM
221	 5-[4-(2-Acetylamino-ethylamino)-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-5-yl]-nicotinic acid	MS(ES): 445 (M+1) for $C_{20}H_{18}ClFN_6O_3$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.79 (s, 3H), 6.98 (br s, 1H), 7.3 (t, *J* = 9.16 Hz, 1H), 7.67 (m, 1H), 7.85 (s, 1H), 7.91 (s, 1H), 8.15(dd, *J* = 6.86, 2.52 Hz, 1H), 8.22 (s, 1H), 8.77 (s, 1H), 9.03 (s, 1H), 9.49 (s, 1H).	5-[4-(2-Acetylamino-ethylamino)-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester **(Example 94)**
222	 5-{2-(3-Chloro-4-fluoro-phenylamino)-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-5-yl}-nicotinic acid	MS(ES): 449 (M-1) and 451(M+1) for $C_{22}H_{16}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.67 (d, *J* = 5.8 Hz, 2H), 7.16 (t, *J* = 9.12 Hz, 1H), 7.23 (t, *J* = 1.64 Hz, 1H), 7.32 (d, *J* = 7.88 Hz, 1H), 7.48-7.55 (m, 2H), 7.70-7.74 (m, 1H), 7.91-7.93 (m, 2H), 8.31 (t, *J* = 2.08 Hz, 1H), 8.51 (dd, *J* = 4.8, 0.76 Hz, 1H), 8.86 (d, *J* = 2.24 Hz, 1H), 9.05 (d, *J* = 1.96 Hz, 1H), 9.42 (s, 1H).	5-{2-(3-Chloro-4-fluoro-phenylamino)-4-[(pyridin-2-ylmethyl)-amino]-pyrimidin-5-yl}-nicotinic acid ethyl ester **(Example 95)**
223	 5-{2-(3-Chloro-4-fluoro-phenylamino)-4-[(pyridin-3-ylmethyl)-amino]-pyrimidin-5-yl}-nicotinic acid	MS(ES): 449.1(M-1) for $C_{22}H_{16}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.60 (d, *J* = 5.76 Hz, 2H), 7.22 (t, *J* = 9.04 Hz, 1H), 7.31-7.34 (m, 1H), 7.5-7.56 (m, 2H), 7.73 (d, *J* = 8.08 Hz, 1H), 7.90 (s, 1H), 8.02 (dd, *J* = 6.72, 2.24 Hz, 1H), 8.24 (br s, 1H), 8.41 (br s, 1H), 8.56 (br s, 1H), 8.80 (br s, 1H), 9.04 (br s, 1H), 9.46 (br s, 1H).	5-{2-(3-Chloro-4-fluoro-phenylamino)-4-[(pyridin-3-ylmethyl)-amino]-pyrimidin-5-yl}-nicotinic acid ethyl ester **(Example 96)**

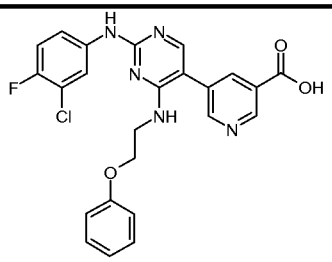
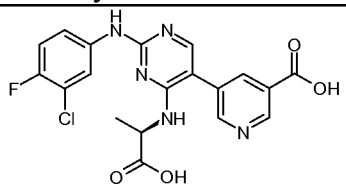
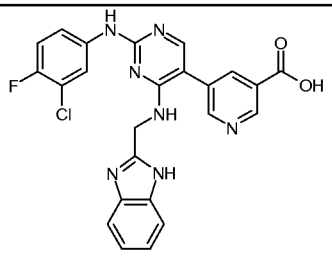
Ex	Compound	Data	SM
224	 5-{2-(3-Chloro-4-fluoro-phenylamino)-4-[(pyridin-4-ylmethyl)-amino]-pyrimidin-5-yl}-nicotinic acid	MS(ES): 451 (M+1) for $C_{22}H_{16}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.65 (d, J = 6.04 Hz, 2H), 7.20 (t, J = 9.08 Hz, 1H), 7.42 (dd, J = 7.66, 3.44 Hz, 1H), 7.53 (d, J = 5.04 Hz, 1H), 7.71 (br s, 1H), 7.86 (d, J = 6.00 Hz, 1H), 7.95 (s, 1H), 8.30 (t, J = 2.16 Hz, 1H), 8.59 (d, J = 6.12 Hz, 2H), 8.87 (d, J = 2.24 Hz, 1H), 9.07 (d, J = 2.00 Hz, 1H), 9.56 (br s, 1H).	5-{2-(3-Chloro-4-fluoro-phenylamino)-4-[(pyridin-4-ylmethyl)-amino]-pyrimidin-5-yl}-nicotinic acid ethyl ester **(Example 97)**
225	 5-[4-(2-*tert*-Butoxycarbonylamino-ethylamino)-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-5-yl]-nicotinic acid	MS(ES): 503.1 (M+1) for $C_{23}H_{24}ClFN_6O_4$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (s, 9H), 3.19 (br s, 2H), 3.39 (br s, 2H), 6.85 (m, 1H), 6.91 (m, 1H), 7.31 (t, J = 9.08 Hz, 1H), 7.68 (br s, 1H), 7.84 (s, 1H), 8.14 (d, J = 5.16 Hz, 2H) 8.18 (s, 1H), 8.76 (s, 1H), 9.02 (d, J = 1.56 Hz, 1H), 9.47 (s, 1H).	5-[4-(2-*tert*-Butoxycarbonylamino-ethylamino)-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester **(Example 98)**
226	 5-[4-(2-Carbamoyl-ethylamino)-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-5-yl]-nicotinic acid	MS(ES):431 (M+1) for $C_{19}H_{16}ClFN_6O_3$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.4 (t, J = 7.08Hz, 2H), 3.55 (m, 2H), 6.8 (br s, 1H), 6.93 (m, 1H), 7.24-7.29 (m, 2H), 7.70-7.72 (m, 1H), 7.85 (s, 1H), 8.15 (m, 1H), 8.74 (s, 1H), 9.01 (s, 1H), 9.46 (s, 1H).	5-[4-(2-Carbamoyl-ethylamino)-2-(3-chloro-4-fluoro-phenylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester **(Example 99)**

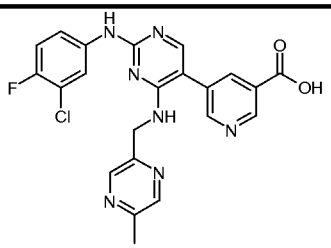
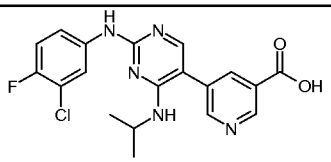
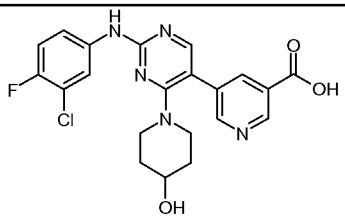
Ex	Compound	Data	SM
227	 5-[2-(3-Chloro-4-fluoro-phenylamino)-4-(2-morpholin-4-yl-ethylamino)-pyrimidin-5-yl]-nicotinic acid	MS(ES):473 (M+1) for $C_{22}H_{22}ClFN_6O_3$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (s, 4H), 3.49 (m, 6H), 6.56 (m, 1H), 7.28 (t, *J* = 8.96 Hz, 1H), 7.65-7.67 (m, 1H), 7.78 (s, 1H), 8.06 (s, 1H), 8.17 (dd, *J* = 6.86, 2.44 Hz, 1H), 8.45 (s, 1H), 8.91 (s, 1H), 9.40 (s, 1H).	5-[2-(3-Chloro-4-fluoro-phenylamino)-4-(2-morpholin-4-yl-ethylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester **(Example 100)**
228	 5-[2-(3-Chloro-4-fluoro-phenylamino)-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-5-yl]-nicotinic acid	MS(ES): 465.2(M) for $C_{23}H_{18}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.03 (t, *J* = 7 Hz, 2H), 3.72 (q, *J* = 6.64 Hz, 2H), 7.08 (t, *J* = 5.68 Hz, 1H), 7.18-7.27 (m, 3H), 7.66-7.70 (m, 2H), 7.85 (s, 1H), 8.14-8.18 (m, 2H), 8.44 (d, *J* = 4.08 Hz, 1H), 8.71(d, *J* = 1.88 Hz, 1H), 9.01 (d, *J* = 1.64 Hz, 1H), 9.47 (s, 1H), 13.4 (br s, 1H).	5-[2-(3-Chloro-4-fluoro-phenylamino)-4-(2-pyridin-2-yl-ethylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester **(Example 101)**
229	 5-[2-(3-Chloro-4-fluoro-phenylamino)-4-(2-pyridin-3-yl-ethylamino)-pyrimidin-5-yl]-nicotinic acid	MS(ES):465 (M+1) for $C_{23}H_{18}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.9 (t, *J* = 7 Hz, 2H), 3.6 (t, *J* = 6.7 Hz, 2 H), 7.01 (t, *J* = 5.48 Hz, 1H), 7.26 -7.32 (m, 2H), 7.62 -7.64 (m, 2H), 7.85 (s, 1H), 8.15(t, *J* = 1.96 Hz, 1H), 8.2(dd, *J* = 8, 2.56 Hz, 1H), 8.40 (m, 2H), 8.68 (s, 1H), 9.01 (s, 1H), 9.47 (s, 1H).	5-[2-(3-Chloro-4-fluoro-phenylamino)-4-(2-pyridin-3-yl-ethylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester **(Example 102)**

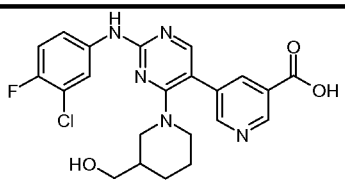
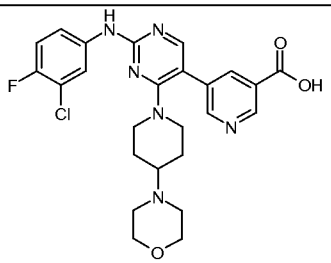
Ex	Compound	Data	SM
230	 5-[2-(3-Chloro-4-fluoro-phenylamino)-4-(2-pyridin-4-yl-ethylamino)-pyrimidin-5-yl]-nicotinic acid	^{1}H NMR (400 MHz, DMSO-d_6): δ 2.90 (t, J = 7.08 Hz, 2H), 3.58-3.64 (m, 2H), 7.01 (t, J = 5.40 Hz, 1H), 7.2-7.3 (m, 3H), 7.60 (m, 1H), 7.85 (s, 1H), 8.15-8.19 (m, 2H), 8.45 (dd, J = 4.48, 1.44 Hz, 2H), 8.69 (d, J = 2.20 Hz, 1H), 9.02 (d, J = 2.00 Hz, 1H), 9.48 (s, 1H).	5-[2-(3-Chloro-4-fluoro-phenyl amino)-4-(2-pyridin-4-yl-ethylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester **(Example 103)**
231	 5-{2-(3-Chloro-4-fluoro-phenylamino)-4-[2-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-ethylamino]-pyrimidin-5-yl}-nicotinic acid	MS(ES):519 (M-1) for $C_{22}H_{22}ClFN_6O_4S$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.68(br s, 2H), 2.91 (br s, 4H), 3.02 (br s, 4H), 3.46 (br s, 2H), 6.78 (br s, 1H), 7.28 (m, 1H), 7.85 (m, 1H), 8.2 (m, 2H), 8.74 (s, 1H), 9 (s, 1H), 9.43 (s, 1H), 13.4(br s, 1H).	5-{2-(3-Chloro-4-fluoro-phenylamino) -4-[2-(1,1-dioxo-1λ^6-thiomorpholi n-4-yl)-ethylamino]-pyrimidin-5-yl}-nicotinic acid ethyl ester **(Example 104)**
232	 5-{2-(3-Chloro-4-fluoro-phenylamino)-4-[3-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-propylamino]-pyrimidin-5-yl}-nicotinic acid	MS(ES): 535 (M+1) for $C_{23}H_{24}ClFN_6O_4S$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.71-1.74 (t, J = 13.48 Hz, 2H), 2.49-2.54 (m, 2H), 2.83 (s, 4H), 3.0 (s, 4H), 3.37-3.42 (m, 4H), 6.95-6.97 (t, J = 4.8 Hz, 1H), 7.31 (t, J = 9.16 Hz, 1H), 7.58-7.62 (m, 1H), 7.84 (s, 1H), 8.19 (s, 1H), 8.25-8.26 (dd, J = 6.92, 2.44 Hz, 1H), 8.76 (s, 1H), 9.0 (s, 1H), 9.48 (s, 1H).	5-{2-(3-Chloro-4-fluoro-phenylamino) -4-[3-(1,1-dioxo-1λ^6-thiomorpholi n-4-yl)-propylamino] -pyrimidin-5-yl}-nicotinic acid ethyl ester **(Example 105)**

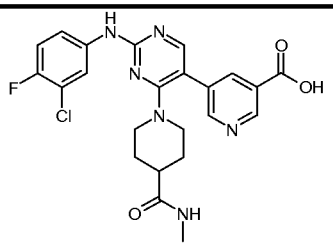
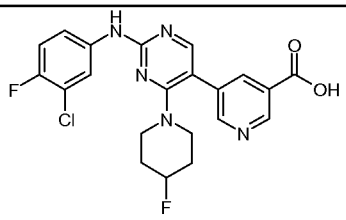
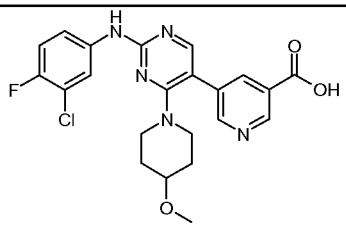
Ex	Compound	Data	SM
233	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(3-morpholin-4-ylpropylamino)pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES): 487 (M+1) for $C_{23}H_{24}ClFN_6O_3$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.00 (s, 2H), 3.05 (br s, 4H), 3.44 (d, J = 5.44 Hz, 4H), 3.79 (br s, 4H), 7.07 (s, 1H), 7.34 (t, J = 9.04 Hz, 1H), 7.64 (d, J = 8.44 Hz, 1H), 7.89 (s, 1H), 8.21 (t, J = 7.00 Hz, 2H), 8.80 (s, 1H), 9.04 (s, 1H), 9.54 (s, 1H).	5-[2-(3-Chloro-4-fluoro-phenylamino)-4-(3-morpholin-4-yl-propylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester **(Example 106)**
234	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(2-methoxyethylamino)pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES):418 (M+1) for $C_{19}H_{17}ClFN_5O_3$. ^{1}H NMR (400 MHz DMSO-d_6): δ 3.25 (s, 3H), 3.49-3.54 (m, 4H), 6.92 (d, *J* = 5.16 Hz, 1H), 7.29 (t, *J* = 9.12 Hz, 1H), 7.60-7.64 (m, 1H), 7.86 (s, 1H), 8.18- 8.21 (m, 2H), 8.74 (s, 1H), 9.02 (s, 1H), 9.48 (s, 1H).	5-[2-(3-Chloro-4-fluoro-phenylamino)-4-(2-methoxy-ethylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester **(Example 144)**
235	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(oxolan-2-ylmethylamino)pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES): 444 (M+1) for $C_{21}H_{19}ClFN_5O_3$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.59-1.62 (m, 1H), 1.78-1.83 (m, 2H), 1.89-1.90 (m, 1H), 3.37-3.45 (m, 2H), 3.60-3.63 (m, 1H), 3.72-4.07 (m, 1H), 4.08-4.10 (m, 1H), 6.92-6.95 (m, 1H), 7.3 (t, *J* = 9.12 Hz, 1H), 7.59-7.63 (m, 1H), 7.86 (s, 1H), 8.18–8.22 (m, 2H), 8.75 (d, *J* = 2.12 Hz, 1H), 9.05 (d, *J* =2 Hz, 1H), 9.48 (s, 1H).	ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(oxolan-2-ylmethylamino)pyrimidin-5-yl]pyridine-3-carboxylate **(Example 108)**

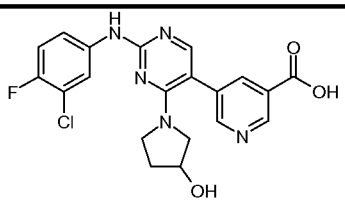
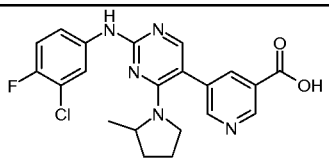
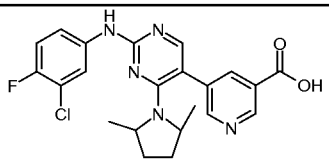
Ex	Compound	Data	SM
236	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(2-propan-2-yloxyethylamino)pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES):446.1 (M) for $C_{21}H_{21}ClFN_5O_3$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.04 (d, *J* = 6.08 Hz, 6H), 3.48-3.56 (m, 5H), 6.80 (s, 1H), 7.28 (t, *J* = 9.12 Hz, 1H), 7.63 (ddd, *J* = 9.04, 4.20, 2.68 Hz, 1H), 7.85 (s, 1H), 8.16-8.20 (m, 2H), 8.68 (d, *J* = 1.80 Hz, 1H), 9.01 (d, *J* = 1.52 Hz, 1H), 9.46 (s, 1H).	ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(2-propan-2-yloxyethylamino)pyrimidin-5-yl]pyridine-3-carboxylate **(Example 109)**
237	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(furan-2-ylmethylamino)pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES): 440(M+1) for $C_{21}H_{15}ClFN_5O_3$. ^{1}H NMR (400 MHz DMSO-d_6): δ 4.6 (d, *J* = 5.64 Hz, 2H), 6.25 (d, *J* = 2.96 Hz, 1H), 6.36 (s, 1H),7.27 (t, *J* = 9.16 Hz, 1H), 7.44 (t, *J* = 5.24 Hz, 1H), 7.55 (s, 1H), 7.57-7.61(m, 1H), 7.90 (s, 1H),8.13 (dd, *J* = 6.66, 2.28 Hz, 1H),8.20 (s, 1H), 8.70 (d, *J* = 1.4 Hz, 1H), 9.03 (s, 1H), 9.49 (s,1H).	ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(furan-2-ylmethylamino)pyrimidin-5-yl]pyridine-3-carboxylate **(Example 110)**
238	 5-[4-(carboxymethylamino)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES):418 (M+1) for $C_{18}H_{13}ClFN_5O_4$ ^{1}H NMR (400 MHz DMSO-d_6): δ 4.0 (d, *J* = 5.92 Hz, 2H), 7.2 (t, *J* = 6 Hz, 1H), 7.26 (t, *J* = 9.12 Hz, 1H), 7.65 (ddd, *J* = 9.1, 4.24, 2.6 Hz, 1H), 7.93 (s, 1H), 9.04(d, *J* = 1.96 Hz), 8.03 (dd, *J* = 6.8, 2.43 Hz, 1H), 8.24 (t, *J* = 2.12 Hz, 1H), 8.8 (d, *J* = 2.2 Hz, 1H), 9.48 (s,1H). 12.6(br s, 1H), 13.6 (br s, 1H).	ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[(2-ethoxy-2-oxoethyl)amino]pyrimidin-5-yl]pyridine-3-carboxylate **(Example 111)**

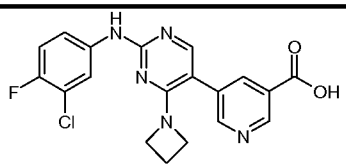
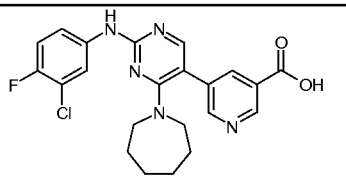
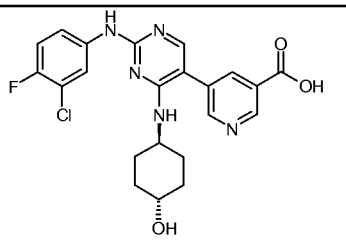
Ex	Compound	Data	SM
239	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(2-phenoxyethylamino)pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES):480.1 (M+1) for $C_{24}H_{19}ClFN_5O_3$. ^{1}H NMR (400 MHz DMSO-d_6): δ 3.73-3.75 (m, 2H), 4.12-4.14 (m, 2H), 6.90-6.94 (m, 3H), 7.18 (br s, 1H), 7.22-7.27 (m, 3H), 7.6-7.7 (m, 1H), 7.89(s, 1H), 8.18-8.20 (m, 1H), 8.22 (s, 1H), 8.76 (d, *J* = 2.16 Hz, 1H), 9.04 (d, *J* = 2Hz, 1H), 9.54 (s, 1H), 13.55 (br s, 1H).	ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[(2-ethoxy-2-oxoethyl)amino]pyrimidin-5-yl]pyridine-3-carboxylate **(Example 112)**
240	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[[(2R)-1-hydroxy-1-oxopropan-2-yl]amino]pyrimidin-5-yl]pyridine-3-carboxylic acid	MS (ESI) : 432.1 (M+1) for $C_{19}H_{15}ClFN_5O_4$. ^{1}H NMR (400 MHz DMSO-*d_6*): δ 1.39 (d, *J* = 7.24 Hz, 3H), 4.64-4.68 (m, 1H), 6.98 (d, *J* = 7.34 Hz, 1H), 7.27 (t, *J* = 9.04 Hz, 1H), 7.64-7.68 (m, 1H), 7.91 (s, 1H), 8.02 (d, *J* = 4.4 Hz, 1H), 8.24 (s, 1H), 8.80 (s, 1H), 9.03 (s, 1H), 9.48 (s, 1H), 13.1 (br s, 1H).	ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[(2-ethoxy-2-oxoethyl)amino]pyrimidin-5-yl]pyridine-3-carboxylate **(Example 113)**
241	 5-[4-(1H-benzimidazol-2-ylmethylamino)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES): 490.2 (M+1) for $C_{24}H_{17}ClFN_7O_2$. ^{1}H NMR (400 MHz DMSO-d_6): δ 4.78 (d, *J* = 5.56 Hz, 2H), 7.04 (t, *J* = 9.36 Hz,1H), 7.10-7.12 (m, 2H), 7.49-7.54 (m, 4H), 7.85 (d, *J* = 3.96 Hz, 1H), 7.96 (s, 1H), 8.36 (s, 1H),8.90 (s, 1H), 9.04 (d, *J* = 1.56 Hz, 1H), 9.44 (s, 1H), 12.29 (br s, 1H).	ethyl 5-[4-(1*H*-benzimidazol-2-ylmethylamino)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl]pyridine-3-carboxylate hydrochloride **(Example 208)**

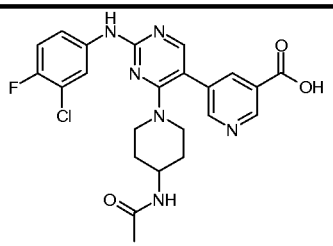
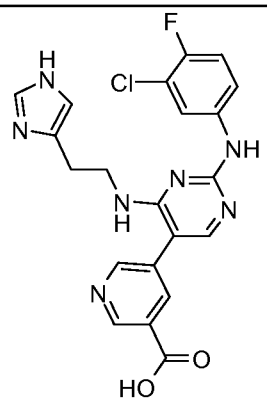
Ex	Compound	Data	SM
242	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[(5-methylpyrazin-2-yl)methylamino]pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES): 466 (M+1) for $C_{22}H_{17}ClFN_7O_2$. 400 MHz DMSO-d_6): δ 2.43 (s, 3H), 4.67 (d, *J* = 5.76 Hz, 2H), 7.20 (t, *J* = 9.12 Hz, 1H), 7.51 (dt, *J* = 8.47, 4.04 Hz, 1H), 7.56 (t, *J* = 5.72 Hz, 1H), 7.92 (s, 1H), 7.96 (dd, *J* = 6.54, 2.44 Hz, 1H), 8.29 (t, *J* = 2.00 Hz, 1H), 8.48 (d, *J* = 5.80 Hz, 1H), 8.84 (d, *J* = 2.04 Hz, 1H), 9.05 (d, *J* = 1.88 Hz, 1H), 9.44 (s, 1H), 13.5 (br s, 1H).	ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[(5-methylpyrazin-2-yl)methylamino]pyrimidin-5-yl]pyridine-3-carboxylate **(Example 115)**
243	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(propan-2-ylamino)pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES):402 (M+1) for $C_{19}H_{17}ClFN_5O_2$ ^{1}H NMR (400 MHz DMSO-d_6): δ 1.17 (d, *J* = 6.56 Hz, 6H), 4.32-4.38 (m, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 7.3 (t, *J* = 9.16 Hz, 1H), 7.55-7.59 (m, 1H), 7.82 (s, 1H), 8.17 (t, *J* = 2.0 Hz, 1H), 8.28 (dd, *J* = 6.9, 2.48 Hz, 1H), 8.75 (d, *J* = 1.96 Hz, 1H), 9.02 (d, *J* = 1.72 Hz, 1H), 9.46 (s, 1H), 13.5 (br s, 1H).	ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(propan-2-ylamino)pyrimidin-5-yl]pyridine-3-carboxylate **(Example 116)**
244	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(4-hydroxypiperidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES):444 (M+1) for $C_{21}H_{19}ClFN_5O_3$ ^{1}H NMR (400 MHz DMSO-d_6): δ 1.31-1.33 (m, 2H), 1.66-1.69 (m, 2H), 2.94 (t, *J* = 10.12 Hz, 2H), 3.51-3.53 (m, 2H), 3.63-3.64 (br s, 1H), 4.71 (br s, 1H), 7.33 (t, *J* = 9.12 Hz, 1H), 7.59-7.61 (m, 1H), 8.10 (s, 1H), 8.21-8.23 (m, 1H), 8.27 (s, 1H), 8.85 (s, 1H), 8.98 (s, 1H), 9.67 (s, 1H), 13.5 (br s, 1H).	ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(4-hydroxypiperidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylate **(Example 117)**

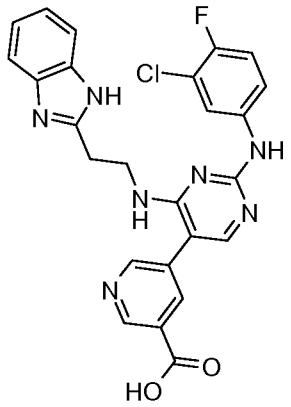
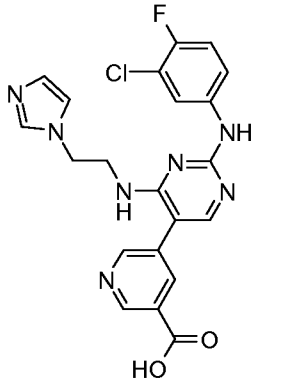
Ex	Compound	Data	SM
245	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(hydroxymethyl)piperidin-1-yl]pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES):458 (M+1) for $C_{22}H_{21}ClFN_5O_3$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.12 (m, 1H), 1.37 (m, 1H), 1.53 (m, 2H), 1.66 (m, 1H), 2.56 (t, J = 12.20 Hz, 1H), 2.75 (t, J = 10.64 Hz, 1H), 3.10-3.19 (m, 2H), 3.58 (d, J = 12.44 Hz, 1H), 3.75 (d, J = 11.64 Hz, 1H), 4.39 (br s, 1H), 7.31 (t, J = 9.04 Hz, 1H), 7.64-7.68 (m, 1H), 8.09 (s, 1H), 8.17 (dd, J = 6.78, 2.44 Hz, 1H), 8.27 (s, 1H), 8.84 (d, J = 1.68 Hz, 1H), 8.97 (s, 1H), 9.65 (s, 1H), 13.5 (br s, 1H).	ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(hydroxymethyl)piperidin-1-yl]pyrimidin-5-yl]pyridine-3-carboxylate **(Example 118)**
246	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(4-morpholin-4-ylpiperidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES): 513 (M+1) for $C_{25}H_{26}ClFN_6O_3$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.35-1.40 (m, 2H), 1.68-1.71 (m, 2H), 2.30-2.40 (m, 1H), 2.40-2.50 (m, 4H), 2.77 (t, J = 11.76 Hz, 2H), 3.54 (br s, 4H), 3.72 (d, J = 12.88 Hz, 2H), 7.33 (t, J = 9.16 Hz, 1H), 7.59-7.63 (m, 1H), 8.13 (s, 1H), 8.21 (dd, J = 6.84, 2.48 Hz, 1H), 8.32 (s, 1H), 8.87 (s, 1H), 8.98 (s,1H), 9.68 (s, 1H).	ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(4-morpholin-4-ylpiperidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylate **(Example 119)**

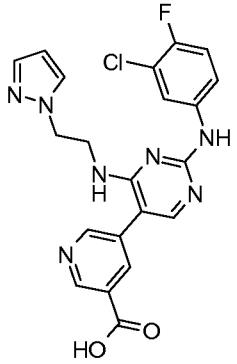
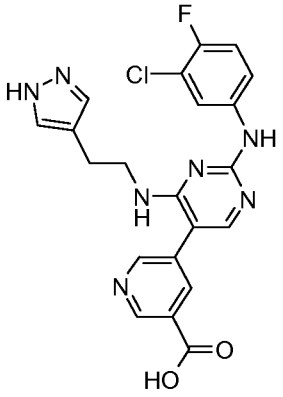
Ex	Compound	Data	SM
247	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(methylcarbamoyl)piperidin-1-yl]pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES): 485 (M+1) for $C_{23}H_{22}ClFN_6O_3$ ^{1}H NMR (400 MHz DMSO-d_6): δ 1.46-1.60 (m, 4H), 2.25-2.30 (m, 1H), 2.52 (d, J = 4.56 Hz, 3H), 2.79 (t, J = 11.32 Hz, 2H), 3.72(d, J = 13.04 Hz, 2H), 7.33 (t, J = 9.08 Hz, 1H), 7.6 (ddd, J = 9.06, 4.22, 2.68 Hz, 1H), 7.71 (d, J = 4.4 Hz, 1H), 8.1 (s, 1H), 8.21 (dd, J = 6.92,2.64 Hz, 1H), 8.26 (s, 1H), 8.85 (s, 1H), 8.98 (s, 1H), 9.68 (s, 1H).	ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(methylcarbamoyl)piperidin-1-yl]pyrimidin-5-yl]pyridine-3-carboxylate **(Example 120)**
248	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(4-fluoropiperidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES): 446 (M+1) for $C_{21}H_{18}ClF_2N_5O_2$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.62-1.67 (m, 2H), 1.78-1.89 (m, 2H), 3.16-3.33 (m, 4H), 4.83 (d, J = 48.68 Hz, 1H), 7.33 (t, J = 9.08 Hz, 1H), 7.61 (ddd, J = 9.06, 4.16, 2.76 Hz, 1H), 8.14 (s, 1H), 8.19 (dd, J = 6.88, 2.60 Hz, 1H), 8.31 (t, J = 1.92 Hz, 1H), 8.89 (d, J = 1.96 Hz, 1H), 8.99 (d, J = 1.72 Hz, 1H), 9.72 (s, 1H), 13.7 (br s, 1H).	ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(4-fluoropiperidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylate **(Example 121)**
249	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(4-methoxypiperidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES): 458 (M+1) for $C_{22}H_{21}ClFN_5O_3$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.34-1.39 (m, 2H), 1.75-1.80 (m, 2H), 2.97-3.02(m, 2H), 3.21 (s, 3H), 3.50-3.60 (m, 2H), 7.33 (t, J = 9.12 Hz, 1H), 7.59-7.63 (m, 1H), 8.11 (s, 1H), 8.2 (dd, J = 6.9, 2.52 Hz, 1H), 8.35 (t, J = 2 Hz, 1H), 8.83 (d, J = 2.12 Hz, 1H), 8.97 (d, J = 1.88 Hz, 1H), 9.67 (s, 1H).	ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(4-methoxypiperidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylate **(Example 122)**

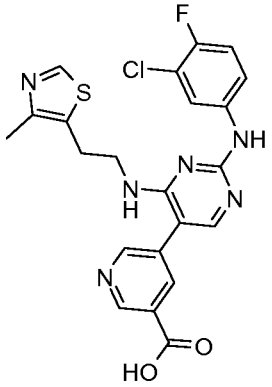
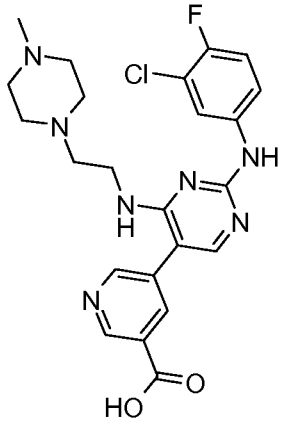
Ex	Compound	Data	SM
250	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(3-hydroxypyrrolidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES): 428 (M) for $C_{20}H_{17}ClFN_5O_3$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.75 (m, 1H), 1.83-1.85 (m, 1H), 2.8 (br s, 1H), 3.20 (m, 3H), 4.2 (br s, 1H), 4.9 (br s, 1H), 7.32 (t, J = 9.32 Hz, 1H), 7.64-7.66 (m, 1H), 7.95 (s, 1H), 8.10 (br s, 1H), 8.25 (d, J = 4.64 Hz, 1H), 8.74 (br s, 1H), 9.0 (s, 1H), 9.56 (s, 1H).	ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(3-hydroxypyrrolidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylate **(Example 123)**
251	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(2-methylpyrrolidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES): 428 (M+1) for $C_{21}H_{19}ClFN_5O_2$. ^{1}H NMR (400 MHz DMSO-d_6): δ 1.27 (d, J = 6.0 Hz, 3H), 1.48-1.63 (m, 2H), 1.77-1.78 (m, 1H), 2.03-2.08 (m, 1H), 2.66-2.75 (m, 1H), 2.86 (m, 1H), 4.26-4.29 (m, 1H), 7.34 (t, J = 9.16 Hz, 1H), 7.56 (dd, J = 4.64, 2.36 Hz, 1H), 7.99 (s, 1H), 8.14 (s, 1H), 8.24 (d, J = 6.8 Hz, 1H), 8.75 (s, 1H), 8.99 (s, 1H), 9.7 (br s, 1H), 13.7 (br s, 1H).	ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(2-methylpyrrolidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylate **(Example 124)**
252	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(2,5-dimethylpyrrolidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES):440 (M-1) for $C_{22}H_{21}ClFN_5O_2$. ^{1}H NMR (400 MHz DMSO-d_6): δ 0.98 (d, J = 6.28 Hz, 6H), 1.58-1.64 (m, 2H), 1.90-1.98 (m, 2H), 3.96 (br s, 2H), 7.31 (t, J = 9.12 Hz, 1H), 7.53-7.57 (m, 1H), 7.80 (s, 1H), 8.14 (s, 1H), 8.27 (dd, J= 6.92, 2.48 Hz, 1H), 8.69 (br s, 1H), 8.98 (d, J = 1.76 Hz, 1H), 9.49 (s, 1H).	ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-(2,5-dimethylpyrrolidin-1-yl)pyrimidin-5-yl]pyridine-3-carboxylate **(Example 125)**

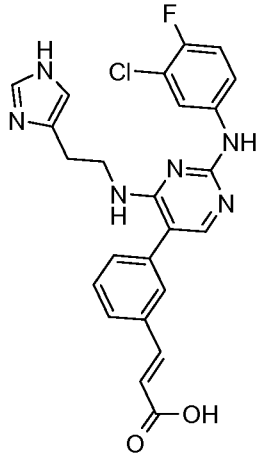
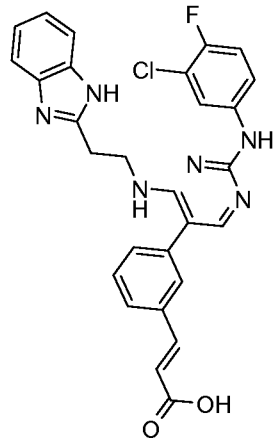
Ex	Compound	Data	SM
253	 5-[4-(azetidin-1-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES):400 (M+1) for $C_{19}H_{15}ClFN_5O_2$. ^{1}H NMR (400 MHz DMSO-d_6): δ 2.19 (m, 2H), 3.84 (br s, 4H), 7.42 (t, J = 9.12 Hz, 1H), 7.57 (m, 1H), 7.98 (s, 1H), 8.05 (dd, J = 2.48, 6.72 Hz, 1H), 8.24 (t, J = 1.96 Hz, 1H), 8.81 (d, J = 2.04 Hz, 1H), 9.07 (d, J = 1.85 Hz, 1H), 10.47 (br s, 1H), 13.7 (br s, 1H).	ethyl 5-[4-(azetidin-1-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl]pyridine-3-carboxylate **(Example 126)**
254	 5-[4-(azepan-1-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES): 442(M+1) for $C_{22}H_{21}ClFN_5O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.41 (br s, 4H), 1.61 (br s, 4H), 3.32 (br s, 4H), 7.32 (t, J = 9.04 Hz, 1H), 7.56 (dt, J = 8.47, 4.24 Hz, 1H), 7.91 (s, 1H), 8.11 (t, J = 2.04 Hz, 1H), 8.26 (dd, J = 6.92, 2.60 Hz, 1H), 8.75 (d, J = 2.16 Hz, 1H), 8.98 (d, J = 1.84 Hz, 1H), 9.56 (s, 1H)	ethyl 5-[4-(azepan-1-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl]pyridine-3-carboxylate **(Example 127)**
255	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[(4-hydroxycyclohexyl)amino]pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES): 458 (M+1) for $C_{22}H_{21}ClFN_5O_3$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (m, 4H), 1.84 (m, 4H), 3.97 (m, 1H), 4.54 (m, 1H), 6.57 (d, J = 7.96 Hz, 1H), 7.29 (t, J = 8.92 Hz, 1H), 7.55 (d, J = 7.84 Hz, 1H), 7.82 (s, 1H), 8.16 (s, 1H), 8.27 (d, J = 5.76 Hz, 1H), 8.73 (s, 1H), 9.00 (s, 1H), 9.47 (s, 1H), 13.50 (s, 1H).	ethyl 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[(*trans*-4-hydroxycyclohexyl)amino]pyrimidin-5-yl]pyridine-3-carboxylate **(Example 128)**

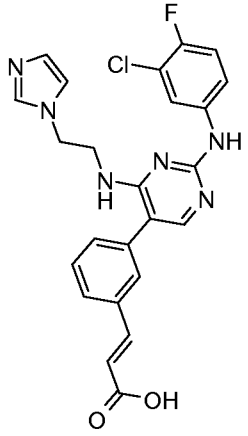
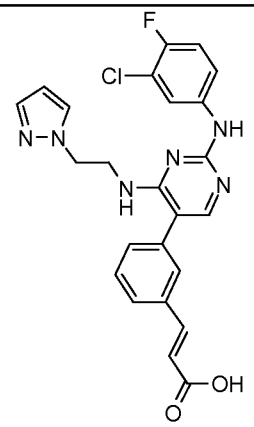
Ex	Compound	Data	SM
256	 5-[4-(4-acetamidopiperidin-1-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl]pyridine-3-carboxylic acid	MS(ES): 485 (M+1) for $C_{23}H_{22}ClFN_6O_3$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.22-1.29 (m, 2H), 1.64-1.67 (m, 2H), 1.78 (s, 3H), 2.90 (t, J = 11.72 Hz, 2H), 3.65 (d, J = 13.28 Hz, 1H), 3.71 (br s, 2H), 7.33 (t, J = 9.04 Hz, 1H), 7.61-7.62 (m, 1H), 7.82 (d, J = 7.56 Hz, 1H), 8.10 (s, 1H), 8.20-8.21 (m, 1H), 8.26 (s, 1H), 8.83 (s, 1H), 8.97 (s, 1H), 9.70 (s, 1H).	ethyl 5-[4-(4-acetamidopiperidin-1-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl]pyridine-3-carboxylate **(Example 129)**
257	 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-imidazol-4-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylic acid	MS(ES): 454 (M+1) for $C_{21}H_{17}ClFN_7O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.80 (t, *J* = 7.00 Hz,2H), 3.59-3.60 (m, 2H), 6.83 (s, 1H), 7.01 (t, *J* = 5.04 Hz,1H), 7.25 (t, *J* = 9.08 Hz,1H), 7.51 (s, 1H), 7.73 (dt, *J* = 3.76, 5.96 Hz, 1H), 7.81 (s, 1H), 8.13-8.16 (m, 2H), 8.57 (d, *J* = 1.88 Hz, 1H), 8.97 (d, *J* = 1.32 Hz, 1H), 9.43 (s, 1H).	ethyl 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-imidazol-4-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylate **(Example 154)**

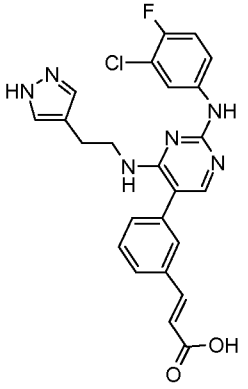
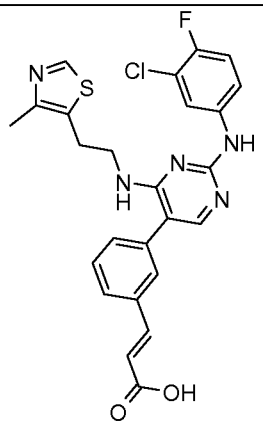
Ex	Compound	Data	SM
258	 5-(4-{[2-(1*H*-benzimidazol-2-yl)ethyl]amino}-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl)pyridine-3-carboxylic acid	MS(ES): 504 (M+1) for $C_{25}H_{19}ClFN_7O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.14 (t, *J* = 6.72 Hz, 2H), 3.82-3.84 (m, 2H), 7.11 (dd, *J* = 2.88, 5.74 Hz, 2H), 7.25 (t, *J* = 9.24 Hz, 2H), 7.45 (dd, *J* = 3.20, 5.06 Hz, 2H), 7.73 (dd, *J* = 8.20, Hz, 1H), 7.89 (s, 1H), 8.15-8.17 (m, 1H), 8.22 (s, 1H), 8.77 (s, 1H), 9.02 (s, 1H), 9.51 (s, 1H), 12.5 (br s, 1H).	ethyl 5-(4-{[2-(1*H*-benzimidazol-2-yl)ethyl]amino}-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl)pyridine-3-carboxylate **(Example 155)**
259	 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-imidazol-1-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylic acid	MS(ES): 454 (M+1) for $C_{21}H_{17}ClFN_7O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (br s, 2H), 4.37 (br s, 2H),7.02 (br s, 1H), 7.31-7.37 (m, 2H), 7.55 (br s, 1H), 7.62 (m, 1H), 7.90 (br s, 1H), 8.14 (br s, 1H), 8.65 (br s, 1H), 8.71 (br s, 1H), 9.02 (br s, 1H), 9.52 (br s, 1H).	ethyl 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-imidazol-1-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylate **(Example 130)**

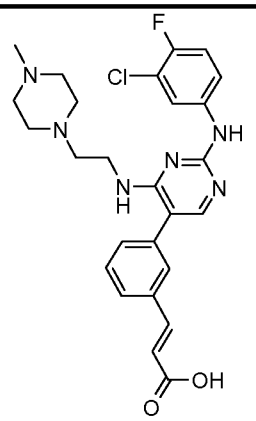
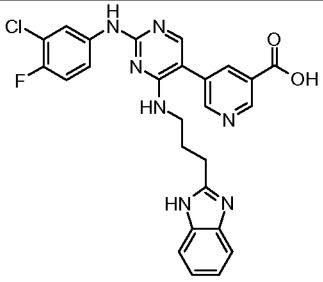
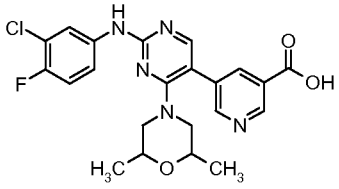
Ex	Compound	Data	SM
260	 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-pyrazol-1-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylic acid	MS(ES): 452 (M-1) for $C_{21}H_{17}ClFN_7O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (q, *J* = 5.80 Hz, 2H), 4.36 (t, *J* = 6.12 Hz, 2H), 6.22 (t, *J* = 2.00 Hz, 1H), 6.97 (t, *J* = 5.32 Hz, 1H), 7.31 (t, *J* = 9.12 Hz, 1H), 7.43 (d, *J* = 1.64 Hz, 1H), 7.68-7.72 (m, 2H), 7.88 (s, 1H), 8.12 (dd, *J* = 6.86, 2.60 Hz, 1H), 8.16 (t, *J* = 2.08 Hz, 1H), 8.70 (d, *J* = 2.16 Hz, 1H), 9.02 (d, *J* = 1.92 Hz, 1H), 9.50 (s, 1H).	ethyl 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-pyrazol-1-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylate **(Example 131)**
261	 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-pyrazol-4-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylic acid	MS(ES): 454 (M+1) for $C_{21}H_{17}ClFN_7O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.73 (br s, 2H), 3.59 (br s, 2H), 7.00 (br s, 1H), 7.24 (t, *J* = 9.16 Hz, 1H), 7.45 (br s, 2H), 7.64 (br s, 1H), 7.85 (s, 1H), 8.18 (s, 2H), 8.72 (br s, 1H), 9.03 (br s, 1H), 9.45 (s, 1H), 13.00 (br s, 1H).	ethyl 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-pyrazol-4-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylate **(Example 156)**

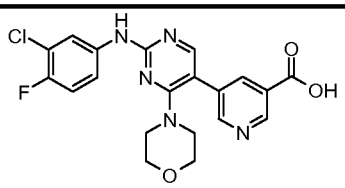
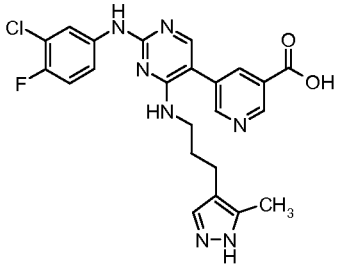
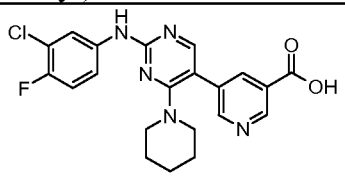
Ex	Compound	Data	SM
262	 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(4-methyl-1,3-thiazol-5-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylic acid	MS(ES): 485 (M+1) for $C_{22}H_{18}ClFN_6O_2S$. ^{1}H NMR (400 MHz,DMSO-d_6): δ 2.25 (s, 3H), 3.06 (t, *J* = 6.92 Hz, 2H), 3.56-3.57 (m, 2H), 7.05 (t, *J* = 5.52 Hz, 1H), 7.29 (t, *J* = 9.12 Hz, 1H), 7.65 (td, *J* = 3.88, 8.67 Hz, 1H), 7.88 (s, 1H), 8.14 (dd, *J* = 2.48, 6.84 Hz, 1H), 8.18 (t, *J* = 1.92 Hz, 1H), 8.73 (d, *J* = 2.00 Hz, 1H), 8.79 (s, 1H), 9.03 (d, *J* = 1.64 Hz, 1H), 9.49 (s, 1H), 13.50 (br s, 1H).	ethyl 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(4-methyl-1,3-thiazol-5-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylate **(Example 157)**
263	 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(4-methylpiperazin-1-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylic acid	MS(ES): 484 (M-1) and 969 (2M-1) for $C_{23}H_{25}ClFN_7O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39 (s, 3H), 2.50-2.70 (m, 10H), 3.47-3.49 (m, 2H), 6.75 (t, *J* = 4.56 Hz, 1H), 7.30 (t, *J* = 9.12 Hz, 1H), 7.65 (ddd, *J* = 2.76, 4.00, 8.97 Hz, 1H), 7.87 (s, 1H), 8.18 (dd, *J* = 2.52, 6.84 Hz, 1H), 8.22 (t, *J* = 1.96 Hz, 1H), 8.72 (d, *J* = 2.12 Hz, 1H), 9.01 (d, *J* = 1.84 Hz, 1H), 9.47 (s, 1H).	ethyl 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(4-methylpiperazin-1-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylate **(Example 132)**

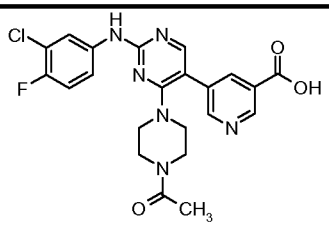
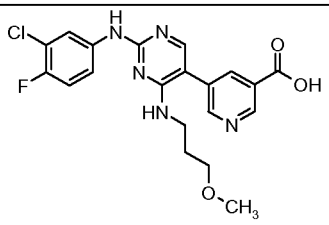
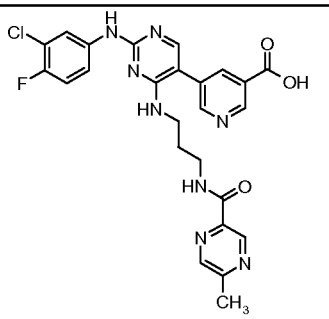
Ex	Compound	Data	SM
264	 (2*E*)-3-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-imidazol-4-yl)ethyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoic acid	MS(ES): 479 (M+1) for $C_{24}H_{20}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.82 (br s, 2H), 3.63 (br s, 2H), 6.57 (d, *J* = 15.40 Hz, 1H), 6.81-6.85 (m, 2H), 7.26 (t, *J* = 9.04 Hz, 1H), 7.35 (d, *J* = 7.04 Hz, 1H), 7.46 (t, *J* = 7.44 Hz, 1H), 7.53-7.56 (m, 2H), 7.61-7.63 (m, 2H), 7.71 (br s, 1H), 7.82 (s, 1H), 8.18 (d, *J* = 5.12 Hz, 1H), 9.40 (s, 1H).	ethyl (2*E*)-3-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-imidazol-4-yl)ethyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoate) **(Example 183)**
265	 (2*E*)-3-[3-(4-{[2-(1*H*-benzimidazol-2-yl)ethyl]amino}-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl)phenyl]prop-2-enoic acid	MS(ES): 529 (M+1) for $C_{28}H_{22}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.16-3.19 (m, 2H), 3.85-3.87 (m, 2H), 6.57 (d, *J* = 16.04 Hz, 1H), 6.99 (t, *J* = Hz, 1H), 7.13-7.15 (m, 2H), 7.25 (t, *J* = 9.04 Hz, 1H), 7.35-7.42 (m, 2H), 7.46-7.49 (m, 2H), 7.59 (d, *J* = 15.96 Hz, 1H), 7.66-7.72 (m, 3H), 7.85 (s, 1H), 8.17 (dd, *J* = 2.24, 6.68 Hz, 1H), 9.44 (s, 1H), 12.44 (br s, 1H).	ethyl (2*E*)-3-[3-(4-{[2-(1*H*-benzimidazol-2-yl)ethyl]amino}-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl)phenyl]prop-2-enoate **(Example 184)**

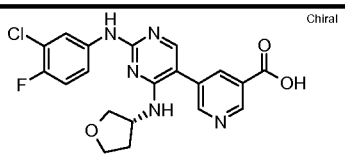
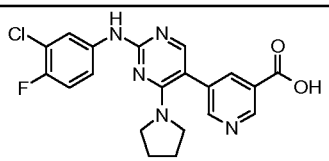
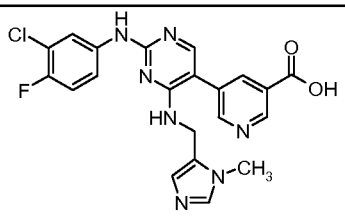
Ex	Compound	Data	SM
266	 (2*E*)-3-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-imidazol-1-yl)ethyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoic acid	MS(ES): 479 (M+1) for $C_{24}H_{20}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.67-3.69 (m, 2H), 4.23-4.26 (m, 2H), 6.58 (d, *J* = 16.00 Hz, 1H), 6.75 (t, *J* = 5.44 Hz, 1H), 6.94 (br s, 1H), 7.19 (br s, 1H), 7.28-7.34 (m, 2H), 7.47 (t, *J* = 7.68 Hz, 1H), 7.57-7.70 (m, 5H), 7.84 (s, 1H), 8.17 (dd, *J* = 2.48, 6.88 Hz, 1H), 9.42 (s, 1H).	ethyl (2*E*)-3-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-imidazol-1-yl)ethyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoate **(Example 196)**
267	 (2*E*)-3-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-pyrazol-1-yl)ethyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoic acid	MS(ES): 477 (M-1) for $C_{24}H_{20}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.75 (q, *J* = 5.72 Hz, 2H), 4.38 (t, *J* = 6.12 Hz, 2H), 6.26 (t, *J* = 1.84 Hz, 1H), 6.56 (d, *J* = 16.00 Hz, 1H), 6.67 (t, *J* = 5.24 Hz, 1H), 7.28 (m, 1H), 7.33 (m, 1H), 7.45 (m, 2H), 7.57 (s, 1H), 7.61 (d, *J* = 16.04 Hz, 1H), 7.68 (d, *J* = 13.60 Hz, 1H), 7.72 (d, *J* = 2.00 Hz, 1H), 7.85 (s, 1H), 8.14 (dd, *J* = 6.80, 2.60 Hz, 1H), 9.44 (s, 1H).	ethyl (2*E*)-3-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-pyrazol-1-yl)ethyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoate **(Example 197)**

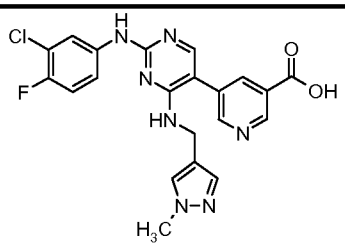
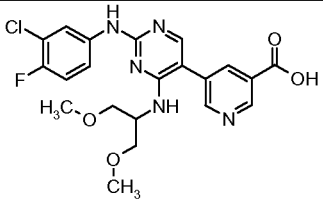
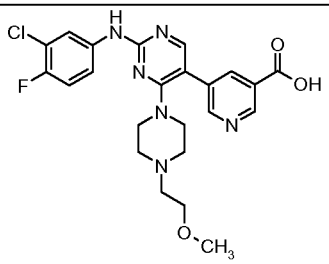
Ex	Compound	Data	SM
268	 (2*E*)-3-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-pyrazol-4-yl)ethyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoic acid	MS(ES): 479 (M+1) for $C_{24}H_{20}ClFN_6O_2$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.74 (t, *J* = 7.36 Hz, 2H), 3.54-3.59 (m, 2H), 6.57 (d, *J* = 16.04 Hz, 1H), 6.66-6.68 (m, 1H), 7.23 (t, *J* = 9.12 Hz, 1H), 7.35 (d, *J* = 7.44 Hz, 1H), 7.42 (s, 1H), 7.46 (t, *J* = 7.56 Hz, 1H), 7.58-7.68 (m, 4H), 7.81 (s, 1H), 8.18 (dd, *J* = 3.72, 7.58 Hz, 1H), 9.38 (br s, 1H), 12.50 (br s, 1H).	ethyl (2*E*)-3-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-pyrazol-4-yl)ethyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoate **(Example 185)**
269	 (2*E*)-3-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(4-methyl-1,3-thiazol-5-yl)ethyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoic acid	MS(ES): 510 (M+1) for $C_{25}H_{21}ClFN_5O_2S$. ^{1}H NMR (400 MHz,DMSO-d_6): δ 2.22 (s, 3H), 3.06 (t, *J* = 6.92 Hz, 2H), 3.57-3.59 (m, 2H), 6.57 (d, *J* = 16.04 Hz, 1H), 6.84 (br s, 1H), 7.28 (t, *J* = 9.12 Hz, 1H), 7.37 (d, *J* = 7.60 Hz, 1H), 7.48 (t, *J* = 7.32 Hz, 1H), 7.59-7.69 (m, 4H), 7.83 (d, *J* = 1.08 Hz, 1H), 8.13 (d, *J* = 5.88 Hz, 1H), 8.79 (d, *J* = 0.92 Hz, 1H), 9.43 (s, 1H), 12.44 (br s, 1H).	ethyl (2*E*)-3-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(4-methyl-1,3-thiazol-5-yl)ethyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoate **(Example 186)**

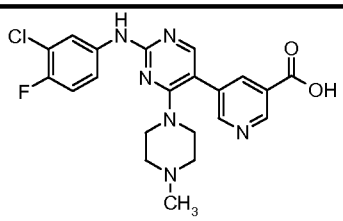
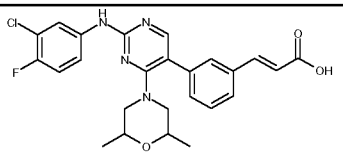
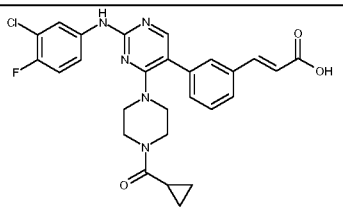
Ex	Compound	Data	SM
270	 (2*E*)-3-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(4-methylpiperazin-1-yl)ethyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoic acid	MS(ES): 509 (M-1) $C_{26}H_{28}ClFN_6O_2$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.10 (s, 3H), 2.20 -2.3 (m, 6H), 3.45-3.47 (m, 2H), 6.46 (t, *J* = 4.68 Hz, 1H), 6.58 (d, *J* = 16.00 Hz, 1H), 7.28 (t, *J* = 9.12 Hz, 1H), 7.41 (d, *J* = 7.72 Hz, 1H), 7.50 (t, *J* = 7.68 Hz, 1H), 7.57 (d, *J* = 16.04 Hz, 1H), 7.65-7.69 (m, 3H), 7.84 (s, 1H), 8.19 (dd, *J* = 2.52, 6.86 Hz, 1H), 9.41 (s, 1H).	ethyl (2*E*)-3-[3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(4-methylpiperazin-1-yl)ethyl]amino}pyrimidin-5-yl)phenyl]prop-2-enoate **(Example 198)**
271	 5-(4-(3-(1H-benzo[d]imidazol-2-yl)propylamino)-2-(3-chloro-4-fluorophenylamino)pyrimidin-5-yl)nicotinic acid	MS(ES): 518 (M+1) for $C_{26}H_{21}ClFN_7O_2$ ^{1}H NMR (300 MHz, DMSO-*d6*) δ ppm 2.09 - 2.32 (m, 2 H) 3.13 (t, J=7.44 Hz, 2 H) 3.50 (q, J=5.59 Hz, 2 H) 7.16 - 7.42 (m, 1 H) 7.48 (dd, J=6.12, 3.11 Hz, 2 H) 7.59 - 8.15 (m, 5 H) 8.11 - 8.36 (m, 1 H) 8.63 - 8.85 (m, 1 H) 9.02 - 9.32 (m, 1 H) 10.24 (s, 1 H) 10.43 (s, 1 H) 14.70 (s, 1 H)	ethyl 5-(4-(3-(1H-benzo[d]imidazol-2-yl)propylamino)-2-(3-chloro-4-fluorophenylamino)pyrimidin-5-yl)nicotinate **(Example 140)**
272	 5-(2-(3-chloro-4-fluorophenylamino)-4-(2,6-dimethylmorpholino)pyrimidin-5-yl)nicotinic acid	MS(ES): 458 (M+1) for $C_{22}H_{21}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-*d6*) δ ppm 0.96 (d, J=6.03 Hz, 6 H) 2.37 - 2.60 (m, 2 H) 3.40 - 3.75 (m, 4 H) 7.33 (t, J=9.14 Hz, 1 H) 7.54 (d, J=11.68 Hz, 1 H) 8.03 - 8.39 (m, 3 H) 8.88 (d, J=2.07 Hz, 1 H) 8.99 (d, J=1.88 Hz, 1 H) 9.73 (s, 1 H) 13.55 (s, 1 H)	ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(2,6-dimethylmorpholino)pyrimidin-5-yl)nicotinate **(Example 139)**

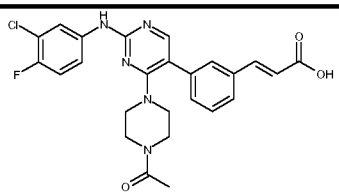
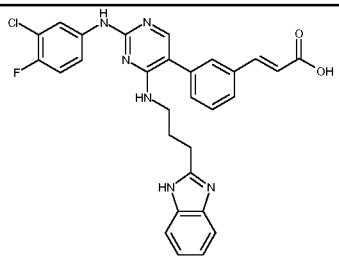
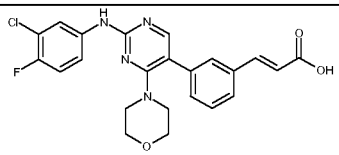
Ex	Compound	Data	SM
273	 5-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)nicotinic acid	MS(ES): 430 (M+1) for $C_{20}H_{17}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 3.11 - 3.27 (m, 4 H) 3.42 - 3.71 (m, 4 H) 7.33 (t, J=9.23 Hz, 1 H) 7.49 - 7.78 (m, 1 H) 8.02 - 8.23 (m, 2 H) 8.34 (t, J=2.07 Hz, 1 H) 8.90 (d, J=2.07 Hz, 1 H) 8.99 (d, J=1.88 Hz, 1 H) 9.72 (s, 1 H)	5-[2-(3-Chloro-4-fluoro-phenylamino)-4-(2-methoxy-ethylamino)-pyrimidin-5-yl]-nicotinic acid ethyl ester **(Example 107)**
274	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(5-methyl-1H-pyrazol-4-yl)propylamino)pyrimidin-5-yl)nicotinic acid	MS(ES): 482 (M+1) for $C_{23}H_{21}ClFN_7O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.63 - 1.94 (m, 2 H) 2.07 (s, 3 H) 2.30 - 2.46 (m, 2 H) 3.30 - 3.56 (m, 2 H) 6.87 (t, J=4.14 Hz, 1 H) 7.16 - 7.43 (m, 2 H) 7.48 - 7.71 (m, 1 H) 7.79 (s, 1 H) 8.10 (s, 1 H) 8.27 (dd, J=6.88, 2.54 Hz, 1 H) 8.56 (s, 1 H) 8.95 (d, J=1.88 Hz, 1 H) 9.43 (s, 1 H)	ethyl 5-(2-(3-chloro-4-fluorophenyl amino)-4-(3-(5-methyl-1H-pyrazol-4-yl)propylamino)pyrimidin-5-yl)nicotinate **(Example 153)**
275	 5-(2-(3-chloro-4-fluorophenylamino)-4-(piperidin-1-yl)pyrimidin-5-yl)nicotinic acid	MS(ES): 428 (M+1) for $C_{21}H_{19}ClFN_5O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.32 - 1.68 (m, 6 H) 2.99 - 3.28 (m, 4 H) 7.32 (t, J=9.04 Hz, 1 H) 7.49 - 7.81 (m, 1 H) 8.10 (s, 1 H) 8.22 (dd, J=6.88, 2.54 Hz, 1 H) 8.30 (t, J=2.07 Hz, 1 H) 8.87 (d, J=2.26 Hz, 1 H) 8.98 (d, J=1.88 Hz, 1 H) 9.67 (s, 1 H) 13.52 (s, 1 H)	ethyl 5-(2-(3-chloro-4-fluorophenyl amino)-4-(piperidin-1-yl)pyrimidin-5-yl)nicotinate **(Example 152)**

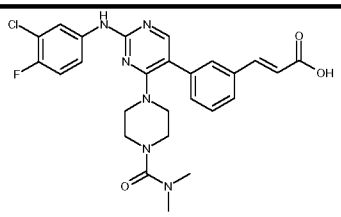
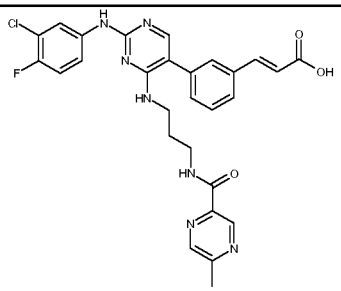
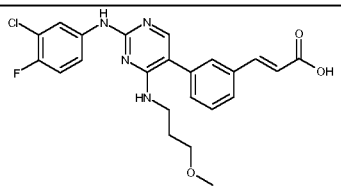
Ex	Compound	Data	SM
276	 5-(4-(4-acetylpiperazin-1-yl)-2-(3-chloro-4-fluorophenylamino)pyrimidin-5-yl)nicotinic acid	MS(ES): 471 (M+1) for $C_{22}H_{20}ClFN_6O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.95 (s, 3 H) 3.05 - 3.81 (m, 8 H) 7.34 (t, J=9.14 Hz, 1 H) 7.64 (d, J=9.23 Hz, 1 H) 7.95 - 8.24 (m, 2 H) 8.32 (s, 1 H) 8.89 (d, J=1.88 Hz, 1 H) 8.92 - 9.14 (m, 1 H) 9.73 (s, 1 H) 13.51 (s, 1 H)	ethyl 5-(4-(4-acetylpiperazin-1-yl)-2-(3-chloro-4-fluorophenylamino)pyrimidin-5-yl)nicotinate **(Example 142)**
277	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)nicotinic acid	MS(ES): 432 (M+1) for $C_{20}H_{19}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.56 - 1.97 (m, 2 H) 3.18 (s, 3 H) 3.28 - 3.47 (m, 4 H) 7.40 (t, J=9.04 Hz, 1 H) 7.47 - 7.67 (m, 1 H) 7.68 - 7.97 (m, 2 H) 8.08 (dd, J=6.78, 2.45 Hz, 1 H) 8.23 (t, J=1.98 Hz, 1 H) 8.77 (d, J=2.07 Hz, 1 H) 9.09 (d, J=1.88 Hz, 1 H) 10.24 (s, 1 H) 13.63 (s, 1 H)	ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)nicotinate **(Example 143)**
278	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(5-methylpyrazine-2-carboxamido)propylamino)pyrimidin-5-yl)nicotinic acid	MS(ES): 537 (M+1) for $C_{25}H_{22}ClFN_8O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.70 - 2.06 (m, 2 H) 2.56 (s, 3 H) 3.34 - 3.56 (m, 4 H) 7.03 (s, 1 H) 7.28 (t, J=9.04 Hz, 1 H) 7.48 - 7.75 (m, 1 H) 7.85 (s, 1 H) 8.01 - 8.38 (m, 2 H) 8.54 (s, 1 H) 8.78 (d, J=2.07 Hz, 1 H) 8.91 (t, J=5.84 Hz, 1 H) 8.98 (d, J=1.32 Hz, 1 H) 9.04 (d, J=1.88 Hz, 1 H) 9.48 (s, 1 H) 13.43 (s, 1 H)	ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(5-methylpyrazine-2-carboxamido)propylamino)pyrimidin-5-yl)nicotinate **(Example 141)**

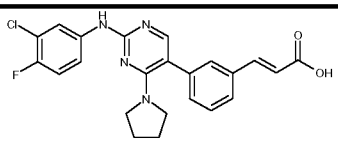
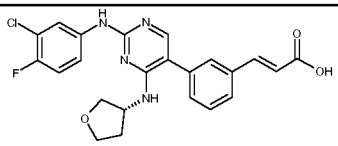
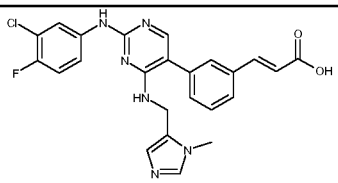
Ex	Compound	Data	SM
279	 (R)-5-(2-(3-chloro-4-fluorophenylamino)-4-(tetrahydrofuran-3-ylamino)pyrimidin-5-yl)nicotinic acid	MS(ES): 430 (M+1) for $C_{20}H_{17}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.71 - 2.05 (m, 1 H) 2.05 - 2.34 (m, 1 H) 3.59 (dd, J=8.76, 4.62 Hz, 1 H) 3.63 - 3.86 (m, 2 H) 3.94 (dd, J=8.85, 6.41 Hz, 1 H) 4.44 - 4.76 (m, 1 H) 6.94 (d, J=6.03 Hz, 1 H) 7.32 (t, J=9.14 Hz, 1 H) 7.49 - 7.71 (m, 1 H) 7.86 (s, 1 H) 8.06 - 8.39 (m, 2 H) 8.75 (d, J=2.26 Hz, 1 H) 9.02 (d, J=1.88 Hz, 1 H) 9.52 (s, 1 H) 13.45 (s, 1 H)	(R)-ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(tetrahydrofuran-3-ylamino)pyrimidin-5-yl)nicotinate **(Example 146)**
280	 5-(2-(3-chloro-4-fluorophenylamino)-4-(pyrrolidin-1-yl)pyrimidin-5-yl)nicotinic acid	MS(ES): 414 (M+1) for $C_{20}H_{17}ClFN_5O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.57 - 1.93 (m, 4 H) 3.00 - 3.24 (m, 4 H) 7.31 (t, J=9.14 Hz, 1 H) 7.54 - 7.77 (m, 1 H) 7.94 (s, 1 H) 8.10 (t, J=2.07 Hz, 1 H) 8.24 (dd, J=6.97, 2.45 Hz, 1 H) 8.74 (d, J=2.07 Hz, 1 H) 8.98 (d, J=2.07 Hz, 1 H) 9.54 (s, 1 H) 13.50 (s, 1 H)	ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(pyrrolidin-1-yl)pyrimidin-5-yl)nicotinate **(Example 147)**
281	 5-(2-(3-chloro-4-fluorophenylamino)-4-((1-methyl-1H-imidazol-5-yl)methylamino)pyrimidin-5-yl)nicotinic acid	MS(ES): 454 (M+1) for $C_{21}H_{17}ClFN_7O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) d ppm 3.14 - 3.37 (m, 4 H) 3.75 - 3.98 (m, 4 H) 7.27 (d, J=3.77 Hz, 1 H) 7.34 (t, J=9.14 Hz, 1 H) 7.48 - 7.65 (m, 1 H) 7.69 (d, J=3.77 Hz, 1 H) 8.10 (dd, J=6.88, 2.54 Hz, 1 H) 8.21 (s, 1 H) 9.82 (s, 1 H) 13.10 (s, 1 H)	ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-((1-methyl-1H-imidazol-5-yl)methylamino)pyrimidin-5-yl)nicotinate **(Example 145)**

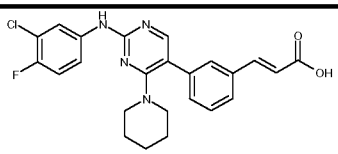
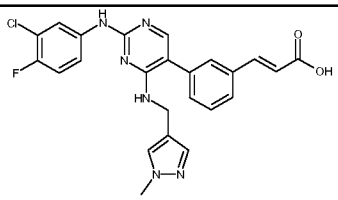
Ex	Compound	Data	SM
282	 5-(2-(3-chloro-4-fluorophenylamino)-4-((1-methyl-1H-pyrazol-4-yl)methylamino)pyrimidin-5-yl)nicotinic acid	MS(ES): 454 (M+1) for $C_{21}H_{17}ClFN_7O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 3.73 (s, 3 H) 4.38 (d, J=5.65 Hz, 2 H) 7.11 - 7.42 (m, 3 H) 7.54 (s, 1 H) 7.57 - 7.75 (m, 1 H) 7.86 (s, 1 H) 7.98 - 8.35 (m, 2 H) 8.75 (d, J=2.26 Hz, 1 H) 9.02 (d, J=1.88 Hz, 1 H) 9.46 (s, 1 H) 13.48 (s, 1 H)	ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-((1-methyl-1H-pyrazol-4-yl)methylamino)pyrimidin-5-yl)nicotinate **(Example 148)**
283	 5-(2-(3-chloro-4-fluorophenylamino)-4-(1,3-dimethoxypropan-2-ylamino)pyrimidin-5-yl)nicotinic acid	MS(ES): 462 (M+1) for $C_{21}H_{21}ClFN_5O_4$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 3.25 (s, 6 H) 3.36 - 3.63 (m, 4 H) 4.42 - 4.82 (m, 1 H) 6.52 (d, J=8.67 Hz, 1 H) 7.29 (t, J=9.14 Hz, 1 H) 7.45 - 7.72 (m, 1 H) 7.88 (s, 1 H) 8.03 - 8.40 (m, 2 H) 8.75 (d, J=2.26 Hz, 1 H) 9.02 (d, J=2.07 Hz, 1 H) 9.48 (s, 1 H) 13.45 (s, 1 H)	ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(1,3-dimethoxypropan-2-ylamino)pyrimidin-5-yl)nicotinate **(Example 149)**
284	 5-(2-(3-chloro-4-fluorophenylamino)-4-(4-(2-methoxyethyl)piperazin-1-yl)pyrimidin-5-yl)nicotinic acid	MS(ES): 487 (M+1) for $C_{23}H_{24}ClFN_6O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 2.30 - 2.45 (m, 6 H) 3.11 - 3.27 (m, 7 H) 3.39 (t, J=5.84 Hz, 2 H) 7.33 (t, J=9.14 Hz, 1 H) 7.44 - 7.78 (m, 1 H) 7.96 - 8.24 (m, 2 H) 8.31 (s, 1 H) 8.87 (d, J=1.88 Hz, 1 H) 8.98 (d, J=1.88 Hz, 1 H) 9.71 (s, 1 H) 13.50 (s, 1 H)	ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(4-(2-methoxyethyl)piperazin-1-yl)pyrimidin-5-yl)nicotinate **(Example 150)**

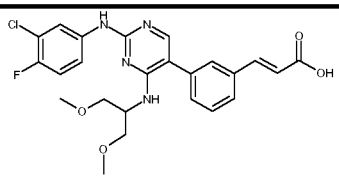
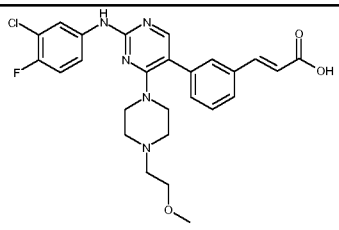
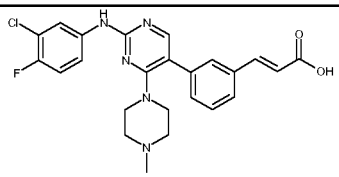
Ex	Compound	Data	SM
285	 5-(2-(3-chloro-4-fluorophenylamino)-4-(4-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinic acid	MS(ES): 443 (M+1) for $C_{21}H_{20}ClFN_6O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 2.21 (s, 3 H) 2.31 - 2.44 (m, 4 H) 3.15 - 3.35 (m, 4 H) 7.33 (t, J=9.04 Hz, 1 H) 7.61 (dd, J=4.90, 3.20 Hz, 1 H) 8.00 - 8.25 (m, 2 H) 8.30 (s, 1 H) 8.86 (d, J=1.32 Hz, 1 H) 8.98 (s, 1 H) 9.72 (s, 1 H)	ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(4-methylpiperazin-1-yl)pyrimidin-5-yl)nicotinate **(Example 151)**
286	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(2,6-dimethylmorpholino)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 483 (M+1) for $C_{25}H_{24}ClFN_4O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 0.94 (d, J=6.03 Hz, 6 H) 2.18 - 2.57 (m, 2 H) 3.41 - 3.72 (m, 4 H) 6.60 (d, J=16.01 Hz, 1 H) 7.32 (t, J=9.04 Hz, 1 H) 7.39 - 7.72 (m, 5 H) 7.75 (s, 1 H) 8.06 (s, 1 H) 8.23 (dd, J=6.78, 2.45 Hz, 1 H) 9.62 (s, 1 H) 12.44 (s, 1 H)	(E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(2,6-dimethylmorpholino)pyrimidin-5-yl)phenyl)acrylate **(Example 163)**
287	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(4-(cyclopropanecarbonyl)piperazin-1-yl)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 522 (M+1) for $C_{27}H_{25}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 0.53 - 0.83 (m, 4 H) 1.77 - 2.06 (m, 1 H) 3.16 - 3.40 (m, 4 H) 3.41 - 3.81 (m, 4 H) 6.59 (d, J=16.01 Hz, 1 H) 7.33 (t, J=9.14 Hz, 1 H) 7.40 - 7.70 (m, 5 H) 7.73 (s, 1 H) 7.99 - 8.22 (m, 2 H) 9.63 (s, 1 H)	(E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(4-(cyclopropanecarbonyl)piperazin-1-yl)pyrimidin-5-yl)phenyl)acrylate **(Example 199)**

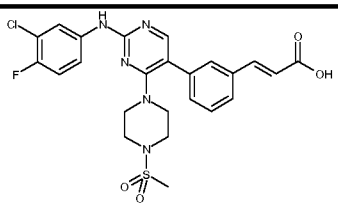
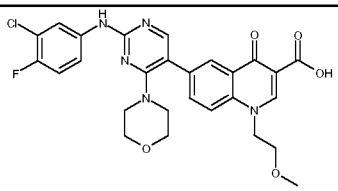
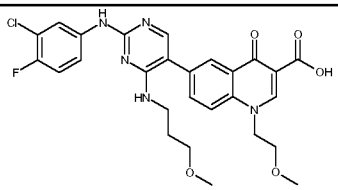
Ex	Compound	Data	SM
288	 (E)-3-(3-(4-(4-acetylpiperazin-1-yl)-2-(3-chloro-4-fluorophenylamino)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 496 (M+1) for $C_{25}H_{23}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.94 (s, 3 H) 3.03 - 3.67 (m, 8 H) 6.56 (d, J=16.01 Hz, 1 H) 7.10 - 7.79 (m, 7 H) 7.91 - 8.24 (m, 2 H) 9.62 (s, 1 H)	(E)-ethyl 3-(3-(4-(4-acetylpiperazin-1-yl)-2-(3-chloro-4-fluorophenylamino)pyrimidin-5-yl)phenyl)acrylate **Example 162)**
289	 (E)-3-(3-(4-(3-(1H-benzo[d]imidazol-2-yl)propylamino)-2-(3-chloro-4-fluorophenylamino)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 543 (M+1) for $C_{29}H_{24}ClFN_6O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 2.06 - 2.24 (m, 2 H) 3.00 - 3.14 (m, 2 H) 3.46 - 3.60 (m, 2 H) 6.59 (d, J=16.01 Hz, 1 H) 6.99 (s, 1 H) 7.26 (t, J=9.14 Hz, 1 H) 7.30 - 7.45 (m, J=6.97 Hz, 3 H) 7.48 (t, J=7.63 Hz, 1 H) 7.52 - 7.78 (m, 6 H) 7.83 (s, 1 H) 8.20 (dd, J=6.78, 2.64 Hz, 1 H) 9.51 (s, 1 H) 12.46 (s, 1 H) 14.13 (s, 1 H)	(E)-ethyl 3-(3-(4-(3-(1*H*-benzo[d]imidazol-2-yl)propylamino)-2-(3-chloro-4-fluorophenylamino)pyrimidin-5-yl)phenyl)acrylate **(Example 200)**
290	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 455 (M+1) for $C_{23}H_{20}ClFN_4O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 3.10 - 3.24 (m, 4 H) 3.44 - 3.75 (m, 4 H) 6.60 (d, J=16.20 Hz, 1 H) 7.32 (t, J=9.14 Hz, 1 H) 7.41 - 7.56 (m, 2 H) 7.54 - 7.71 (m, 3 H) 7.78 (s, 1 H) 7.95 - 8.31 (m, 2 H) 9.62 (s, 1 H) 12.38 (s, 1 H)	(E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)phenyl)acrylate **(Example 166)**

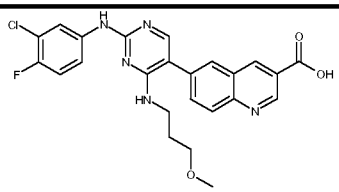
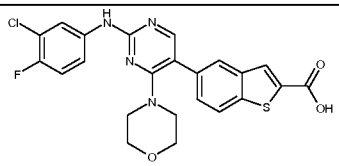
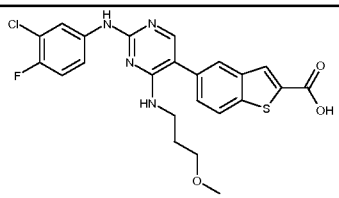
Ex	Compound	Data	SM
291	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(4-(dimethylcarbamoyl)piperazin-1-yl)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 525 (M+1) for $C_{26}H_{26}ClFN_6O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 2.70 (s, 6 H) 2.94 - 3.17 (m, 4 H) 3.15 - 3.30 (m, 4 H) 6.60 (d, J=16.20 Hz, 1 H) 7.33 (t, J=9.14 Hz, 1 H) 7.39 - 7.57 (m, 2 H) 7.54 - 7.72 (m, 3 H) 7.76 (s, 1 H) 7.93 - 8.22 (m, 2 H) 9.62 (s, 1 H) 12.43 (s, 1 H)	(E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(4-(dimethylcarbamoyl)piperazin-1-yl)pyrimidin-5-yl)phenyl)acrylate **(Example 164)**
292	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(5-methylpyrazine-2-carboxamido)propylamino)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 562 (M+1) for $C_{28}H_{25}ClFN_7O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.70 - 2.04 (m, 2 H) 2.56 (s, 3 H) 3.34 - 3.62 (m, 4 H) 6.59 (d, J=16.01 Hz, 1 H) 6.83 (t, J=4.90 Hz, 1 H) 7.27 (t, J=9.14 Hz, 1 H) 7.39 - 7.56 (m, 2 H) 7.55 - 7.75 (m, 4 H) 7.81 (s, 1 H) 8.23 (dd, J=6.97, 2.45 Hz, 1 H) 8.54 (d, J=0.94 Hz, 1 H) 8.78 - 9.15 (m, 2 H) 9.40 (s, 1 H) 12.37 (s, 1 H)	(E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(5-methylpyrazine-2-carboxamido)propylamino)pyrimidin-5-yl)phenyl)acrylate **(Example 165)**
293	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 457 (M+1) for $C_{23}H_{22}ClFN_4O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.67 - 1.96 (m, 2 H) 3.16 (s, 3 H) 3.35 - 3.58 (m, 4 H) 6.58 (d, J=16.20 Hz, 1 H) 6.64 - 6.89 (m, 1 H) 7.29 (t, J=9.04 Hz, 1 H) 7.36 - 7.58 (m, 2 H) 7.57 - 7.76 (m, 4 H) 7.80 (s, 1 H) 8.06 - 8.40 (m, 1 H) 9.42 (s, 1 H) 12.42 (s, 1 H)	(E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)phenyl)acrylate **(Example 167)**

Ex	Compound	Data	SM
294	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(pyrrolidin-1-yl)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 439 (M+1) for $C_{23}H_{20}ClFN_4O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.63 - 1.94 (m, 4 H) 3.05 - 3.23 (m, 4 H) 6.54 (d, J=16.01 Hz, 1 H) 7.14 - 7.76 (m, 8 H) 7.86 (s, 1 H) 8.25 (dd, J=6.97, 2.64 Hz, 1 H) 9.44 (s, 1 H)	(E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(pyrrolidin-1-yl)pyrimidin-5-yl)phenyl)acrylate **(Example 202)**
295	 (R,E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(tetrahydrofuran-3-ylamino)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 455 (M+1) for $C_{23}H_{20}ClFN_4O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 3.14 - 3.37 (m, 4 H) 3.75 - 3.98 (m, 4 H) 7.27 (d, J=3.77 Hz, 1 H) 7.34 (t, J=9.14 Hz, 1 H) 7.48 - 7.65 (m, 1 H) 7.69 (d, J=3.77 Hz, 1 H) 8.10 (dd, J=6.88, 2.54 Hz, 1 H) 8.21 (s, 1 H) 9.82 (s, 1 H) 13.10 (s, 1 H)	(R,E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(tetrahydrofuran-3-ylamino)pyrimidin-5-yl)phenyl)acrylate **(Example 169)**
296	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-((1-methyl-1H-imidazol-5-yl)methylamino)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 479 (M+1) for $C_{24}H_{20}ClFN_6O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 3.44 - 3.67 (s, 3 H) 4.53 (d, J=5.46 Hz, 2 H) 6.57 (d, J=16.01 Hz, 1 H) 6.80 (s, 1 H) 7.02 (t, J=5.46 Hz, 1 H) 7.28 (t, J=9.14 Hz, 1 H) 7.36 - 7.45 (m, 1 H) 7.43 - 7.55 (m, 2 H) 7.53 - 7.75 (m, 4 H) 7.84 (s, 1 H) 8.12 (dd, J=6.78, 2.64 Hz, 1 H) 9.38 (s, 1 H) 12.42 (s, 1 H)	(E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-((1-methyl-1H-imidazol-5-yl)methylamino)pyrimidin-5-yl)phenyl)acrylate **(Example 172)**

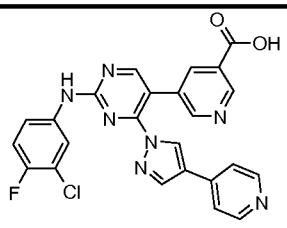
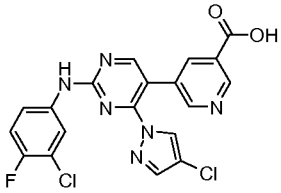
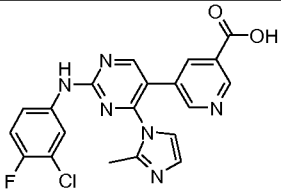
Ex	Compound	Data	SM
297	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(piperidin-1-yl)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 453 (M+1) for $C_{24}H_{22}ClFN_4O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 3.14 - 3.37 (m, 4 H) 3.75 - 3.98 (m, 4 H) 7.27 (d, J=3.77 Hz, 1 H) 7.34 (t, J=9.14 Hz, 1 H) 7.48 - 7.65 (m, 1 H) 7.69 (d, J=3.77 Hz, 1 H) 8.10 (dd, J=6.88, 2.54 Hz, 1 H) 8.21 (s, 1 H) 9.82 (s, 1 H) 13.10 (s, 1 H)	(E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(piperidin-1-yl)pyrimidin-5-yl)phenyl)acrylate **(Example 171)**
298	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-((1-methyl-1H-pyrazol-4-yl)methylamino)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 479 (M+1) for $C_{24}H_{20}ClFN_6O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 3.74 (s, 3 H) 4.39 (d, J=5.65 Hz, 2 H) 6.43 (d, J=16.01 Hz, 1 H) 6.85 - 7.04 (m, 1 H) 7.05 - 7.58 (m, 8 H) 7.58 - 7.73 (m, 1 H) 7.80 (s, 1 H) 8.18 (dd, J=6.88, 2.54 Hz, 1 H) 9.37 (s, 1 H)	(E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-((1-methyl-1H-pyrazol-4-yl)methylamino)pyrimidin-5-yl)phenyl)acrylate **(Example 168)**

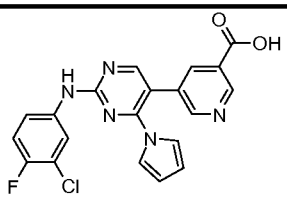
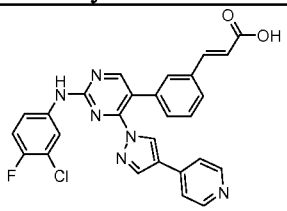
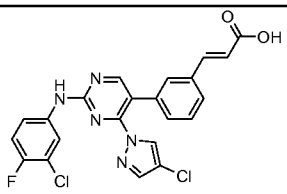
Ex	Compound	Data	SM
299	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(1,3-dimethoxypropan-2-ylamino)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 487 (M+1) for $C_{24}H_{24}ClFN_4O_4$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 3.25 (s, 6 H) 3.36 - 3.61 (m, 4 H) 4.32 - 4.81 (m, 1 H) 6.09 (d, J=8.48 Hz, 1 H) 6.57 (d, J=16.01 Hz, 1 H) 7.28 (t, J=9.14 Hz, 1 H) 7.37 - 7.48 (m, 1 H) 7.51 (t, J=7.54 Hz, 1 H) 7.59 - 7.75 (m, 4 H) 7.88 (s, 1 H) 8.15 (dd, J=6.69, 2.54 Hz, 1 H) 9.43 (s, 1 H) 12.44 (s, 1 H)	(E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(1,3-dimethoxypropan-2-ylamino)pyrimidin-5-yl)phenyl)acrylate **(Example 173)**
300	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(4-(2-methoxyethyl)piperazin-1-yl)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 512 (M+1) for $C_{26}H_{27}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 2.20 - 2.48 (m, 6 H) 3.09 - 3.27 (m, 7 H) 3.38 (t, J=5.65 Hz, 2 H) 6.60 (d, J=16.01 Hz, 1 H) 7.32 (t, J=9.14 Hz, 1 H) 7.43 - 7.54 (m, 2 H) 7.53 - 7.70 (m, 3 H) 7.76 (s, 1 H) 8.05 (s, 1 H) 8.17 (dd, J=6.50, 1.98 Hz, 1 H) 9.61 (s, 1 H) 12.43 (s, 1 H)	(E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(4-(2-methoxyethyl)piperazin-1-yl)pyrimidin-5-yl)phenyl)acrylate **(Example 201)**
301	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(4-methylpiperazin-1-yl)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 468 (M+1) for $C_{24}H_{23}ClFN_5O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.95 - 2.40 (m, 7 H) 2.98 - 3.28 (m, 4 H) 6.60 (d, J=16.01 Hz, 1 H) 7.32 (t, J=9.14 Hz, 1 H) 7.40 - 7.55 (m, 2 H) 7.54 - 7.73 (m, 3 H) 7.76 (s, 1 H) 8.08 (s, 1 H) 8.18 (d, J=6.22 Hz, 1 H) 9.63 (s, 1 H) 12.44 (s, 1 H)	(E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(4-methylpiperazin-1-yl)pyrimidin-5-yl)phenyl)acrylate **(Example 170)**

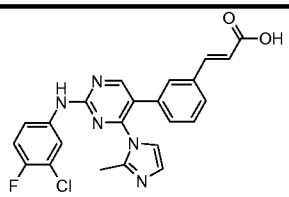
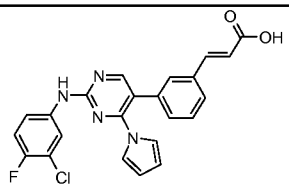
Ex	Compound	Data	SM
302	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 532 (M+1) for $C_{24}H_{23}ClFN_5O_4S$ ^{1}H NMR (300 MHz, DMSO-*d6*) δ ppm 2.86 (s, 3 H) 2.98 - 3.20 (m, 4 H) 3.32 - 3.49 (m, 4 H) 6.62 (d, J=16.01 Hz, 1 H) 7.34 (t, J=9.14 Hz, 1 H) 7.43 - 7.58 (m, 2 H) 7.57 - 7.73 (m, 3 H) 7.79 (s, 1 H) 8.06 - 8.23 (m, 2 H) 9.67 (s, 1 H) 12.40 (s, 1 H)	(E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-5-yl)phenyl)acrylate **(Example 174)**
303	 6-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	MS(ES): 554 (M+1) for $C_{27}H_{25}ClFN_5O_5$ ^{1}H NMR (300 MHz, DMSO-*d6*) δ ppm 3.11 - 3.28 (m, 7 H) 3.44 - 3.65 (m, 4 H) 3.73 (t, J=4.24 Hz, 2 H) 4.56 - 5.04 (m, 2 H) 7.34 (t, J=9.14 Hz, 1 H) 7.52 - 7.77 (m, 1 H) 7.97 - 8.30 (m, 4 H) 8.46 (d, J=1.70 Hz, 1 H) 8.92 (s, 1 H) 9.72 (s, 1 H) 15.18 (s, 1 H)	ethyl 6-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **(Exmaple 175)**
304	 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	MS(ES): 556 (M+1) for $C_{27}H_{27}ClFN_5O_5$ ^{1}H NMR (300 MHz, DMSO-*d6*) δ ppm 1.63 - 1.95 (m, 2 H) 3.18 (s, 3 H) 3.23 (s, 3 H) 3.36 - 3.52 (m, 4 H) 3.73 (t, J=4.43 Hz, 2 H) 4.82 (t, J=4.05 Hz, 2 H) 7.01 (s, 1 H) 7.31 (t, J=9.14 Hz, 1 H) 7.50 - 7.72 (m, 1 H) 7.81 - 7.90 (m, 1 H) 7.88 - 8.03 (m, 1 H) 8.06 - 8.28 (m, 2 H) 8.35 (d, J=2.07 Hz, 1 H) 8.94 (s, 1 H) 9.54 (s, 1 H) 15.21 (s, 1 H)	ethyl 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **(Example 177)**

Ex	Compound	Data	SM
305	 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)quinoline-3-carboxylic acid	MS(ES): 482 (M+1) for $C_{24}H_{21}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.65 - 1.95 (m, 2 H) 3.15 (s, 3 H) 3.24 - 3.49 (m, 4 H) 7.40 (t, J=9.04 Hz, 1 H) 7.51 - 7.68 (m, 1 H) 7.80 - 8.00 (m, 2 H) 8.01 - 8.34 (m, 3 H) 9.01 (s, 1 H) 9.34 (d, J=2.07 Hz, 1 H)	methyl 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)quinoline-3-carboxylate **(Example 181)**
306	 5-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)benzo[b]thiophene-2-carboxylic acid	MS(ES): 485 (M+1) for $C_{23}H_{18}ClFN_4O_3S$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 3.14 - 3.37 (m, 4 H) 3.75 - 3.98 (m, 4 H) 7.27 (d, J=3.77 Hz, 1 H) 7.34 (t, J=9.14 Hz, 1 H) 7.48 - 7.65 (m, 1 H) 7.69 (d, J=3.77 Hz, 1 H) 8.10 (dd, J=6.88, 2.54 Hz, 1 H) 8.21 (s, 1 H) 9.82 (s, 1 H) 13.10 (s, 1 H)	methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)benzo[b]thiophene-2-carboxylate **(Example 182)**
307	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)benzo[b]thiophene-2-carboxylic acid	MS(ES): 487 (M+1) for $C_{23}H_{20}ClFN_4O_3S$ ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.62 - 1.99 (m, 2 H) 3.14 (s, 3 H) 3.34 - 3.58 (m, 4 H) 6.65 (t, J=5.37 Hz, 1 H) 7.10 - 7.38 (m, 2 H) 7.47 (s, 1 H) 7.57 - 7.71 (m, 1 H) 7.79 (s, 2 H) 7.88 (d, J=8.10 Hz, 1 H) 8.24 (dd, J=6.88, 2.54 Hz, 1 H) 9.35 (s, 1 H)	methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)benzo[b]thiophene-2-carboxylate **(Example 180)**

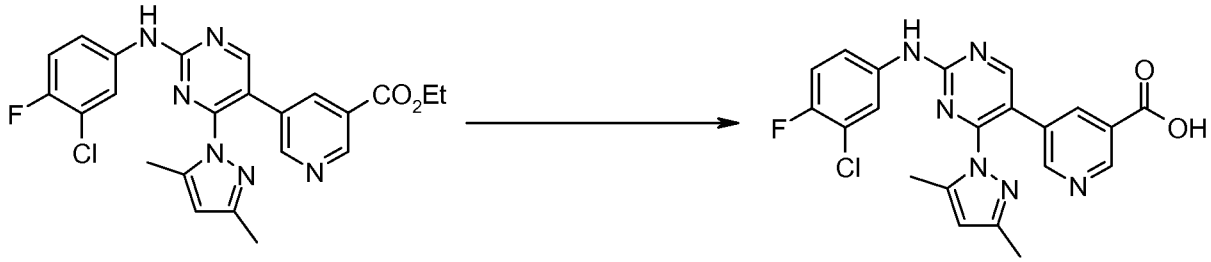
The following examples were prepared using the general method described above for **Example 214** using 1N sodium hydroxide (1-2 equivalents), dioxane or THF as solvent and the starting material (SM) indicated.

Ex	Compound	Data	SM
308	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyridin-4-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 488 (M+1) for $C_{24}H_{15}ClFN_7O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.43 (t, *J* = 8.92 Hz, 1H), 7.68-7.72 (m, 3H), 8.09 (s, 1H), 8.13 (d, *J* = 4.76 Hz, 1H), 8.25 (s, 1H), 8.58-8.72 (m, 4H), 8.98 (s, 1H), 9.06 (s, 1H), 10.38 (s, 1H).	Ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyridin-4-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate **(Example 203)**
309	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(4-chloro-1*H*-pyrazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 445 (M+1) for $C_{19}H_{11}C_{l2}FN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.42 (t, *J* = 9.08 Hz, 1H), 7.72 (d, *J* = 2.52 Hz, 1H), 7.74 (s, 1H), 8.02 (d, *J* = 4.44 Hz, 1H), 8.09 (s, 1H), 8.58 (s, 1H), 8.64 (s, 1H), 8.71 (s, 1H), 8.99 (s, 1H), 10.34 (br s, 1H), 13.50 (br s, 1H).	ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(4-chloro-1*H*-pyrazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylate **(Example 135)**
310	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2-methyl-1*H*-imidazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 425 (M+1) for $C_{20}H_{14}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 3H), 6.80 (s, 1H), 7.04 (s, 1H), 7.41 (t, *J* = 8.85 Hz, 1H), 7.66 (m, 1H), 7.98 (s, 1H), 8.06 (d, *J* = 4.36 Hz, 1H)), 8.52 (s, 1H), 8.90 (s, 1H), 8.97 (s, 1H), 10.42 (s, 1H), 13.6 (br s, 1H).	ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2-methyl-1*H*-imidazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylate **(Example 205)**

Ex	Compound	Data	SM
311	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-pyrrol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 410 (M+1) for $C_{20}H_{13}ClFN_5O_2$ ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.16 (d, *J* = 1.92 Hz, 2H), 6.90 (d, *J* = 1.96 Hz, 2H), 7.40 (t, *J* = 5.44 Hz, 1H), 7.69-7.73 (m, 1H), 8.00 (s, 1H), 8.11 (dd, *J* = 2.56, 6.76 Hz, 1H), 8.34 (d, *J* = 1.64 Hz, 1H), 8.53 (s, 1H), 8.94 (s, 1H), 10.19 (s, 1H).	ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-pyrrol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylate **(Example 138)**
312	 (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyridin-4-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 513 (M+1) for $C_{27}H_{18}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.52 (d, *J* = 16.60 Hz, 1H), 7.16 (d, *J* = 1.44 Hz, 1H), 7.18-7.53 (m, 2H), 7.57-7.67 (m, 5H), 7.73-7.76 (m, 1H), 8.16 (d, *J* = 4.96 Hz, 1H), 8.26 (s, 1H), 8.57 (d, *J* = 1.44 Hz, 1H), 8.74 (s, 1H), 8.98 (s, 1H), 10.34 (s, 1H), 12.20 (br s, 1H).	ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyridin-4-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate **(Example 188)**
313	 (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(4-chloro-1*H*-pyrazol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 470 (M+1) for $C_{22}H_{14}Cl_2FN_5O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.51 (d, *J* = 15.96 Hz, 1H), 7.11 (d, *J* = 7.72 Hz, 1H), 7.33-7.45 (m, 3H), 7.51-7.57 (m, 2H), 7.71-7.74 (m, 1H), 7.75 (s, 1H), 8.06 (dd, *J* = 2.40, 6.54 Hz, 1H), 8.46 (s, 1H), 8.71 (s, 1H), 10.31 (br s, 1H).	ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(4-chloro-1*H*-pyrazol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoate **(Example 159)**

Ex	Compound	Data	SM
314	 (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2-methyl-1*H*-imidazol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 450 (M+1) for $C_{23}H_{17}ClFN_5O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.10 (s, 3H), 6.47 (d, *J* = 16.00 Hz, 1H), 6.82 (br s, 1H), 7.09 (s, 1H), 7.10 (s, 1H), 7.35-7.42 (m, 2H), 7.45 (s, 1H), 7.50 (d, *J* = 16.00 Hz, 1H), 7.62-7.69 (m, 2H), 8.07-8.08 (m, 1H), 8.86 (s, 1H), 10.35 (s, 1H), 12.47 (br s, 1H).	ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2-methyl-1*H*-imidazol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoate **(Example 190)**
315	 (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-pyrrol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 433 (M-1) for $C_{23}H_{16}ClFN_4O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.16 (t, *J* = 1.92 Hz, 2H), 6.51 (d, *J* = 16.00 Hz, 1H), 6.92 (t, *J* = 2.04 Hz, 2H), 7.21 (d, *J* = 7.56 Hz, 1H), 7.35-7.43 (m, 3H), 7.54 (s, 1H), 7.62 (d, *J* = 7.92 Hz, 1H), 7.68-7.71 (m, 1H), 8.11 (dd, *J* = 2.48, 6.74 Hz, 1H), 8.55 (s, 1H), 10.16 (s, 1H).	ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-pyrrol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoate **(Example 195)**

Example 316: 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylic acid



Example 133 **Example 316**

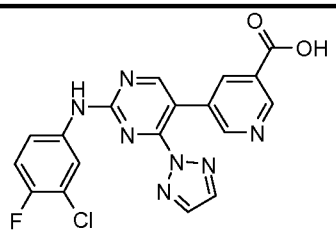
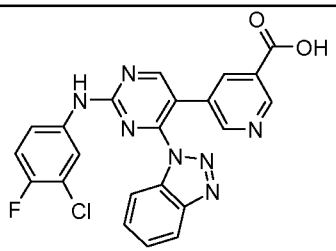
Ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylate (**Example 133**, 100 mg, 0.22 mmol) was dissolved in tetrahydrofuran (1 ml) and treated with a suspension of aqueous barium hydroxide (35 mg, 0.88 mmol) in water (1 ml). The mixture was allowed to stir at room temperature for 4 h. After completion of the

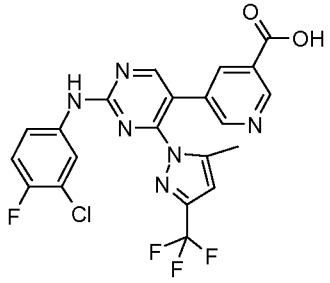
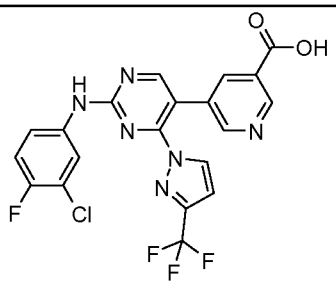
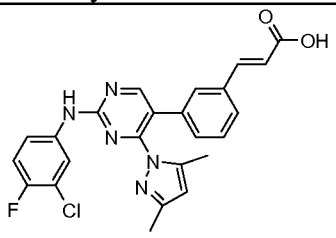
reaction, the mixture was then carefully acidified with 1 N HCl and the precipitate that formed was filtered, washed with water, and dried to yield the title compound (65 mg).

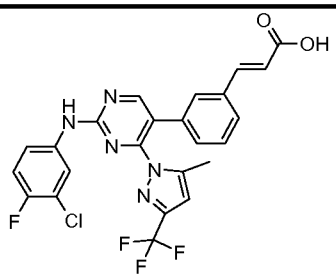
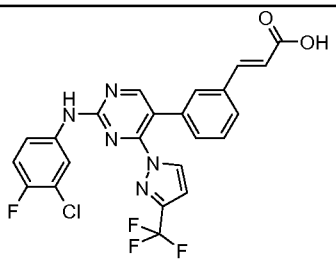
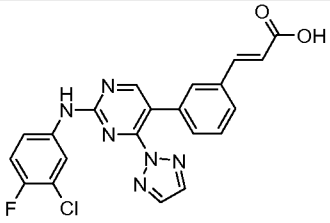
MS(ES): 439 (M+1) for $C_{21}H_{16}ClFN_6O_2$.

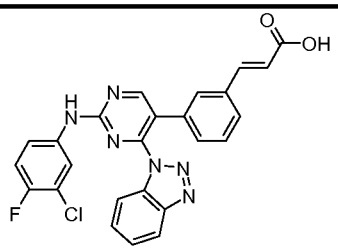
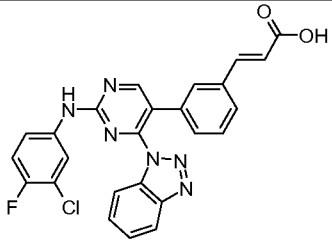
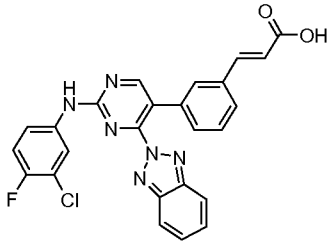
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.92 (s, 3H), 2.36 (s, 3H), 6.07 (s, 1H), 7.41 (t, J = 9.08 Hz, 1H), 7.62-7.67 (m, 1H), 7.88 (t, J = 2.12 Hz, 1H), 8.09 (dd, J = 2.48, 6.74 Hz, 1H), 8.37 (d, J = 1.80 Hz, 1H), 8.83 (s, 1H), 8.91 (d, J = 1.88 Hz, 1H), 10.28 (s, 1H).

The following examples were prepared using the general method described above for **Example 316** using barium hydroxide (2-4 equivalents), dioxane or THF and the starting material (SM) indicated.

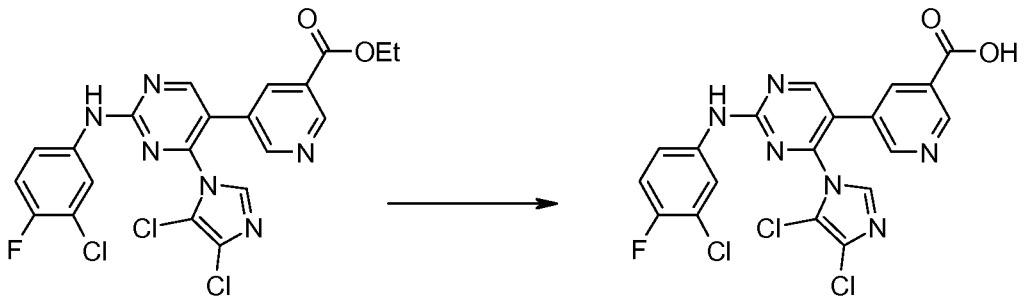
Ex	Compound	Data	SM
317	 5-{4-(2*H*-1,2,3-triazol-2-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 412 (M+1) for $C_{18}H_{11}ClFN_7O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.43 (t, J = 9.20 Hz, 1H), 7.76-7.80 (m, 1H), 7.96 (s, 1H), 8.12 (s, 2H), 8.23 (d, J = 4.40 Hz, 1H), 8.55 (d, J = 1.60 Hz, 1H), 8.87 (s, 1H), 9.00 (br s, 1H), 10.571 (s, 1H).	ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-1,2,3-triazol-2-yl)pyrimidin-5-yl}pyridine-3-carboxylate **(Example 206)**
318	 5-{4-(1*H*-benzotriazol-1-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 462 (M+1) for $C_{22}H_{13}ClFN_7O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.43 (t, J = 9.08 Hz, 1H), 7.53-7.58 (m, 1H), 7.63-7.66 (m, 1H), 7.71-7.75 (m, 1H), 8.12-8.16 (m, 3H), 8.32 (d, J = 8.16 Hz, 1H), 8.68 (d, J = 2.16 Hz, 1H), 8.91 (s, 1H), 9.00 (d, J = 1.92 Hz, 1H), 10.47 (s, 1H), 13.50 (br s, 1H).	ethyl 5-{4-(1*H*-benzotriazol-1-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}pyridine-3-carboxylate **(Example 209)**

Ex	Compound	Data	SM
319	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 493 (M+1) for $C_{21}H_{13}ClF_4N_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.42 (s, 3H), 6.77 (s, 1H), 7.43 (t, *J* = 9.08 Hz, 1H), 7.64-7.68 (m, 1H), 7.82 (t, *J* = 2.04 Hz, 1H), 8.06 (d, *J* = 4.24 Hz, 1H), 8.53 (d, *J* = 1.92 Hz, 1H), 8.95 (d, *J* = 1.76 Hz, 1H), 8.99 (s, 1H), 10.48 (s, 1H), 13.40 (br s, 1H).	ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate **(Example 134)**
320	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 479 (M+1) for $C_{20}H_{11}ClF_4N_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.04 (d, *J* = 2.60 Hz, 1H), 7.43 (t, *J* = 9.12 Hz, 1H), 7.73 (ddd, *J* = 2.64, 4.12, 9.02 Hz, 1H), 8.00 (s, 1H), 8.07 (dd, *J* = 2.96, 6.94 Hz, 1H), 8.53 (s, 1H), 8.59 (s, 1H), 8.82 (s, 1H), 8.99 (s, 1H), 10.46 (s, 1H).	ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate **(Example 136)**
321	 (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 464 (M+1) for $C_{24}H_{19}ClFN_5O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.03 (s, 3H), 2.13 (s, 3H), 6.03 (s, 1H), 6.42 (d, *J* = 16.00 Hz, 1H), 7.04 (d, *J* = 7.80 Hz, 1H), 7.31-7.35 (m, 2H), 7.40 (t, *J* = 9.00 Hz, 1H), 7.51 (d, *J* = 16.12 Hz, 1H), 7.56 (d, *J* = 7.52 Hz, 1H), 7.66 (m, 1H), 8.11 (dd, *J* = 2.68, 6.86 Hz, 1H), 8.87 (s, 1H), 10.29 (s, 1H), 12.50 (br s, 1H).	ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(3,5-dimethyl-1*H*-pyrazol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoate **(Example 158)**

Ex	Compound	Data	SM
322	 (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 518 (M+1) for $C_{24}H_{16}ClF_4N_5O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.22 (s, 3H), 6.44 (d, *J* = 15.92 Hz, 1H), 6.72 (s, 1H), 7.04 (d, *J* = 7.60 Hz, 1H), 7.33-7.37 (m, 2H), 7.42 (t, *J* = 9.12 Hz, 1H), 7.49 (d, *J* = 15.96 Hz, 1H), 7.61 (d, *J* = 7.92 Hz, 1H), 7.65-7.67 (m, 1H), 8.08 (d, *J* = 4.52 Hz, 1H), 8.98 (s, 1H), 12.4 (br s, 1H).	ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate **(Example 187)**
323	 (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 504 (M+1) for $C_{23}H_{14}ClF_4N_5O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.48 (d, *J* = 16.00 Hz, 1H), 7.00 (d, *J* = 2.36 Hz, 1H), 7.14 (d, *J* = 7.56 Hz, 1H), 7.35-7.43 (m, 2H), 7.52 (s, 1H), 7.54 (d, *J* = 15.84 Hz, 1H), 7.64 (d, *J* = 7.68 Hz, 1H), 7.71-7.73 (m, 1H), 8.12 (dd, *J* = 2.48, 6.66 Hz, 1H), 8.35 (s, 1H), 8.83 (s, 1H), 10.43 (s, 1H), 12.42 (br s, 1H).	ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate **(Example 160)**
324	 (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-1,2,3-triazol-2-yl)pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 437 (M+1) for $C_{21}H_{14}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.50 (d, *J* = 16.40 Hz, 1H), 7.00 (d, *J* = 8.00 Hz, 1H), 7.34 (t, *J* = 7.60 Hz, 1H), 7.42 (t, *J* = 9.20 Hz, 1H), 7.46 (br s, 1H), 7.48 (d, *J* = 15.60 Hz, 1H), 7.61 (d, *J* = 8.00 Hz, 1H), 7.74-7.77 (m, 1H), 8.10 (s, 2H), 8.20 (dd, *J* = 2.40, 6.60 Hz, 1H), 8.88 (br s, 1H), 10.52 (br s, 1H).	ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-1,2,3-triazol-2-yl)pyrimidin-5-yl}phenyl)prop-2-enoate **(Example 191)**

Ex	Compound	Data	SM
325	 (2*E*)-3-(3-{4-(1*H*-benzotriazol-1-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 487 (M+1) for $C_{25}H_{16}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.40 (d, *J* = 16.00 Hz, 1H), 6.89 (d, *J* = 7.88 Hz, 1H), 7.23 (t, *J* = 7.80 Hz, 1H), 7.39-7.47 (m, 2H), 7.51-7.52 (m, 2H), 7.57 (d, *J* = 7.80 Hz, 1H), 7.72-7.75 (m, 1H), 7.93-7.96 (m, 2H), 8.18 (dd, *J* = 2.68, 6.70 Hz, 1H), 9.03 (s, 1H), 10.64 (s, 1H).	ethyl (2*E*)-3-(3-{4-(1*H*-benzotriazol-1-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}phenyl)prop-2-enoate **(Example 194)**
326	 (2*E*)-3-(3-{4-(1*H*-benzotriazol-1-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}phenyl)prop-2-enoic acid and  (2*E*)-3-(3-{4-(2*H*-benzotriazol-2-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 487 (M+1) for $C_{25}H_{16}ClFN_6O_2$. Mixture of regioisomers: ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.40 (d, J = 16.04 Hz, 1H), 6.46 (d, J = 16.00 Hz, 1H), 6.89 (d, J = 7.72 Hz, 1H), 7.10 (d, J = 7.96 Hz, 1H), 7.24 (t, J = 7.96 Hz, 1H), 7.30 (t, J = 7.64 Hz, 1H), 7.38-7.45 (m, 2H), 7.49-7.72 (m, 8H), 7.95 (dd, J = 3.04, 6.68 Hz, 1H), 8.13-8.19 (m, 3H), 8.93 (s, 1H), 9.03 (s, 1H), 12.5 (br s, 1H).	ethyl (2*E*)-3-(3-{4-(1*H*-benzotriazol-1-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}phenyl)prop-2-enoate and ethyl (2*E*)-3-(3-{4-(2*H*-benzotriazol-2-yl)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}phenyl)prop-2-enoate

Example 327: 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(4,5-dichloro-1*H*-imidazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylic acid



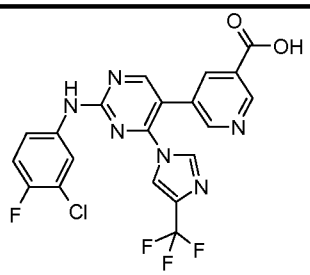
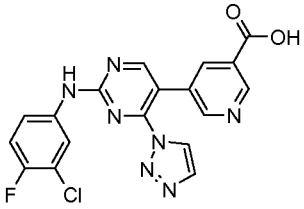
Example 133 **Example 327**

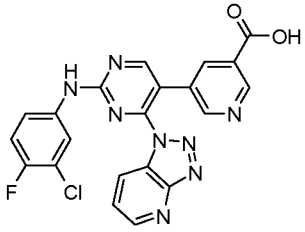
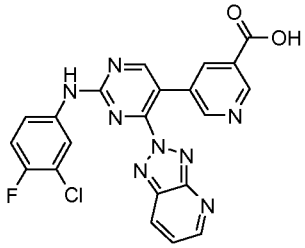
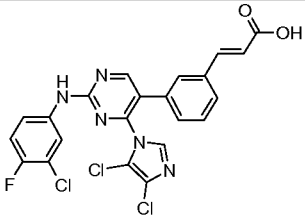
To a solution of ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(4,5-dichloro-1*H*-imidazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylate **Example 133** (289 mg, 0.57 mmol) in 1,2-dichloroethane, was added trimethyltin hydroxide (10 eq, 5.7 mmol) and the mixture was heated to 80-85 °C until TLC analysis indicated a complete reaction. After completion of the reaction, the mixture was concentrated in vacuum and the residue was taken up in ethyl acetate (~15 mL). The organic layer was washed with 5 % HCl, brine and dried over anhydrous Na_2SO_4. Removal of the solvent afforded the crude carboxylic acid. The crude compound was purified by RP-HPLC (Kromosil C18 column) to provide (150 mg) of pure 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(4,5-dichloro-1*H*-imidazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylic acid.

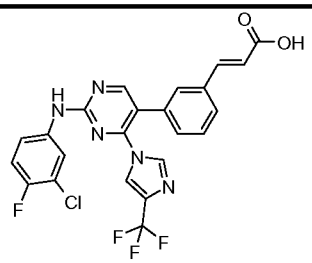
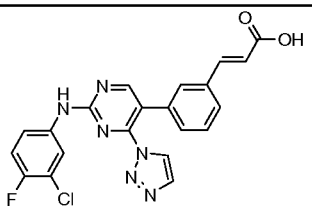
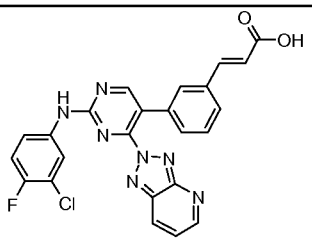
MS(ES): 479 (M+1) for $C_{19}H_{10}Cl_3FN_6O_2$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.42 (t, J = 9.12 Hz, 1H), 7.69 (ddd, J = 2.76, 4.04, 9.05 Hz, 1H), 7.97 (br s, 1H), 8.05 (ddd, J = 1.92, 6.48 Hz, 1H), 8.12 (br s, 1H), 8.60 (br s, 1H), 9.01 (br s, 1H), 9.04 (s, 1H), 10.62 (s, 1H), 13.59 (br s, 1H).

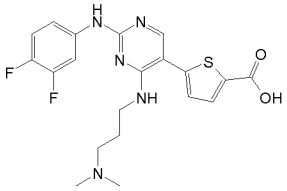
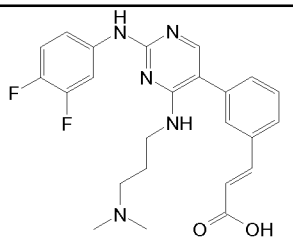
The following examples were prepared using the general method described above for **(Example 327)** using trimethyltin hydroxide and the starting material (SM) indicated.

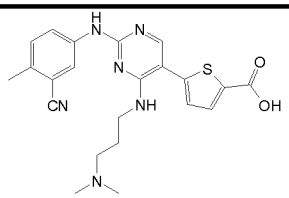
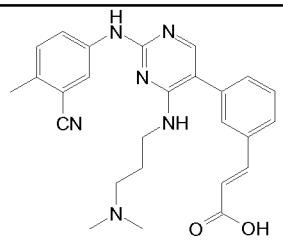
Ex	Compound	Data	SM
328	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(trifluoromethyl)-1*H*-imidazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 479 (M+1) for $C_{20}H_{11}ClF_4N_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.42 (t, *J* = 9.12 Hz, 1H), 7.70 (ddd, *J* = 2.76, 4.18, 9.08 Hz, 1H), 7.89 (t, *J* = 1.08 Hz, 1H), 8.01 (s, 1H), 8.06 (dd, *J* = 2.52, 6.76 Hz, 1H), 8.10 (t, *J* = 2.08 Hz, 1H), 8.65 (d, *J* = 2.16 Hz, 1H), 8.89 (s, 1H), 9.04 (d, *J* = 1.88 Hz, 1H), 10.49 (s, 1H).	ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(trifluoromethyl)-1*H*-imidazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate (Example 204)
329	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-1,2,3-triazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 412 (M+1) for $C_{18}H_{11}ClFN_7O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.42 (t, J = 8.80 Hz, 1H), 7.73-7.75 (m, 1H), 7.94 (s, 1H), 8.03 (m, 2H), 8.56 (s, 1H), 8.61 (s, 1H), 8.89 (s, 1H), 8.99 (s, 1H), 10.51 (br s, 1H).	ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-1,2,3-triazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylate (Example 207)

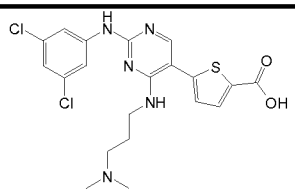
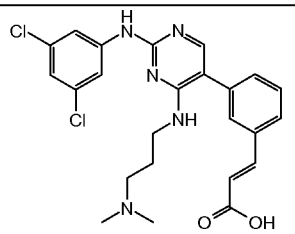
Ex	Compound	Data	SM
330	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-[1,2,3]triazolo[4,5-b]pyridin-1-yl)pyrimidin-5-yl}pyridine-3-carboxylic acid and  5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-[1,2,3]triazolo[4,5-b]pyridin-2-yl)pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 461 (M-1) for $C_{21}H_{12}ClFN_8O_2$. Mixture of regioisomers: ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.42 (t, J = 9.08 Hz, 1H), 7.56-7.59 (m, 2H), 7.78-7.81 (m, 2H), 7.95 (s, 1H), 8.11-8.13 (m, 2H), 8.18-8.20 (m, 1H), 8.43 (br s, 1H), 8.48-8.50 (m, 1H), 8.64 (s, 1H), 8.65-8.82 (m, 2H), 8.90-8.94 (m, 3H), 8.99-9.02 (m, 2H), 10.48 (br s, 1H), 10.71 (br s, 1H).	ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-[1,2,3]triazolo[4,5-b]pyridin-1-yl)pyrimidin-5-yl}pyridine-3-carboxylate and ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-[1,2,3]triazolo[4,5-b]pyridin-2-yl)pyrimidin-5-yl}pyridine-3-carboxylate **(Example 208)**
331	 (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(4,5-dichloro-1*H*-imidazol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 504 (M+1) and 506 (M+3) for $C_{22}H_{13}Cl_3FN_5O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.51 (d, *J* = 16.04 Hz, 1H), 7.10 (d, *J* = 7.80 Hz, 1H), 7.39 (d, *J* = 1.76 Hz, 1H), 7.41 (t, *J* = 8.76 Hz, 1H), 7.54 (d, *J* = 16.00 Hz, 1H), 7.55 (s, 1H), 7.66-7.70 (m, 2H), 8.04-8.07 (m, 2H), 8.97 (s, 1H), 10.54 (s, 1H).	ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(4,5-dichloro-1*H*-imidazol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoate **(Example 161)**

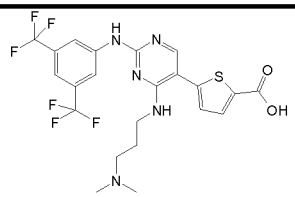
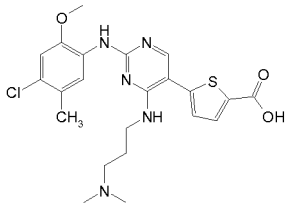
Ex	Compound	Data	SM
332	 (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(trifluoromethyl)-1*H*-imidazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 504 (M+1) for $C_{23}H_{14}ClF_4N_5O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.52 (d, *J* = 16.00 Hz, 1H), 7.24 (d, *J* = 7.84 Hz, 1H), 7.39-7.47 (m, 2H), 7.56 (d, *J* = 16.00 Hz, 1H), 7.64 (s, 1H), 7.67-7.72 (m, 2H), 7.80 (d, *J* = 1.08 Hz, 1H), 7.94 (s, 1H), 8.07 (dd, *J* = 2.52, 6.62 Hz, 1H), 8.82 (s, 1H), 10.42 (s, 1H), 12.47 (br s, 1H).	ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(trifluoromethyl)-1*H*-imidazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate **(Example 189)**
333	 (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-1,2,3-triazol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 437 (M+1) for $C_{21}H_{14}ClFN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d6): δ 6.49 (d, *J* = 16.04 Hz, 1H), 7.09 (d, *J* = 7.76 Hz, 1H), 7.36 (t, *J* = 7.76 Hz, 1H), 7.41 (t, *J* = 9.08 Hz, 1H), 7.52 (d, *J* = 15.56 Hz, 1H), 7.54 (s, 1H), 7.63 (d, *J* = 7.84 Hz, 1H), 7.70-7.74 (m, 1H), 7.92 (d, *J* = 0.88 Hz, 1H), 8.05-8.09 (m, 1H), 8.51 (s, 1H), 8.89 (s, 1H), 10.48 (s, 1H), 12.45 (br s, 1H).	ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-1,2,3-triazol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoate **(Example 192)**
334	 (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-[1,2,3]triazolo[4,5-*b*]pyridin-2-yl)pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES) : 486 (M-1) for $C_{24}H_{15}ClFN_7O_2$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.42 (d, J = 16.40 Hz, 1H), 6.94 (d, J = 8.00 Hz, 1H), 7.26 (t, J = 8.00 Hz, 1H), 7.43 (t, J = 9.20 Hz, 1H), 7.49 (d, J = 16.00 Hz, 1H), 7.58-7.61 (m, 3H), 7.75-7.77 (m, 1H), 8.18 (dd, J = 2.40, 6.40 Hz, 1H), 8.52 (d, J = 8.40 Hz, 1H), 8.92 (d, J = 2.80 Hz, 1H), 9.05 (br s, 1H), 10.68 (s, 1H), 12.42 (br s, 1H).	ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-[1,2,3]triazolo[4,5-*b*]pyridin-2-yl)pyrimidin-5-yl}phenyl)prop-2-enoate **(Example 193)**

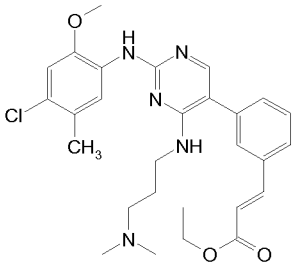
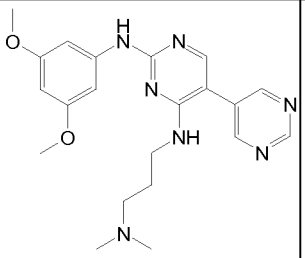
The following examples were prepared using the general method described for **Example 1** using the starting materials (SM) indicated.

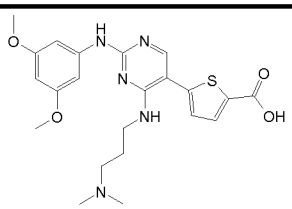
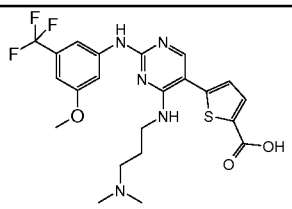
Ex	Compound	Data	SM
335	 5-(2-(3,4-difluorophenyl amino)-4-(3-(dimethyl amino)propylamino) pyrimidin-5-yl)thiophene-2-carboxylic acid	MS: ES+ 434 for $C_{20}H_{21}F_2N_5O_2S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.86 - 2.02 (m, 2 H) 2.75 (d, *J*=4.52 Hz, 6 H) 2.98 - 3.11 (m, 2 H) 3.44 (q, *J*=6.15 Hz, 2 H) 7.27 (d, *J*=3.96 Hz, 1 H) 7.35 - 7.46 (m, 2 H) 7.57 (br. s., 1 H) 7.76 (d, *J*=3.96 Hz, 1 H) 7.83 - 7.97 (m, 1 H) 8.04 (s, 1 H) 9.58 (br. s., 1 H) 10.19 (br. s., 1 H)	5-borono thiophene-2-carboxylic acid and 5-Bromo-N^2-(3,4-difluoro-phenyl)-N^4-(3-dimethylamin o-propyl)-pyrimidine-2,4-diamine hydrochlorid e salt **(Intermediat e 27)**
336	 (E)-3-(3-(2-(3,4-difluoro phenylamino)-4-(3-(dimethylamino) propylamino)pyrimid in-5-yl)phenyl)acrylic acid	MS: ES 454 for $C_{24}H_{25}F_2N_5O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.85 - 2.00 (m, 2 H) 2.75 (d, *J*=4.71 Hz, 6 H) 3.04 (ddd, *J*=10.13, 5.27, 5.13 Hz, 2 H) 3.42 (q, *J*=6.09 Hz, 2 H) 6.61 (d, 1 H) 7.28 - 8.01 (m, 10 H) 9.57 (br. s., 1 H) 10.50 (br. s., 1 H)	(E)-3-(3-boronophenyl) acrylic acid and 5-Bromo-N^2-(3,4-difluoro-phenyl)-N^4-(3-dimethylamin o-propyl)-pyrimidine-2,4-diamine hydrochlorid e salt **(Intermediate 27)**

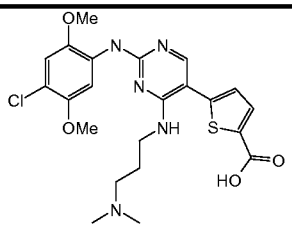
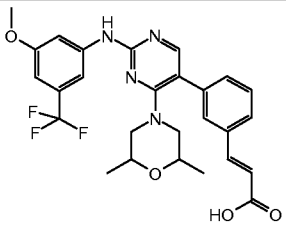
Ex	Compound	Data	SM
337	 5-(2-(3-cyano-4-methyl phenylamino)-4-(3-(dimethylamino)propyl amino)pyrimidin-5-yl) thiophene-2-carboxylic acid	MS: ES+ 437 for $C_{22}H_{24}N_6O_2S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.87 - 2.05 (m, 2 H) 2.43 (s, 3 H) 2.76 (d, *J*=4.71 Hz, 6 H) 3.08 (dt, *J*=10.31, 5.11 Hz, 2 H) 3.45 (q, *J*=6.22 Hz, 2 H) 7.26 (d, *J*=3.96 Hz, 1 H) 7.34 - 7.50 (m, 2 H) 7.69 - 7.81 (m, 2 H) 8.04 (s, 1 H) 8.28 (d, *J*=2.26 Hz, 1 H) 9.47 (br. s., 1 H) 10.03 (br. s., 1 H)	5-borono thiophene-2-carboxylic acid and 5-[5-Bromo-4-(3-dimethylamino-propylamino)-pyrimidin-2-ylamino]-2-methyl-benzonitrile **(Intermediate 28)**
338	 (E)-3-(3-(2-(3-cyano-4-methylphenylamino)-4-(3-(dimethylamino) propylamino)pyrimidin-5-yl)phenyl)acrylic acid	MS: ES+ 457 for $C_{26}H_{28}N_6O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.88 - 2.02 (m, 2 H) 2.45 (s, 3 H) 2.76 (d, *J*=4.71 Hz, 6 H) 3.07 (dt, *J*=10.27, 5.23 Hz, 2 H) 3.43 (q, *J*=6.03 Hz, 2 H) 6.61 (d, 1 H) 7.35 - 7.83 (m, 8 H) 7.91 (s, 1 H) 8.25 (d, *J*=2.07 Hz, 1 H) 9.53 (br. s., 1 H) 10.31 (br. s., 1 H)	(E)-3-(3-boronophenyl) acrylic acid and 5-[5-Bromo-4-(3-dimethylamino-propylamino)-pyrimidin-2-ylamino]-2-methyl-benzonitrile **(Intermediate 28)**

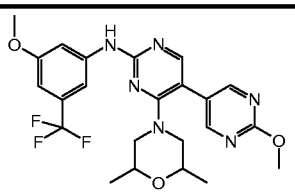
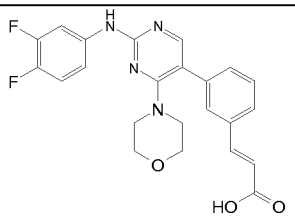
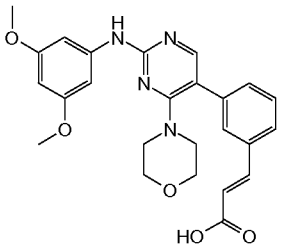
Ex	Compound	Data	SM
339	 5-(2-(3,5-dichloro phenylamino)-4-(3-(dimethylamino)propyl amino)pyrimidin-5-yl) thiophene-2-carboxylic acid	MS: ES+ 466 for $C_{20}H_{21}Cl_2N_5O_2S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.90 - 2.05 (m, 2 H) 2.76 (d, *J*=4.71 Hz, 6 H) 3.09 (ddd, *J*=10.31, 5.37, 5.23 Hz, 2 H) 3.40 - 3.52 (m, 2 H) 7.12 (t, 1 H) 7.20 - 7.31 (m, 2 H) 7.76 (d, *J*=3.77 Hz, 1 H) 7.90 (d, *J*=1.88 Hz, 2 H) 8.04 (s, 1 H) 9.37 (br. s., 1 H) 9.89 (s, 1 H)	5-borono thiophene-2-carboxylic acid and 5-Bromo-N^2-(3,5-dichloro-phenyl)-N^4-(3-dimethylamino-propyl)-pyrimidine-2,4-diamine hydrochloride salt **(Intermediate 32)**
340	 (E)-3-(3-(2-(3,5-dichloro phenylamino)-4-(3-(dimethylamino)propyl amino)pyrimidin-5-yl) phenyl)acrylic acid	MS: ES+ 486 for $C_{24}H_{25}Cl_2N_5O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.90 - 2.04 (m, 2 H) 2.76 (d, *J*=4.71 Hz, 6 H) 3.08 (dt, *J*=10.22, 5.16 Hz, 2 H) 3.44 (q, *J*=5.53 Hz, 2 H) 6.61 (d, 1 H) 7.18 (s, 1 H) 7.32 - 7.43 (m, 1 H) 7.43 - 7.49 (m, 1 H) 7.53 (t, *J*=7.82 Hz, 1 H) 7.64 (d, *J*=16.01 Hz, 1 H) 7.71 - 7.77 (m, 2 H) 7.87 (d, *J*=1.70 Hz, 2 H) 7.92 (s, 1 H) 9.45 (br. s., 1 H) 10.16 (br. s., 1 H)	(E)-3-(3-boronophenyl)acrylic acid and 5-Bromo-N^2-(3,5-dichloro-phenyl)-N^4-(3-dimethylamino-propyl)-pyrimidine-2,4-diamine hydrochloride salt **(Intermediate 32)**

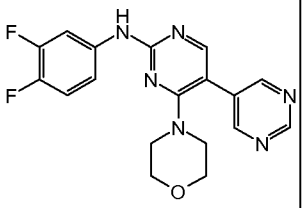
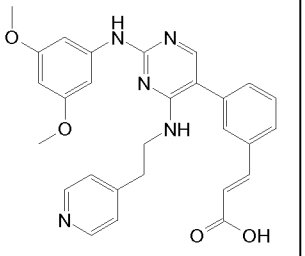
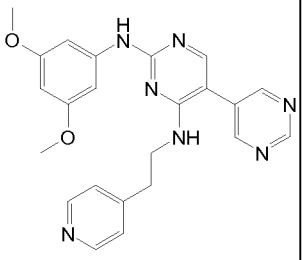
Ex	Compound	Data	SM
341	 5-(2-(3,5-bis(trifluoromethyl)phenylamino)-4-(3-(dimethylamino)propyl amino)pyrimidin-5-yl) thiophene-2-carboxylic acid	MS: ES+ 534 for $C_{22}H_{21}F_6N_5O_2S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.88 - 2.02 (m, 2 H) 2.74 (d, *J*=4.52 Hz, 6 H) 2.99 - 3.12 (m, 2 H) 3.42 - 3.56 (m, 2 H) 7.19 - 7.33 (m, 2 H) 7.59 (s, 1 H) 7.76 (d, *J*=3.77 Hz, 1 H) 8.07 (s, 1 H) 8.51 (s, 2 H) 9.47 (br. s., 1 H) 10.20 (s, 1 H)	5-borono thiophene-2-carboxylic acid and N^2-(3,5-Bis-trifluoromethyl-phenyl)-5-bromo-N^4-(3-dimethylamino-propyl)-pyrimidine-2,4-diamine **(Intermediate 33)**
342	 5-(2-(4-chloro-2-methoxy-5-methylphenylamino)-4-(3-(dimethylamino)propyl amino)pyrimidin-5-yl) thiophene-2-carboxylic acid	MS: ES+ 476 for $C_{22}H_{26}ClN_5O_3S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.83 - 1.98 (m, 2 H) 2.28 (s, 3 H) 2.74 (d, *J*=4.52 Hz, 6 H) 2.94 - 3.08 (m, 2 H) 3.42 (q, *J*=5.40 Hz, 2 H) 3.85 (s, 3 H) 7.17 (s, 1 H) 7.29 (d, *J*=3.77 Hz, 1 H) 7.77 (d, *J*=3.77 Hz, 1 H) 7.80 - 7.88 (m, 1 H) 7.93 (br. s., 1 H) 8.00 (s, 1 H) 9.04 (br. s., 1 H) 9.56 (br. s., 1 H)	5-borono thiophene-2-carboxylic acid and 5-Bromo-N^2-(4-chloro-2-methoxy-5-methyl-phenyl)-N^4-(3-dimethylamino-propyl)-pyrimidine-2,4-diamine **(Intemediate 29)**

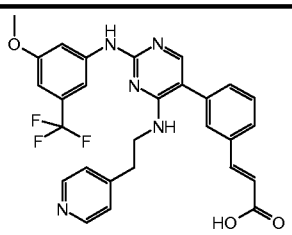
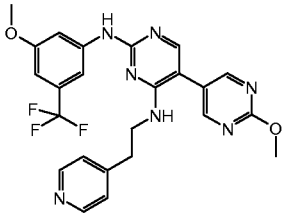
Ex	Compound	Data	SM
343	 (E)-ethyl 3-(3-(2-(4-chloro-2-methoxy-5-methyl phenylamino)-4-(3-(dimethylamino)propyl amino)pyrimidin-5-yl) phenyl)acrylate	MS: ES+ 524 for $C_{28}H_{34}ClN_5O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.25 (t, *J*=7.06 Hz, 3 H) 1.82 - 1.97 (m, 2 H) 2.30 (s, 3 H) 2.73 (d, *J*=4.52 Hz, 6 H) 3.00 (dt, *J*=9.70, 4.95 Hz, 2 H) 3.32 - 3.46 (m, 2 H) 3.86 (s, 3 H) 4.19 (q, *J*=7.10 Hz, 2 H) 6.73 (d, *J*=16.01 Hz, 1 H) 7.24 (s, 1 H) 7.43 - 7.62 (m, 2 H) 7.65 - 7.90 (m, 5 H) 8.18 (t, *J*=4.71 Hz, 1 H) 9.78 (br. s., 2 H)	(E)-3-(3-ethoxy-3-oxo prop-1-enyl) phenylboronic acid and 5-Bromo-N^2-(4-chloro-2-methoxy-5-methyl-phenyl)-N^4-(3-dimethylamino-propyl)-pyrimidine-2,4-diamine **(Intemediate 29)**
344	 N^2-(3,5-dimethoxy phenyl)-N^4-(3-(dimethyl amino)propyl)-5,5'-bi pyrimidine-2,4-diamine	MS: ES+ 410 for $C_{21}H_{27}N_7O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.84 - 2.00 (m, 2 H) 2.74 (d, *J*=4.71 Hz, 6 H) 2.95 - 3.13 (m, 2 H) 3.43 (q, 2 H) 3.75 (s, 6 H) 6.31 (s, 1 H) 6.90 (d, *J*=1.70 Hz, 2 H) 7.98 (s, 1 H) 8.10 (br. s., 1 H) 8.86 (s, 2 H) 9.25 (s, 1 H) 9.65 (br. s., 1 H) 10.36 (br. s., 1 H)	pyrimidin-5-yl boronic acid and 5-Bromo-N^2-(3,5-dimethoxy-phenyl)-N^4-(3-dimethylamino-propyl)-pyrimidine-2,4-diamine hydrochloride salt **(Intermediate 34)**

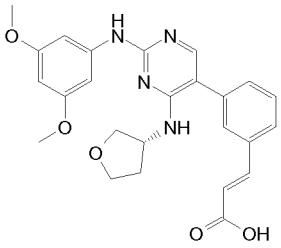
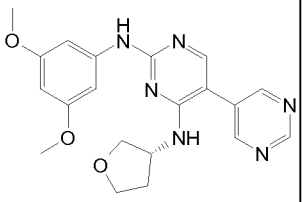
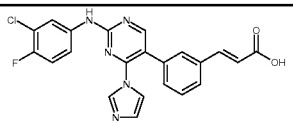
Ex	Compound	Data	SM
345	 5-(2-(3,5-dimethoxy phenylamino)-4-(3-(dimethylamino)propy amino)pyrimidin-5-yl) thiophene-2-carboxylic acid	MS: ES+ 458 for $C_{22}H_{27}N_5O_4S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.88 - 2.02 (m, 2 H) 2.74 (d, 6 H) 3.06 (dt, *J*=10.31, 5.11 Hz, 2 H) 3.46 (q, *J*=6.15 Hz, 2 H) 3.73 (s, 6 H) 6.21 (t, *J*=1.98 Hz, 1 H) 6.97 (d, *J*=2.07 Hz, 2 H) 7.26 (d, *J*=3.96 Hz, 1 H) 7.46 (br. s., 1 H) 7.76 (d, *J*=3.77 Hz, 1 H) 8.00 (s, 1 H) 9.46 (br. s., 1 H) 9.78 (br. s., 1 H)	5-borono thiophene-2-carboxylic acid and 5-Bromo-N^2-(3,5-dimethoxy-phenyl)-N^4-(3-dimethylamino-propyl)-pyrimidine-2,4-diamine hydrochloride salt **(Intermediate 34)**
346	 5-{4-[3-(dimethylamino) propylamino]-2-[3-methoxy-5-(trifluoromethyl) phenylamino]pyrimidin-5-yl}thiophene-2-carboxylic acid	MS: ES+ 496 for $C_{22}H_{24}F_3N_5O_3S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.88 - 2.02 (m, 2 H) 2.74 (d, *J*=4.71 Hz, 6 H) 3.06 (dt, *J*=10.41, 5.25 Hz, 2 H) 3.47 (q, *J*=5.53 Hz, 2 H) 3.82 (s, 3 H) 6.84 (s, 1 H) 7.23 - 7.34 (m, 2 H) 7.62 (s, 1 H) 7.76 (d, *J*=3.77 Hz, 1 H) 7.86 (s, 1 H) 8.04 (s, 1 H) 9.39 (br. s., 1 H) 9.92 (s, 1 H)	5-borono thiophene-2-carboxylic acid and 5-Bromo-N^4-(3-dimethylamino-propyl)-N^2-(3-methoxy-5-trifluoromethyl-phenyl)-pyrimidine-2,4-diamine **(Intermediate 31)**

Ex	Compound	Data	SM
347	 5-(2-(4-chloro-2,5-dimethoxyphenylamino)-4-(3-(dimethylamino) propylamino)pyrimidin-5-yl)thiophene-2-carboxylic acid	MS: ES+ 492 for $C_{22}H_{26}ClN_5O_4S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.84 - 1.97 (m, 2 H) 2.73 (d, *J*=4.52 Hz, 6 H) 2.94 - 3.06 (m, 2 H) 3.46 (q, *J*=6.09 Hz, 2 H) 3.82 (d, *J*=6.59 Hz, 6 H) 7.20 (s, 1 H) 7.28 (d, *J*=3.77 Hz, 1 H) 7.64 (br. s., 1 H) 7.77 (d, *J*=3.96 Hz, 1 H) 7.95 (br. s., 1 H) 8.02 (s, 1 H) 8.76 (br. s., 1 H) 9.45 (br. s., 1 H) 13.30 (br. s., 1 H)	5-borono thiophene-2-carboxylic acid and 5-Bromo-N^2-(4-chloro-2,5-dimethoxy-phenyl)-N^4-(3-dimethylamino-propyl)-pyrimidine-2,4-diamine **(Intermediate 30)**
348	 (E)-3-(3-(4-(2,6-dimethylmorpholino) -2-(3-methoxy-5-(trifluoro methyl)phenylamino) pyrimidin-5-yl)phenyl) acrylic acid	MS: ES+ 529 for $C_{27}H_{27}F_3N_4O_4$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.91 (d, *J*=6.22 Hz, 6 H) 2.50 - 2.59 (m, 2 H) 3.44 - 3.71 (m, 4 H) 3.82 (s, 3 H) 6.62 (d, *J*=16.01 Hz, 1 H) 6.84 (s, 1 H) 7.50 (t, *J*=4.62 Hz, 3 H) 7.63 - 7.71 (m, 2 H) 7.78 (s, 1 H) 7.92 (s, 1 H) 8.08 (s, 1 H) 9.95 (s, 1 H)	(E)-3-(3-boronophenyl) acrylic acid and 5-bromo-4-(2,6-dimethylmorpholino)-N-(3-methoxy-5-(trifluoro methyl)phenyl) pyrimidin-2-amine **(Intermediate 120)**

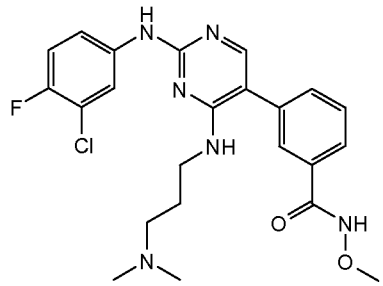
Ex	Compound	Data	SM
349	 4-(2,6-dimethyl morpholino)-2'-methoxy-N-(3-methoxy-5-(trifluoromethyl)phenyl)-5,5'-bipyrimidin-2-amine	MS: ES+ 491 for $C_{23}H_{25}F_3N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.98 (d, *J*=6.22 Hz, 6 H) 2.51 - 2.57 (m, 2 H) 3.49 - 3.67 (m, 4 H) 3.80 (s, 3 H) 3.95 (s, 3 H) 6.79 (s, 1 H) 7.57 (s, 1 H) 7.95 (s, 1 H) 8.11 (s, 1 H) 8.71 (s, 2 H) 9.80 (s, 1 H)	2-methoxy pyrimidin-5-ylboronic acid and 5-bromo-4-(2,6-dimethylmorpholino)-N-(3-methoxy-5-(trifluoro methyl)phenyl) pyrimidin-2-amine **(Intermediate 120)**
350	 (E)-3-(3-(2-(3,4-difluoro phenylamino)-4-morpholinopyrimidin-5-yl) phenyl)acrylic acid	MS: ES+ 439 for $C_{23}H_{20}F_2N_4O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.27 (br. s., 4 H) 3.55 (br. s., 4 H) 6.61 (d, *J*=16.01 Hz, 1 H) 7.27 - 7.72 (m, 7 H) 7.78 (s, 1 H) 7.83 - 7.97 (m, 1 H) 8.06 (s, 1 H) 9.86 (br. s., 1 H)	(E)-3-(3-boronophenyl)acrylic acid and 5-bromo-N-(3,4-difluorophenyl)-4-morpholinopyrimidin-2-amine **(Intermediate 122)**
351	 (E)-3-(3-(2-(3,5-dimethoxy phenylamino)-4-morpholino pyrimidin-5-yl)phenyl) acrylic acid	MS: ES+ 463 for $C_{25}H_{26}N_4O_5$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.33 - 3.42 (m, 4 H) 3.56 (d, 4 H) 3.74 (s, 6 H) 6.23 (t, *J*=2.07 Hz, 1 H) 6.63 (d, *J*=16.01 Hz, 1 H) 6.86 - 6.96 (m, 2 H) 7.51 (d, *J*=4.71 Hz, 2 H) 7.58 - 7.73 (m, 2 H) 7.79 (s, 1 H) 8.03 (s, 1 H) 9.99 (br. s., 1 H)	(E)-3-(3-boronophenyl)acrylic acid and 5-chloro-N-(3,5-dimethoxyphenyl)-4-morpholinopyrimidin-2-amine **(Intermediate 59)**

Ex	Compound	Data	SM
352	 N-(3,4-difluorophenyl)-4-morpholino-5,5'-bipyrimidin-2-amine	MS: ES+ 371 for $C_{18}H_{16}F_2N_6O$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.19 - 3.28 (m, 4 H) 3.52 - 3.62 (m, 4 H) 7.28 - 7.41 (m, 1 H) 7.42 - 7.51 (m, 1 H) 7.96 (ddd, *J*=14.08, 7.49, 2.35 Hz, 1 H) 8.17 (s, 1 H) 8.94 (s, 2 H) 9.13 (s, 1 H) 9.76 (s, 1 H)	pyrimidin-5-yl boronic acid and 5-bromo-N-(3,4-difluorophenyl)-4-morpholinopyrimidin-2-amine **(Intermediate 122)**
353	 (E)-3-(3-(2-(3,5-dimethoxyphenylamino)-4-(2-(pyridin-4-yl) ethylamino) pyrimidin-5-yl)phenyl) acrylic acid	MS: ES+ 498 for $C_{28}H_{27}N_5O_4$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.08 (t, 2 H) 3.64 - 3.78 (m, 8 H) 6.35 (t, 1 H) 6.59 (d, *J*=16.01 Hz, 1 H) 6.83 (d, *J*=2.07 Hz, 2 H) 7.37 (d, *J*=7.72 Hz, 1 H) 7.53 (t, *J*=7.72 Hz, 1 H) 7.57 - 7.71 (m, 4 H) 7.78 (d, *J*=7.91 Hz, 1 H) 7.87 (s, 1 H) 8.07 (br. s., 1 H) 8.70 (d, *J*=6.40 Hz, 2 H) 10.46 (s, 1 H)	(E)-3-(3-boronophenyl)acrylic acid and 5-bromo-N^2-(3,5-dimethoxyphenyl)-N^4-(2-(pyridin-4-yl)ethyl) pyrimidine-2,4-diamine **(Intermediate 57)**
354	 N^2-(3,5-dimethoxyphenyl)-N^4-(2-(pyridin-4-yl)ethyl)-5,5'-bipyrimidine-2,4-diamine	MS: ES+ 430 for $C_{23}H_{23}N_7O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.10 (t, 2 H) 3.63 - 3.78 (m, 8 H) 6.32 (t, *J*=1.98 Hz, 1 H) 6.86 (d, *J*=2.07 Hz, 2 H) 7.74 (d, *J*=6.22 Hz, 2 H) 7.97 (s, 1 H) 8.12 (br. s., 1 H) 8.65 - 8.83 (m, 4 H) 9.24 (s, 1 H) 10.36 (br. s., 1 H)	pyrimidin-5-ylboronic acid and 5-bromo-N^2-(3,5-dimethoxyphenyl)-N^4-(2-(pyridin-4-yl)ethyl) pyrimidine-2,4-diamine **(Intermediate 57)**

Ex	Compound	Data	SM
355	 (E)-3-(3-(2-(3-methoxy-5-(trifluoromethyl)phenyl amino)-4-(2-(pyridin-4-yl) ethylamino) pyrimidin-5-yl)phenyl) acrylic acid	MS: ES+ 536 for $C_{28}H_{24}F_3N_5O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.11 (t, 2 H) 3.72 (q, *J*=6.41 Hz, 2 H) 3.81 (s, 3 H) 6.57 (d, *J*=16.01 Hz, 1 H) 6.95 (s, 1 H) 7.36 (d, *J*=7.91 Hz, 1 H) 7.44 - 7.80 (m, 10 H) 7.92 (s, 1 H) 8.72 (d, *J*=6.41 Hz, 2 H) 10.46 (br. s., 1 H)	(E)-3-(3-boronophenyl)acrylic acid and 5-bromo-N^2-(3-methoxy-5-(trifluoromethyl)phenyl)-N^4-(2-(pyridin-4-yl) ethyl)pyrimidine-2,4-diamine **(Intermediate 121)**
356	 2'-methoxy-N^2-(3-methoxy-5-(trifluoromethyl)phenyl)-N^4-(2-(pyridin-4-yl)ethyl)-5,5'-bipyrimidine-2,4-diamine	MS: ES+ 498 for $C_{24}H_{22}F_3N_7O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.14 (t, 2 H) 3.71 (q, *J*=5.97 Hz, 2 H) 3.79 - 3.87 (m, 3 H) 3.95 (s, 3 H) 7.01 (s, 1 H) 7.47 (s, 1 H) 7.73 (s, 1 H) 7.85 (d, *J*=6.41 Hz, 2 H) 8.01 (s, 1 H) 8.19 (br. s., 1 H) 8.49 - 8.58 (m, 2 H) 8.81 (d, *J*=6.40 Hz, 2 H) 11.08 (br. s., 1 H)	2-methoxy pyrimidin-5-ylboronic acid and 5-bromo-N^2-(3-methoxy-5-(trifluoromethyl)phenyl)-N^4-(2-(pyridin-4-yl) ethyl)pyrimidine-2,4-diamine **(Intermediate 121)**

Ex	Compound	Data	SM
357	 (R,E)-3-(3-(2-(3,5-dimethoxyphenylamino)-4-(tetrahydrofuran-3-ylamino)pyrimidin-5-yl)phenyl)acrylic acid	MS: ES+ 463 for $C_{25}H_{26}N_4O_5$. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.90 - 2.05 (m, 1 H) 2.08 - 2.23 (m, 1 H) 3.49 - 3.93 (m, 10 H) 4.57 - 4.77 (m, 1 H) 6.32 (t, 1 H) 6.60 (d, *J*=16.01 Hz, 1 H) 6.77 - 6.91 (m, 2 H) 7.35 - 8.03 (m, 7 H) 10.24 (br. s., 1 H)	(E)-3-(3-boronophenyl)acrylic acid and (R)-5-bromo-N^2-(3,5-dimethoxyphenyl)-N^4-(tetrahydrofuran-3-yl)pyrimidine-2,4-diamine **(Intermediate 58)**
358	 (R)-N^2-(3,5-dimethoxyphenyl)-N^4-(tetrahydrofuran-3-yl)-5,5'-bipyrimidine-2,4-diamine	MS: ES+ 395 for $C_{20}H_{22}N_6O_3$. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.86 - 2.00 (m, 1 H) 2.07 - 2.30 (m, *J*=12.72, 6.88 Hz, 1 H) 3.52 - 3.95 (m, 9 H) 4.55 - 4.71 (m, 2 H) 6.29 (s, 1 H) 6.89 (s, 2 H) 7.92 (s, 1 H) 7.97 - 8.12 (m, 1 H) 8.81 (s, 2 H) 9.23 (s, 1 H) 10.24 (s, 1 H)	pyrimidin-5-ylboronic acid and (R)-5-bromo-N^2-(3,5-dimethoxyphenyl)-N^4-(tetrahydrofuran-3-yl)pyrimidine-2,4-diamine **(Intermediate 58)**
359	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(1*H*-imidazol-1-yl)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 436 (M+1) for $C_{22}H_{15}ClFN_5O_2$ ^{1}H NMR (300 MHz, DMSO- *d6*) δ ppm 6.53 (d, J=16.01 Hz, 1 H) 6.98 (s, 1 H) 7.14 (s, 1 H) 7.25 (d, J=7.91 Hz, 1 H) 7.32 - 7.51 (m, 2 H) 7.50 - 7.84 (m, 5 H) 8.07 (dd, J=6.78, 2.64 Hz, 1 H) 8.70 (s, 1 H) 10.30 (s, 1 H) 12.46 (s, 1 H)	(E)-3-(3-boronophenyl)acrylic acid and 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-(1*H*-imidazol-1-yl)pyrimidin-2-amine **(Intermediate 118)**

Example 360: 3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino)propylamino)pyrimidin-5-yl)-N-methoxybenzamide

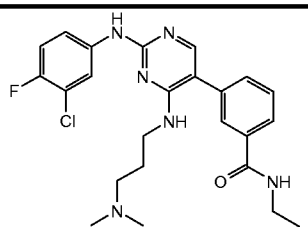
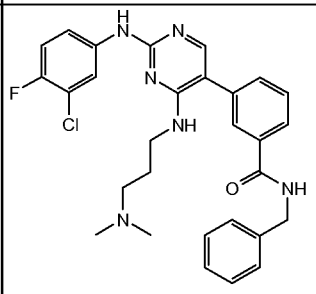
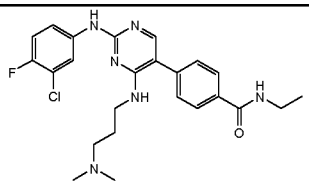


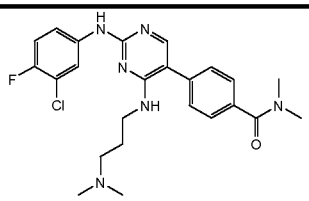
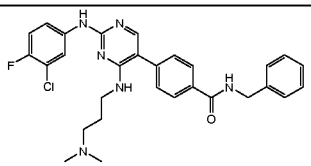
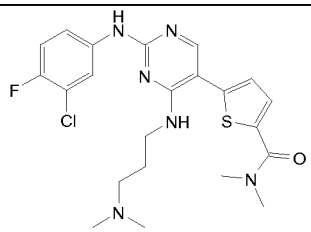
To a stirred solution of 3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[3-(dimethylamino)propyl]amino}pyrimidin-5-yl)benzoic acid (**Example 31**, 52 mg, 0.12 mmol) and triethylamine (0.057 ml, 0.4 mmol) in DMF (1.5 ml) under ambient conditions was added O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU; 44 mg, 0.12 mmol) as a solid. The mixture was stirred for 10 minutes; to it was then added methoxylamine hydrochloride (8 mg, 0.12 mmol) as a solid. The mixture was stirred until complete conversion was seen by LCMS. The reaction mixture was diluted with 1-3 mL water while stirring continued; a light pink precipitate formed. Stirring continued for several minutes, and the vessel was then transferred to an ice bath for 10 minutes. 3-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(dimethylamino)propylamino)pyrimidin-5-yl)-N-methoxybenzamide was collected (22 mg) and characterized by LCMS and ^{1}H NMR.

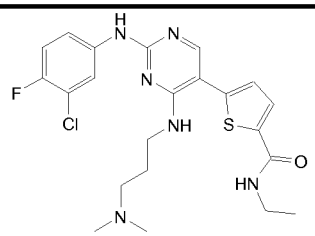
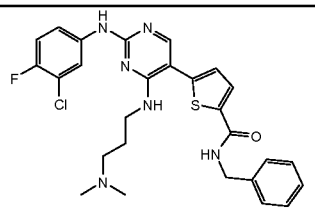
MS: ES+ 473 for $C_{23}H_{26}ClFN_6O_2$

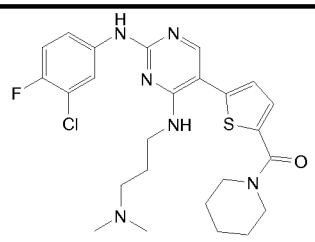
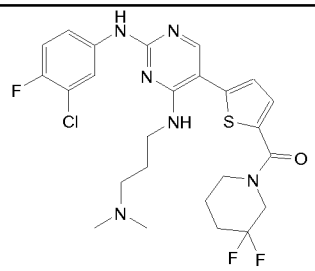
^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.84 - 2.01 (m, 2 H) 2.76 (d, *J*=4.71 Hz, 6 H) 2.97 - 3.12 (m, 2 H) 3.35 - 3.49 (m, 2 H) 3.72 (s, 3 H) 7.42 (t, *J*=9.04 Hz, 1 H) 7.50 - 7.64 (m, 4 H) 7.76 - 7.84 (m, 2 H) 7.89 (s, 1 H) 8.07 (dd, *J*=6.78, 2.64 Hz, 1 H) 9.50 (s, 1 H) 10.22 (s, 1 H) 11.84 (s, 1 H)

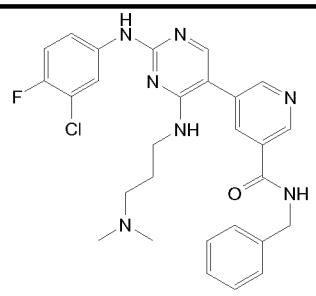
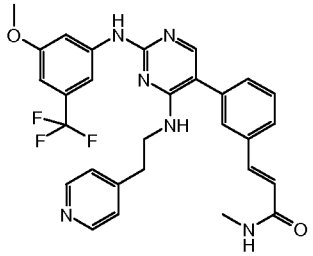
The following examples were prepared using the general HATU coupling method described above for **Example 360** using the starting materials (SM) indicated.

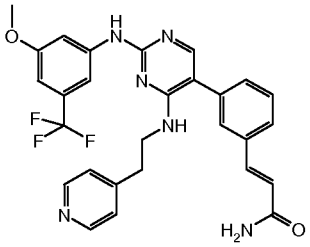
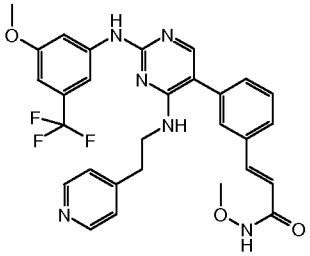
Ex	Compound	Data	SM
361	 3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino) propylamino) pyrimidin-5-yl)-N-ethylbenzamide	MS: ES+ 471 for $C_{24}H_{28}ClFN_6O$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.11 (t, *J*=7.25 Hz, 3 H) 1.59 - 1.75 (m, 2 H) 1.94 (s, 6 H) 2.28 (t, *J*=6.41 Hz, 2 H) 3.18 - 3.36 (m, 2 H) 3.37 - 3.53 (m, 2 H) 7.22 - 7.34 (m, 2 H) 7.44 - 7.68 (m, 3 H) 7.77 - 7.87 (m, 3 H) 8.26 (dd, *J*=6.97, 2.64 Hz, 1 H) 8.50 (t, *J*=5.46 Hz, 1 H) 9.39 (s, 1 H)	Ethylamine and 3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[3-(dimethylamino)propyl]amino}pyrimidin-5-yl)benzoic acid **(Example 31)**
362	 N-benzyl-3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino) propylamino) pyrimidin-5-yl) benzamide	MS: ES+ 533 for $C_{29}H_{30}ClFN_6O$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.56 - 1.75 (m, 2 H) 1.92 (s, 6 H) 2.27 (t, *J*=6.31 Hz, 2 H) 3.37 - 3.51 (m, 2 H) 4.48 (d, *J*=6.03 Hz, 2 H) 7.19 - 7.37 (m, 7 H) 7.48 - 7.58 (m, 2 H) 7.58 - 7.67 (m, 1 H) 7.82 (s, 1 H) 7.85 - 7.92 (m, 2 H) 8.26 (dd, *J*=6.88, 2.54 Hz, 1 H) 9.09 (t, *J*=6.03 Hz, 1 H) 9.39 (s, 1 H)	Benzylamine and 3-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[3-(dimethylamino)propyl]amino}pyrimidin-5-yl)benzoic acid **(Example 31)**
363	 4-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino) propylamino) pyrimidin-5-yl)-N-ethylbenzamide	MS: ES+ 471 for $C_{24}H_{28}ClFN_6O$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.12 (t, *J*=7.16 Hz, 3 H) 1.60 - 1.74 (m, 2 H) 1.98 (s, 6 H) 2.29 (t, *J*=6.41 Hz, 2 H) 3.22 - 3.37 (m, 2 H) 3.43 (q, *J*=6.22 Hz, 2 H) 7.22 - 7.34 (m, 2 H) 7.38 - 7.49 (m, 2 H) 7.57 - 7.67 (m, 1 H) 7.80 (s, 1 H) 7.93 (d, *J*=8.29 Hz, 2 H) 8.25 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.51 (t, *J*=5.56 Hz, 1 H) 9.40 (s, 1 H)	ethylamine and 4-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[3-(dimethylamino)propyl]amino}pyrimidin-5-yl)benzoic acid **(Example 30)**

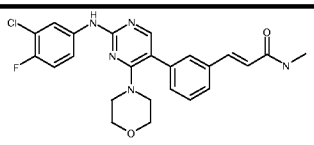
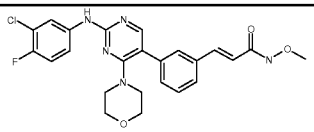
Ex	Compound	Data	SM
364	 4-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino) propylamino) pyrimidin-5-yl)-N,N-dimethylbenzamide	MS: ES+ 471 for $C_{24}H_{28}ClFN_6O$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.91 - 2.07 (m, 2 H) 2.68 (s, 3 H) 2.75 (s, 6 H) 2.98 - 3.02 (m, 2 H) 3.06 (s, 3 H) 3.44 - 3.60 (m, 2 H) 7.00 (t, *J*=5.46 Hz, 1 H) 7.39 (t, *J*=9.14 Hz, 1 H) 7.48 - 7.59 (m, 3 H) 7.64 - 7.73 (m, 1 H) 7.90 (s, 1 H) 8.28 (dd, *J*=6.88, 2.54 Hz, 1 H) 9.50 (s, 1 H) 11.76 (s, 1 H)	Dimethylamine and 4-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[3-(dimethylamino)propyl]amino}pyrimidin-5-yl)benzoic acid **(Example 30)**
365	 N-benzyl-4-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino) propylamino) pyrimidin-5-yl) benzamide	MS: ES+ 533 for $C_{29}H_{30}ClFN_6O$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.62 - 1.73 (m, 2 H) 1.97 (s, 6 H) 2.28 (t, *J*=6.31 Hz, 2 H) 3.38 - 3.50 (m, 2 H) 4.51 (d, *J*=6.03 Hz, 2 H) 7.19 - 7.36 (m, 7 H) 7.47 (d, *J*=8.29 Hz, 2 H) 7.57 - 7.67 (m, 1 H) 7.81 (s, 1 H) 8.00 (d, *J*=8.48 Hz, 2 H) 8.25 (dd, *J*=6.97, 2.64 Hz, 1 H) 9.11 (t, *J*=6.03 Hz, 1 H) 9.41 (s, 1 H)	benzylamine and 4-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[3-(dimethylamino)propyl]amino}pyrimidin-5-yl)benzoic acid **(Example 30)**
366	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino) propylamino) pyrimidin-5-yl)-N,N-dimethylthiophene-2-carboxamide	MS: ES+ 477 for $C_{22}H_{26}ClFN_6OS$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.65 - 1.79 (m, 2 H) 2.05 (s, 6 H) 2.33 (t, *J*=6.12 Hz, 2 H) 2.47 - 2.57 (m, 3 H) 3.34 (s, 3 H) 3.48 (q, *J*=5.97 Hz, 2 H) 7.13 (d, *J*=3.77 Hz, 1 H) 7.30 (t, *J*=9.14 Hz, 1 H) 7.49 - 7.71 (m, 3 H) 7.95 (s, 1 H) 8.23 (dd, *J*=6.78, 2.26 Hz, 1 H) 9.53 (s, 1 H)	dimethylamine and 5-{2-(3-chloro-4-fluorophenylamino)-4-[3-(dimethylamino) propylamino] pyrimidin-5-yl} thiophene-2-carboxylic acid **(Example 17)**

Ex	Compound	Data	SM
367	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino) propylamino) pyrimidin-5-yl)-N-ethylthiophene-2-carboxamide	MS: ES+ 477 for $C_{22}H_{26}ClFN_6OS$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.11 (t, *J*=7.16 Hz, 3 H) 1.64 - 1.76 (m, 2 H) 2.03 (s, 6 H) 2.32 (t, *J*=6.31 Hz, 2 H) 3.20 - 3.31 (m, 2 H) 3.46 (q, *J*=6.03 Hz, 2 H) 7.12 (d, *J*=3.77 Hz, 1 H) 7.23 - 7.35 (m, 1 H) 7.45 - 7.66 (m, 2 H) 7.74 (d, *J*=3.77 Hz, 1 H) 7.92 (s, 1 H) 8.21 (dd, *J*=6.97, 2.64 Hz, 1 H) 8.50 (t, *J*=5.56 Hz, 1 H) 9.51 (s, 1 H)	ethylamine and 5-{2-(3-chloro-4-fluorophenyl amino)-4-[3-(dimethylami no) propylamino] pyrimidin-5-yl} thiophene-2-carboxylic acid **(Example 17)**
368	 N-benzyl-5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino) propylamino) pyrimidin-5-yl) thiophene-2-carboxamide	MS: ES+ 539 for $C_{27}H_{28}ClFN_6OS$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.61 - 1.77 (m, 2 H) 2.03 (s, 6 H) 2.31 (t, *J*=6.22 Hz, 2 H) 3.45 (q, *J*=5.90 Hz, 2 H) 4.46 (d, *J*=5.84 Hz, 2 H) 7.15 (d, *J*=3.77 Hz, 1 H) 7.19 - 7.39 (m, 6 H) 7.44 - 7.66 (m, 2 H) 7.83 (d, *J*=3.96 Hz, 1 H) 7.93 (s, 1 H) 8.22 (dd, *J*=6.97, 2.45 Hz, 1 H) 9.08 (t, *J*=6.03 Hz, 1 H) 9.51 (s, 1 H)	benzylamine and 5-{2-(3-chloro-4-fluorophenyl amino)-4-[3-(dimethylami no) propylamino] pyrimidin-5-yl} thiophene-2-carboxylic acid **(Example 17)**

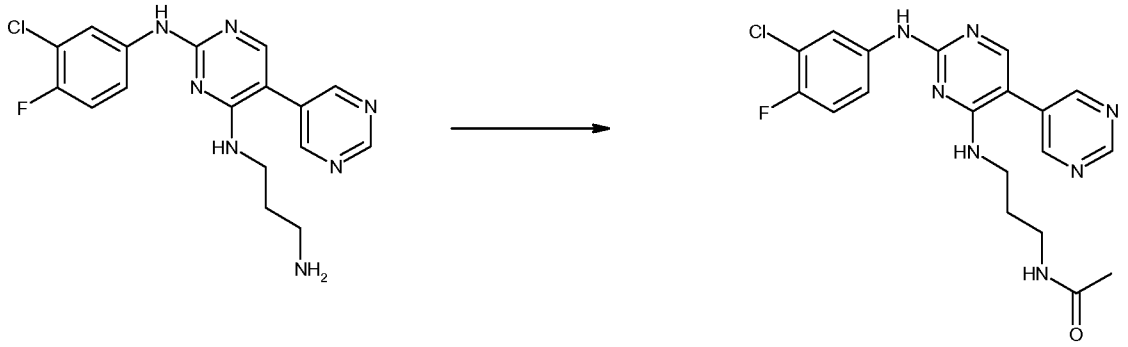
Ex	Compound	Data	SM
369	 (5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino) propylamino) pyrimidin-5-yl) thiophen-2-yl) (piperidin-1-yl) methanone	MS: ES+ 517 for $C_{25}H_{30}ClFN_6OS$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.46 - 1.76 (m, 8 H) 2.04 (s, 6 H) 2.32 (t, *J*=6.31 Hz, 2 H) 3.41 - 3.51 (m, 2 H) 3.57 - 3.68 (m, 4 H) 7.10 (d, *J*=3.58 Hz, 1 H) 7.29 (t, *J*=9.14 Hz, 1 H) 7.39 (d, *J*=3.77 Hz, 1 H) 7.53 (t, *J*=4.80 Hz, 1 H) 7.57 - 7.66 (m, 1 H) 7.93 (s, 1 H) 8.22 (dd, *J*=6.88, 2.54 Hz, 1 H) 9.51 (s, 1 H)	piperidine and 5-{2-(3-chloro-4-fluorophenyl amino)-4-[3-(dimethylami no) propylamino] pyrimidin-5-yl} thiophene-2-carboxylic acid **(Example 17)**
370	 (5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino) propylamino) pyrimidin-5-yl)thiophen-2-yl) (3,3-difluoro piperidin-1-yl) methanone	MS: ES+ 553 for $C_{25}H_{28}ClF_3N_6OS$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.65 - 1.80 (m, 4 H) 2.04 (s, 6 H) 2.08 - 2.20 (m, 2 H) 2.32 (t, *J*=6.31 Hz, 2 H) 3.46 (q, *J*=6.03 Hz, 2 H) 3.70 (br. s., 2 H) 3.99 (t, *J*=11.87 Hz, 2 H) 7.14 (d, *J*=3.77 Hz, 1 H) 7.29 (t, *J*=9.14 Hz, 1 H) 7.48 (d, *J*=3.77 Hz, 1 H) 7.52 - 7.66 (m, 2 H) 7.95 (s, 1 H) 8.21 (dd, *J*=6.97, 2.64 Hz, 1 H) 9.53 (s, 1 H)	3,3-difluoropiperid ine and 5-{2-(3-chloro-4-fluorophenyl amino)-4-[3-(dimethylami no) propylamino] pyrimidin-5-yl} thiophene-2-carboxylic acid **(Example 17)**

Ex	Compound	Data	SM
371	 N-benzyl-5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino) propylamino) pyrimidin-5-yl) nicotinamide	MS: ES+ 534 for $C_{28}H_{29}ClFN_7O$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.85 - 2.00 (m, 2 H) 2.73 (d, *J*=4.71 Hz, 6 H) 2.98 - 3.09 (m, 2 H) 3.33 - 3.47 (m, 2 H) 4.53 (d, *J*=5.84 Hz, 2 H) 7.15 - 7.62 (m, 7 H) 7.92 - 8.39 (m, 4 H) 8.77 (d, *J*=1.88 Hz, 1 H) 9.13 (d, *J*=1.88 Hz, 1 H) 9.34 (t, *J*=5.93 Hz, 1 H) 9.85 (s, 1 H) 10.82 (s, 1 H)	benzylamine and 5-(2-(3-chloro-4-fluorophenyl amino)-4-(3-(dimethylamino)propylamino)pyrimidin-5-yl)nicotinic acid (Example 214)
372	 (E)-3-(3-(2-(3-methoxy-5-(trifluoromethyl)phenyl amino)-4-(2-(pyridin-4-yl) ethylamino)pyrimidin-5-yl) phenyl)-N-methyl acrylamide	MS: ES+ 549 for $C_{29}H_{27}F_3N_6O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.71 (d, 3 H) 3.12 (t, *J*=6.69 Hz, 2 H) 3.72 (q, *J*=6.41 Hz, 2 H) 3.82 (s, 3 H) 6.63 (d, 1 H) 6.98 (s, 1 H) 7.27 - 7.55 (m, 5 H) 7.63 (d, *J*=7.91 Hz, 1 H) 7.70 - 7.87 (m, 4 H) 7.92 (s, 1 H) 8.07 - 8.16 (m, 1 H) 8.75 (d, 2 H) 10.55 (br. s., 1 H)	methylamine and (E)-3-(3-(2-(3-methoxy-5-(trifluoromethyl)phenyl amino)-4-(2-(pyridin-4-yl) ethylamino) pyrimidin-5-yl)phenyl) acrylic acid (Example 355)

Ex	Compound	Data	SM
373	 (E)-3-(3-(2-(3-methoxy-5-(trifluoromethyl)phenylamino)-4-(2-(pyridin-4-yl) ethylamino)pyrimidin-5-yl) phenyl)acrylamide	MS: ES+ 535 for $C_{28}H_{25}F_3N_6O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.10 (t, 2 H) 3.71 (q, *J*=6.28 Hz, 2 H) 3.81 (s, 3 H) 6.63 (d, 1 H) 6.94 (s, 1 H) 7.10 - 7.82 (m, 12 H) 7.90 (s, 1 H) 8.72 (d, *J*=6.22 Hz, 2 H) 10.32 (br. s., 1 H)	ammonia (0.5M) in dioxane and (E)-3-(3-(2-(3-methoxy-5-(trifluoromethyl)phenylamino)-4-(2-(pyridin-4-yl) ethylamino) pyrimidin-5-yl)phenyl) acrylic acid **(Example 355)**
374	 (E)-N-methoxy-3-(3-(2-(3-methoxy-5-(trifluoromethyl)phenylamino)-4-(2-(pyridin-4-yl) ethylamino)pyrimidin-5-yl)phenyl)acrylamide	MS: ES+ 565 for $C_{29}H_{27}F_3N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.14 (t, 2 H) 3.67 (s, 3 H) 3.73 (q, *J*=6.22 Hz, 2 H) 3.82 (s, 3 H) 7.00 (s, 1 H) 7.34 (d, *J*=7.54 Hz, 1 H) 7.45 - 7.57 (m, 5 H) 7.61 - 7.74 (m, 3 H) 7.79 (d, *J*=6.22 Hz, 2 H) 7.95 (s, 2 H) 8.77 (d, *J*=6.22 Hz, 2 H) 10.81 (br. s., 1 H)	methoxyl amine hydrochloride and (E)-3-(3-(2-(3-methoxy-5-(trifluoromethyl)phenylamino)-4-(2-(pyridin-4-yl) ethylamino) pyrimidin-5-yl)phenyl) acrylic acid **(Example 355)**

Ex	Compound	Data	SM
375	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)phenyl)-N-methylacrylamide	MS(ES): 468 (M+1) for $C_{24}H_{23}ClFN_5O_2$ ^{1}H NMR (300 MHz, DMSO-*d*6) d ppm 2.70 (d, J=4.52 Hz, 3 H) 3.23 (m, 4 H) 3.54 (m, 4 H) 6.65 (d, J=15.82 Hz, 1 H) 7.32 (t, J=9.04 Hz, 1 H) 7.38 - 7.57 (m, 4 H) 7.57 - 7.75 (m, 2 H) 7.94 - 8.11 (m, 2 H) 8.14 (dd, J=6.97, 2.64 Hz, 1 H) 9.63 (s, 1 H)	Methylamine and (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)phenyl)acrylic acid **(Example 290)**
376	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)phenyl)-N-methoxyacrylamide	MS(ES): 484 (M+1) for $C_{24}H_{23}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-*d*6) d ppm 3.23 (d, J=3.39 Hz, 4 H) 3.54 (d, J=3.96 Hz, 4 H) 3.66 (s, 3 H) 6.47 (d, J=15.26 Hz, 1 H) 7.32 (t, J=9.14 Hz, 1 H) 7.41 - 7.77 (m, 6 H) 8.07 (s, 1 H) 8.14 (dd, J=6.78, 2.45 Hz, 1 H) 9.63 (s, 1 H) 11.31 (s, 1 H)	Methoxylamine hydrochloride and (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)phenyl)acrylic acid **(Example 290)**

Example 377: N-(3-(2-(3-chloro-4-fluorophenylamino)-5,5'-bipyrimidin-4-ylamino)propyl)acetamide



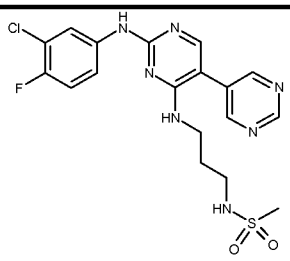
A solution of acetic anhydride (0.012 ml, 0.13 mmol) was added to N'-(3-aminopropyl)-N-(3-chloro-4-fluorophenyl)-5-pyrimidin-5-ylpyrimidine-2,4-diamine hydrochloride (**Example 211**, 53

mg, 0.13 mmol), triethylamine (0.054ml, 0.39 mmol) and methylene chloride (1.5 ml) under nitrogen. The resultant mixture was stirred for 1h, then concentrated under vacuum. The residue was chromatographed using 1-10% methanol/methylene chloride to yield the title compound (38 mg).

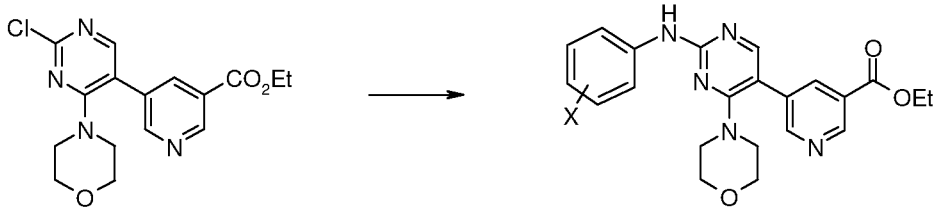
MS(ES): 416 (M+1) for $C_{19}H_{19}ClFN_7O$

^{1}H NMR (300 MHz, DMSO- *d*6) δ ppm 1.53 - 1.73 (m, 2 H) 1.75 (s, 3 H) 3.05 (q, J=6.03 Hz, 2 H) 3.21 - 3.49 (m, 2 H) 7.41 (t, J=9.04 Hz, 1 H) 7.49 - 7.66 (m, 1 H) 7.68 - 7.98 (m, 3 H) 8.06 (dd, J=6.78, 2.64 Hz, 1 H) 8.83 (s, 2 H) 9.23 (s, 1 H) 10.05 (s, 1 H).

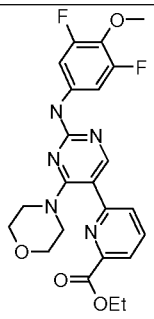
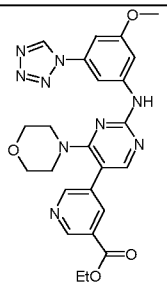
The following examples were prepared by the general method described above for **Example 377** using the starting materials (SM) indicated.

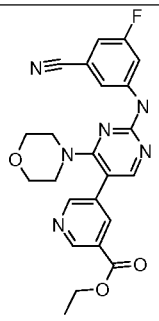
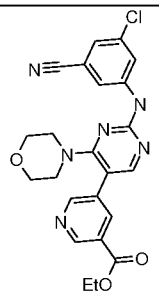
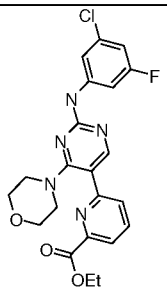
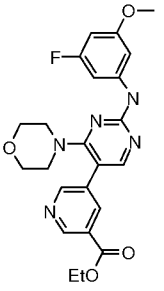
Ex	Compound	Data	SM
378	 N-(3-(2-(3-chloro-4-fluorophenylamino)-5,5'-bipyrimidin-4-ylamino)propyl)methanesulfonamide	MS(ES): 452 (M+1) for $C_{18}H_{19}ClFN_7O_2S$ ^{1}H NMR (300 MHz, DMSO- *d*6) δ ppm 1.61 - 1.94 (m, 2 H) 2.86 (s, 3 H) 2.99 (q, J=6.47 Hz, 2 H) 3.37 - 3.50 (m, 2 H) 6.96 (t, J=5.84 Hz, 1 H) 7.00 - 7.19 (m, 1 H) 7.33 (t, J=9.14 Hz, 1 H) 7.52 - 7.77 (m, 1 H) 7.86 (s, 1 H) 8.18 (dd, J=6.88, 2.17 Hz, 1 H) 8.81 (s, 2 H) 9.17 (s, 1 H) 9.55 (s, 1 H)	methanesulfonyl chloride and N^4-(3-aminopropyl)-N^2-(3-chloro-4-fluorophenyl)-5,5'-bipyrimidine-2,4-diamine **(Example 211)**

General procedure for the coupling of anilines to Intermediate 137



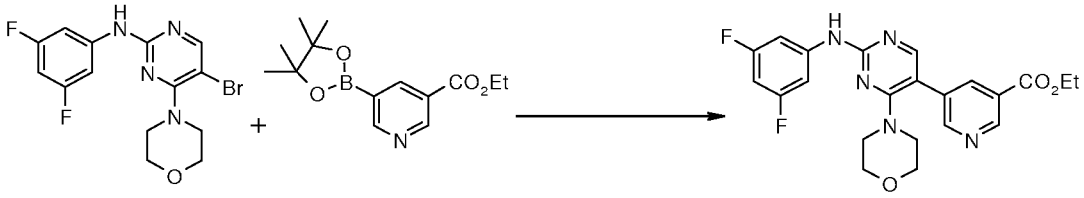
Intermediate 137 (1 eq) was suspended in a suitable solvent (e.g. acetonitrile, dioxane, or ethanol) (20 vol) and treated with the corresponding aniline (1 eq). The reaction was then treated with 4 N HCl (5 vol) in dioxane and refluxed under nitrogen. The reaction was monitored by TLC and then cooled to room temperature, diluted with diethyl ether and the solid was filtered and dried to afford the product. The compounds in the below table were prepared using this method with the specified starting material and solvent.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
6-[2-(3,5-Difluoro-4-methoxy-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-pyridine-2-carboxylic acid ethyl ester **Example 379**[a]		MS(ES): 472 (M+1) for $C_{23}H_{23}F_2N_5O_4$. 400 MHz, DMSO-d_6: δ 1.18 (t, *J* = 6.80 Hz, 3H), 3.22-3.23 (m, 4H), 3.56-3.58 (m, 4H), 3.85 (s, 3H), 4.38 (q, *J* = 7.20 Hz, 2H), 7.58 (d, *J* = 11.60 Hz, 2H), 8.20 (s, 1H), 8.40 (t, *J* = 2.00 Hz, 1H), 8.94 (d, *J* = 2.00 Hz, 1H), 9.02 (d, *J* = 1.60 Hz, 1H), 9.79 (s, 1H).	3,5-Difluoro-4-methoxy-phenylamine
5-[2-(3-Methoxy-5-tetrazol-1-yl-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester **Example 380**[a]		MS(ES): 504.2 (M+1) for $C_{24}H_{25}N_9O_4$. 400 MHz, DMSO-d_6 : δ 1.35 (t, *J* = 7.04 Hz, 3H), 3.26 (d, *J* = 3.80 Hz, 4H), 3.56 (br s, 4H), 3.84 (s, 3H), 4.37 (q, *J* = 6.96 Hz, 2H), 7.11 (d, *J* = 1.80 Hz, 1H), 7.46 (s, 1H), 8.21 (s, 1H), 8.28-8.31 (m, 1H), 8.39 (t, *J* = 2.04 Hz, 1H), 8.94 (d, *J* = 2.04 Hz, 1H), 9.01 (d, *J* = 1.92 Hz, 1H), 9.93 (s, 1H), 10.09 (s, 1H).	3-Methoxy-5-tetrazol-1-yl-phenylamine Hydrochloride

5-[2-(3-Cyano-5-fluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester **Example 381**[b]		MS(ES): 449 (M+1) for $C_{23}H_{21}FN_6O_3$. 400 MHz, DMSO-d6: δ 1.34 (t, *J* = 7.04 Hz, 3H), 3.22-3.24 (m, 4H), 3.55-3.57 (m, 4H), 4.37 (q, *J* = 7.12 Hz, 2H), 7.36 (d, *J* = 9.60 Hz, 1H), 8.02 (d, *J* = 2.04 Hz, 1H), 8.04 (s, 1H), 8.24 (s, 1H), 8.39 (t, *J* = 2.12 Hz, 1H), 8.94 (d, *J* = 2.20 Hz, 1H), 9.02 (d, *J* = 2.00 Hz, 1H), 10.11 (s, 1H).	3-Amino-5-fluoro-benzonitrile
5-[2-(3-Chloro-5-cyano-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester **Example 382**[c]		MS(ES): 465.2 (M+1) for $C_{23}H_{21}ClN_6O_3$. 400 MHz, DMSO-d_6: δ 1.35 (t, *J* = 7.00 Hz, 3H), 3.25 (d, *J* = 3.96 Hz, 4H), 3.50 (t, *J* = 5.08 Hz, 4H), 4.38 (q, *J* = 7.08 Hz, 2H), 7.66 (d, *J* = 1.16 Hz, 1H), 8.10 (d, *J* = 1.12 Hz, 1H), 8.18 (s, 1H), 8.23 (d, *J* = 8.32 Hz, 1H), 8.43 (s, 1H), 8.95 (d, *J* = 1.76 Hz, 1H), 9.07 (d, *J* = 1.48 Hz, 1H), 10.64 (s, 1H).	3-Amino-5-chloro-benzonitrile
6-[2-(3-Chloro-5-fluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-pyridine-2-carboxylic acid ethyl ester **Example 383**[a]		MS(ES): 458.2 (M+1) for $C_{22}H_{21}ClFN_5O_3$. 300 MHz, DMSO-d6: δ 1.34 (t, *J* = 7.11 Hz, 3H), 3.22 (br s, 4H), 3.56 (br s, 4H), 4.37 (q, *J* = 6.96 Hz, 2H), 6.92 (d, *J* = 8.46 Hz, 1H), 7.67 (d, *J* = 12.45 Hz, 1H), 7.77 (s, 1H), 8.21 (s, 1H), 8.39 (s, 1H), 8.94 (s, 1H), 9.01 (s, 1H), 9.95 (s, 1H).	3-Chloro-5-fluoro-phenylamine
5-[2-(3-Fluoro-5-methoxy-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester Example 384[a]		MS(ES): 454 (M+1) for $C_{23}H_{24}FN_5O_4$. 400 MHz, DMSO-d_6: δ 1.36 (t, *J* = 7.20 Hz, 3H), 3.40 (br s, 4H), 3.57 (br s, 4H), 3.78 (s, 3H), 4.39 (q, *J* = 7.20 Hz, 2H), 6.61 (dd, *J* = 2.00, 11.00 Hz, 1H), 7.10-7.13 (m, 2H), 8.21 (s, 1H), 8.42 (t, *J* = 2.00 Hz, 1H), 8.94 (d, *J* = 2.00 Hz, 1H), 9.09 (d, *J* = 2.00 Hz, 1H), 10.79 (br s, 1H).	3-Fluoro-5-methoxy-phenylamine

Solvents used in the reaction (a) acetonitrile (b) ethanol (c) dioxane

Example 385: 5-[2-(3,5-Difluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester

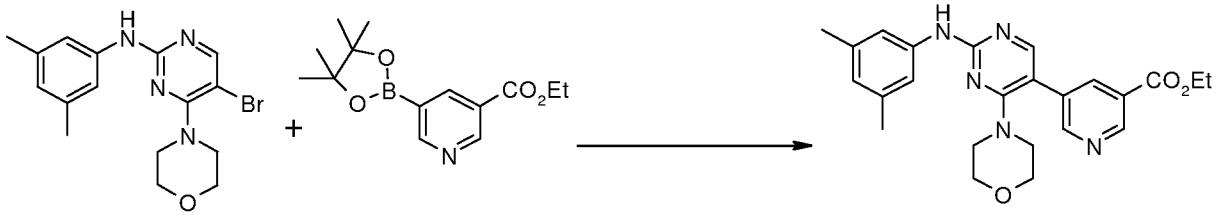


A suspension of **Intermediate 140** (1.3 mmol, 0.5 g), 3-(ethoxycarbonyl)pyridine-5-boronic acid pinacolester (1.4 mmol, 0.4 g), tris(dibenzyledeneacetone)dipalladium(0) (0.4 mmol, 0.19 g), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (0.13 mmol, 0.12 g) and sodium carbonate (1.3mmol, 0.146 g) in acetonitrile/water (10 mL:3 mL) was heated to 90 °C for 30 minutes. The reaction mixture was diluted with ethyl acetate (50 mL) and the organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude compound was purified by silica gel column chromatography using chloroform: methanol (9:1) as an eluent to yield **Example 385** (0.2 g).

MS(ES): 442.2 (M+1) for $C_{22}H_{21}F_2N_5O_3$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.35 (q, *J* = 7.08 Hz, 3H), 3.23 (d, *J* = 3.76 Hz, 4H), 3.57 (d, *J* = 3.64 Hz, 4H), 4.37 (q, *J* = 7.12 Hz, 2H), 6.74 (t, *J* = 2.24 Hz, 1H), 7.54 (d, *J* = 10.12 Hz, 2H), 8.22 (d, *J* = 2.84 Hz, 1H), 8.40 (t, *J* = 1.96 Hz, 1H), 8.94 (d, *J* = 2.04 Hz, 1H), 9.01 (d, *J* = 1.80 Hz, 1H), 9.95 (s, 1H).

Example 386: 5-[2-(3,5-Dimethyl-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester



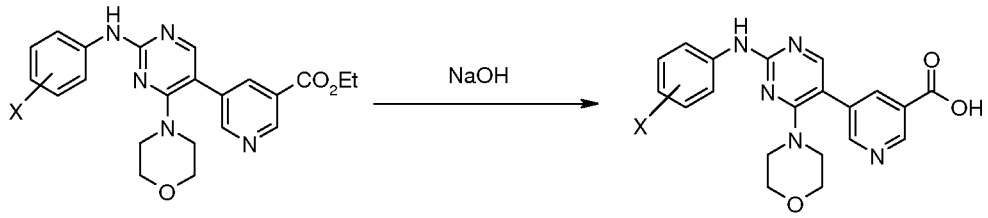
A suspension of **Intermediate 144** (1.3 mmol, 0.5 g), 3-(ethoxycarbonyl)pyridine-5-boronic acid ester (1.4 mmol, 0.4 g), tris(dibenzyledeneacetone)dipalladium(0) (0.4 mmol, 0.19 g), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (0.13 mmol, 0.12 g) and sodium carbonate (1.3mmol, 0.146 g) in acetonitrile/water (20 mL:5 mL) was heated to 90°C for 30 minutes. The reaction mixture was diluted with ethyl acetate (50 mL) and the organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude compound was purified

by silica gel column chromatography using chloroform: methanol (9:1) as an eluent to yield **Example 386** (0.46 mmol, 0.2 g, 33%).

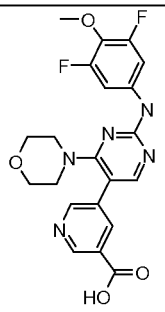
MS(ES): 433 (M) for $C_{24}H_{27}N_5O_3$.

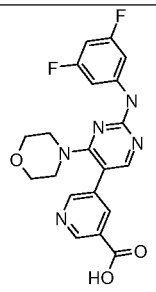
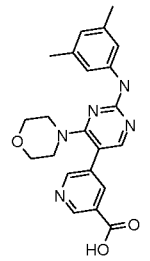
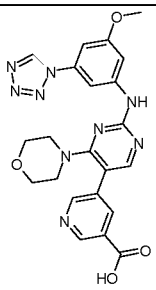
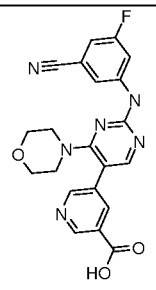
^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.34 (t, J = 7.08 Hz, 3H), 2.22 (s, 6H), 3.21 (t, J = 4.48 Hz, 4H), 3.56 (t, J = 4.16 Hz, 4H), 4.37 (q, J = 7.08 Hz, 2H), 6.58 (s, 1H), 7.40 (s, 2H), 8.15 (s, 1H), 8.38 (t, J = 2.12 Hz, 1H), 8.93 (d, J = 2.2 Hz, 1H), 8.98 (d, J = 1.96 Hz, 1H), 9.39 (s, 1H).

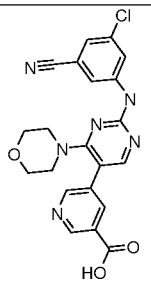
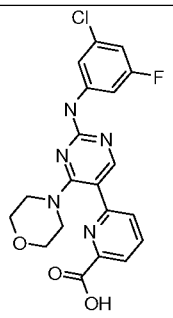
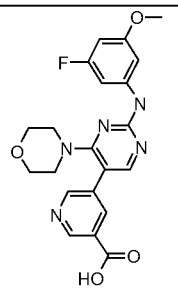
General procedure for the synthesis of 5-(4-Morpholin-4-yl-2-arylamino-pyrimidin-5-yl)-nicotinic acids from the corresponding esters.



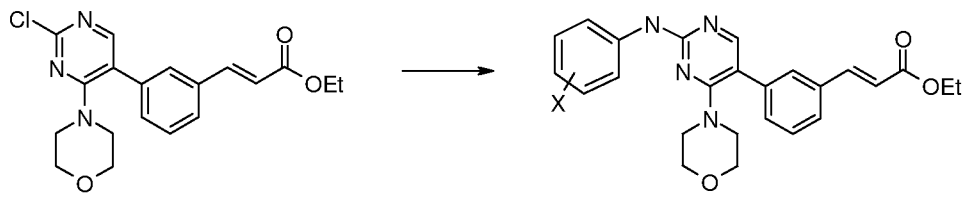
To a solution of carboxylic acid ester derivative (0.46 mmol) in tetrahydrofuran (5 mL) and water (5 mL), 1 N aq. sodium hydroxide (1.84 mmol, 1.84 ml) was added. The reaction was allowed to stir at room temperature for 2 h. After completion of reaction, the reaction mixture was carefully acidified with 1 N HCl and the solid that precipitated was filtered, washed with water and dried under vacuo to yield the desired 5-(4-Morpholin-4-yl-2-arylamino-pyrimidin-5-yl)-nicotinic acid. The compounds in the below table were prepared using this procedure and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
5-[2-(3,5-Difluoro-4-methoxy-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid **Example 387**		MS(ES): 444 (M+1) for $C_{21}H_{19}F_2N_5O_4$. 400 MHz, DMSO-d_6: δ 3.23 (br s, 4H), 3.55-3.56 (m, 4H), 3.90 (s, 3H), 7.57 (d, J = 11.20 Hz, 2H), 8.19 (s, 1H), 8.36 (s, 1H), 8.91 (d, J = 1.60 Hz, 1H), 9.01 (s, 1H), 9.85 (s, 1H), 13.70 (br s, 1H).	6-[2-(3,5-Difluoro-4-methoxy-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-pyridine-2-carboxylic acid ethyl ester **Example 379**

5-[2-(3,5-Difluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid **Example 388**		MS(ES): 414 (M+1) for $C_{20}H_{17}F_2N_5O_3$. 400 MHz, DMSO-d_6: δ 3.23 (d, *J* = 4.20 Hz, 4H), 3.56 (t, *J* = 4.56 Hz, 4H), 6.72 (tt, *J* = 2.28, 9.25 Hz, 1H), 7.54 (dd, *J* = 1.96, 10.44 Hz, 2H), 8.20 (s, 1H), 8.35 (t, *J* = 2.08 Hz, 1H), 8.91 (d, *J* = 2.16 Hz, 1H), 9.00 (d, *J* = 1.92 Hz, 1H), 9.94 (s, 1H), 13.54 (s, 1H).	5-[2-(3,5-Difluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester **Example 385**
5-[2-(3,5-Dimethyl-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid **Example 389**		MS(ES): 406 (M+1) for $C_{22}H_{23}N_5O_3$. 400 MHz, DMSO-d_6: δ 2.22 (s, 6H), 3.21 (m, 4H), 3.56 (m, 4H), 6.58 (s, 1H), 7.4 (s, 2H), 8.13 (s, 1H), 8.33 (s, 1H), 8.89 (br s, 1H), 8.98 (br s, 1H), 9.37 (s, 1H), 13.52 (br s, 1H).	5-[2-(3,5-Dimethyl-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester **Example 386**
5-[2-(3-Methoxy-5-tetrazol-1-yl-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid **Example 390**		MS(ES): 448 (M-28) for $C_{22}H_{21}N_9O_4$. 400 MHz, DMSO-d_6 : δ 3.24 (br s, 4H), 3.56 (br s, 4H), 3.73 (s, 3H), 6.08 (s, 1H), 7.03 (s, 1H), 7.34 (s, 1H), 8.15 (s, 1H), 8.36 (s, 1H), 8.91 (s, 1H), 8.99 (s, 1H), 9.61 (s, 1H), 10.07 (s, 1H).	5-[2-(3-Methoxy-5-tetrazol-1-yl-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester **Example 380**
5-[2-(3-Cyano-5-fluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid **Example 391**		MS(ES): 421 (M+1) for $C_{21}H_{17}FN_6O_3$ 400 MHz, DMSO-d_6: δ 3.25 (br s, 4H), 3.57 (br s, 4H), 7.36 (d, *J* = 7.60 Hz, 1H), 8.03 (s, 1H), 8.05 (s, 1H), 8.23 (s, 1H), 8.36 (br s, 1H), 8.91 (s, 1H), 9.01 (s, 1H), 10.10 (s, 1H), 13.60 (br s, 1H).	5-[2-(3-Cyano-5-fluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester **Example 381**

5-[2-(3-Chloro-5-cyano-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid **Example 392**		MS(ES): 437 (M+1) for $C_{21}H_{17}ClN_6O_3$. 400 MHz, DMSO-d_6: δ 3.24 (br s, 4H), 3.56 (br s, 4H), 7.53 (s, 1H), 8.16 (s, 1H), 8.22 (s, 1H), 8.25 (s, 1H), 8.34 (s, 1H), 8.90 (s, 1H), 9.00 (s, 1H), 10.10 (s, 1H), 13.60 (br s, 1H).	5-[2-(3-chloro-5-cyano-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester **Example 382**
6-[2-(3-Chloro-5-fluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-pyridine-2-carboxylic acid **Example 393**		MS(ES): 430 (M+1) for $C_{20}H_{17}ClFN_5O_3$. 400 MHz, DMSO-d_6: δ 3.24-3.25 (m, 4H), 3.57 (br s, 4H), 6.93 (dd, *J* = 2.00, 8.40 Hz, 1H), 7.69 (d, *J* = 12.00 Hz, 1H), 7.78 (br s, 1H), 8.21 (br s, 1H), 8.36 (t, *J* = 2.00 Hz, 1H), 8.92 (br s, 1H), 9.01 (br s, 1H), 9.96 (br s, 1H), 13.60 (br s, 1H).	6-[2-(3-Chloro-5-fluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-pyridine-2-carboxylic acid ethyl ester **Example 383**
5-[2-(3-Fluoro-5-methoxy-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid **Example 394**		MS(ES): 426 (M+1) for $C_{21}H_{20}FN_5O_4$. 400 MHz, Acetic acid-d : δ 3.61 (br s, 4H), 3.76 (br s, 4H), 3.84 (s, 3H), 6.49 (d, *J* = 10.76 Hz, 1H), 7.10 (s, 1H), 7.21 (d, *J* = 10.4 Hz, 1H), 8.16 (s, 1H), 8.63 (s, 1H), 9.03 (br s, 1H), 9.28 (br s, 1H).	5-[2-(3-Fluoro-5-methoxy-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester **Example 384**

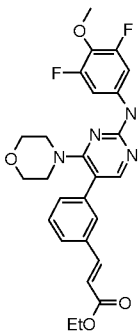
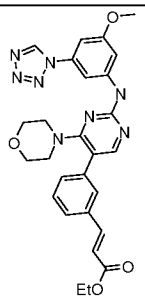
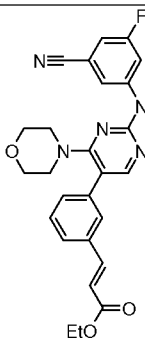
General procedure for the coupling of anilines to Intermediate 145: {(E)-3-[3-(4-Morpholin-4-yl-2-arylamino-pyrimidin-5-yl)-phenyl]-acrylic acid ethyl ester}

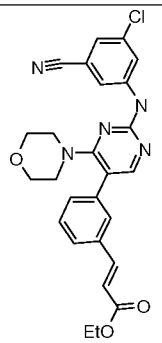
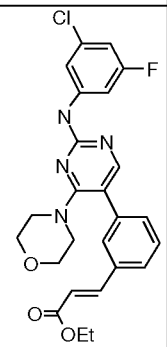
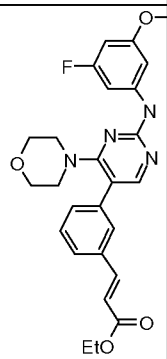


PE-014-002-III PE-014-Int-V

Intermediate 145 (1 eq) was suspended in acetonitrile/ethanol and treated with corresponding aniline (1 eq). The reaction was then treated with 4 N HCl (3 vol) in dioxane and

refluxed under nitrogen for 5 hours. The mixture was cooled to room temperature, diluted with diethyl ether and the solid was filtered and dried to afford the product. The compounds in the below table were prepared using this procedure and the specified starting material and solvent.

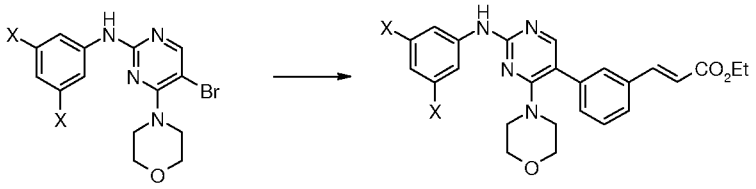
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
(E)-3-{3-[2-(3,5-Difluoro-4-methoxy-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 395**[d]		MS(ES): 497 (M+1) for $C_{26}H_{26}F_2N_4O_4$. 400 MHz, DMSO-d_6: δ 1.26 (t, *J* = 7.08 Hz, 3H), 3.23-3.24 (m, 4H), 3.54-3.56 (m, 4H), 3.83 (s, 3H), 4.20 (q, *J* = 7.12 Hz, 2H), 6.72 (d, *J* = 16.04 Hz, 1H), 7.46-7.66 (m, 4H), 7.68 (br s, 1H), 7.69 (d, *J* = 16.04 Hz, 1H), 7.82 (br s, 1H), 8.08 (br s, 1H), 9.66 (br s, 1H).	3,5-Difluoro-4-methoxy-phenylamine
(E)-3-{3-[2-(3-Methoxy-5-tetrazol-1-yl-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 396**[d]		MS(ES): 529 (M+1) for $C_{27}H_{28}N_8O_4$. 300 MHz, DMSO-d_6: δ 1.25 (t, *J* = 6.00 Hz, 3H), 3.83 (s, 3H), 4.20 (q, 2H), 6.73 (d, *J* = 16.20 Hz, 1H), 7.09 (s, 1H), 7.46-7.56 (m, 3H), 7.67-7.72 (m, 2H), 7.83 (s, 1H), 8.12 (s, 1H), 8.28 (s, 1H), 9.82 (s, 1H), 10.08 (s, 1H).	3-Methoxy-5-tetrazol-1-yl-phenylamine Hydrochloride
(E)-3-{3-[2-(3-Cyano-5-fluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 397**[e]		MS(ES): 474 (M+1) for $C_{26}H_{24}FN_5O_3$. 300 MHz, DMSO-d6: δ 1.25 (t, *J* = 7.02 Hz, 3H), 3.24-3.32 (m, 4H), 3.55 (br s, 4H), 4.19 (q, *J* = 7.02 Hz, 2H), 6.72 (d, *J* = 16.05 Hz, 1H), 7.31 (d, *J* = 7.89 Hz, 1H), 7.46-7.55 (m, 2H), 7.69 (d, *J* = 15.87 Hz, 1H), 7.69 (s, 1H), 7.82 (br s, 1H), 8.00 (m, 1H), 8.04 (br s, 1H), 8.13 (br s, 1H), 10.00 (br s, 1H).	3-Amino-5-fluoro-benzonitrile

(E)-3-{3-[2-(3-Chloro-5-cyano-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 398[d]**		MS(ES): 490.2 (M+1) for $C_{26}H_{24}ClN_5O_3$. 400 MHz, DMSO-d_6: δ 1.27 (t, *J* = 7.20 Hz, 3H), 3.26 (s, 4H), 3.56 (d, *J* = 4.40 Hz, 4H), 4.20 (q, *J* = 7.20 Hz, 2H), 6.74 (d, *J* = 16.00 Hz, 1H), 7.50-7.54 (m, 3H), 7.71 (d, *J* = 16.00 Hz, 1H), 7.71 (s, 1H), 7.85 (s, 1H), 8.16-8.17 (m, 2H), 8.27 (t, *J* = 2.00 Hz, 1H), 10.01 (s, 1H).	3-Amino-5-chloro-benzonitrile
(E)-3-{3-[2-(3-Chloro-5-fluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 399[d]**		MS(ES): 483 (M+1) for $C_{25}H_{24}ClFN_4O_3$. 300 MHz, DMSO-d_6: δ 1.26 (t, *J* = 7.08 Hz, 3H), 3.24 (br s, 4H), 3.55 (br s, 4H), 4.19 (q, *J* = 7.11 Hz, 2H), 6.72 (d, *J* = 16.08 Hz, 1H), 6.90 (d, *J* = 8.25 Hz, 1H), 7.45-7.55 (m, 2H), 7.66-7.72 (m, 3H), 7.77 (s, 1H), 7.83 (s, 1H), 8.11 (s, 1H), 9.84 (s, 1H).	3-Chloro-5-fluoro-phenylamine
(E)-3-{3-[2-(3-Fluoro-5-methoxy-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 400[d]**		MS(ES): 479 (M+1) for $C_{26}H_{27}FN_4O_4$. 400 MHz, DMSO-d6: δ 1.26 (t, *J* = 7.04 Hz, 3H), 3.40 (br s, 4H), 3.56 (br s, 4H), 3.77 (s, 3H), 4.20 (q, *J* = 7.00 Hz, 2H), 6.57 (d, *J* = 10.84 Hz, 1H), 6.74 (d, *J* = 16.04 Hz, 1H), 7.10 (d, *J* = 1.36 Hz, 1H), 7.13 (br s, 1H), 7.49-7.54 (m, 2H), 7.68-7.75 (m, 2H), 7.83 (br s, 1H), 8.07 (br s, 1H), 10.52 (br s, 1H).	3-Fluoro-5-methoxy-phenylamine

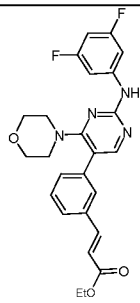
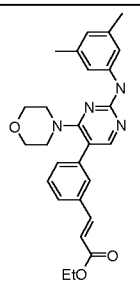
Solvents used in the reaction (d) acetonitrile (e) ethanol

Example 401 (E)-3-{3-[2-(3,5-Difluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester

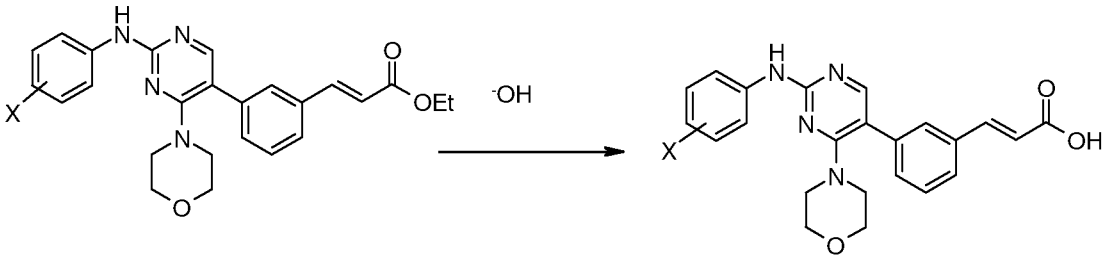
Example 402 (E)-3-{3-[2-(3,5-Dimethyl-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester



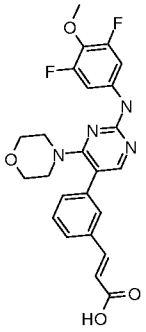
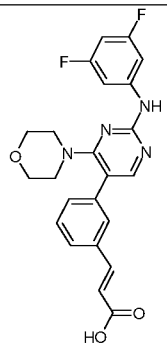
A suspension of the 5-bromopyrimidine derivative (1 eq), ethyl-3-borono cinnamate (1.1 eq), tris(dibenzyledeneacetone)dipalladium(0) (30 mol%), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (10 mol%) and sodium carbonate (1 eq) in acetonitrile/water (20:5 vol) was heated to 90°C for 30 minutes. The reaction mixture was diluted with ethyl acetate (30 vol) and the organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude compound was purified by silica gel column chromatography using petroleum ether: EtOAc (7:3) as an eluent to yield the product. The compounds in the below table were prepared using this method and the specified starting material.

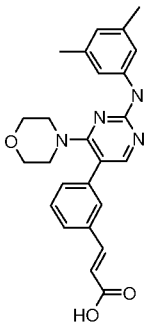
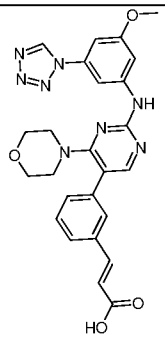
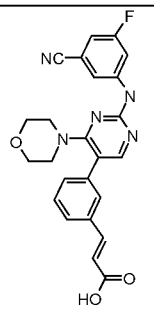
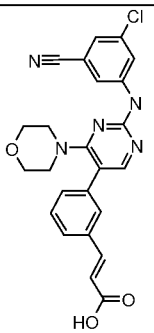
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
(E)-3-{3-[2-(3,5-Difluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 401**		MS(ES): 467.2 (M+1) for $C_{25}H_{24}F_2N_4O_3$. 300 MHz, DMSO-d_6: δ 1.25 (t, J = 6.99 Hz, 3H), 3.23 (s, 4H), 3.55 (s, 4H), 4.19 (q, J = 7.02 Hz, 2H), 6.67-6.75 (m, 2H), 7.45-7.55 (m, 4H), 7.66-7.72 (m, 2H), 7.83 (s, 1H), 8.11 (s, 1H), 9.84 (s, 1H).	(5-Bromo-4-morpholin-4-yl-pyrimidin-2-yl)-(3,5-difluoro-phenyl)-amine **Intermediate 140**
(E)-3-{3-[2-(3,5-Dimethyl-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 402**		MS(ES): 459 (M+1) for $C_{27}H_{30}N_4O_3$. 400 MHz, DMSO-d6: δ 1.25 (t, J = 6.96 Hz, 3H), 2.22 (s, 6H), 3.23 (br s, 4H), 3.55 (br s, 4H), 4.19 (q, J = 6.76 Hz, 2H), 6.56 (s, 1H), 6.72 (d, J = 15.76 Hz, 1H), 7.40 (s, 2H), 7.44-7.54 (m, 2H), 7.64-7.71 (m, 2H), 7.81 (s, 1H), 8.05 (s, 1H), 9.28 (s, 1H).	(5-Bromo-4-morpholin-4-yl-pyrimidin-2-yl)-(3,5-dimethyl-phenyl)-amine **Intermediate 144**

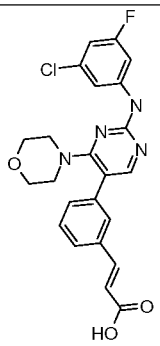
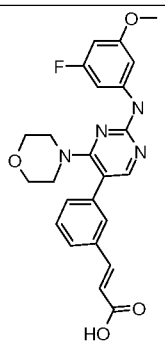
General procedure for the synthesis of (E)-3-[3-(4-Morpholin-4-yl-2-arylamino-pyrimidin-5-yl)-phenyl]-acrylic acid



Ester compound (0.43 mmol, 0.2 g) was dissolved in tetrahydrofuran (5 mL), treated with 1 N aq. sodium hydroxide or Barium hydroxide (1.72 mmol) and was heated at 60 °C for 24 h. The reaction mixture was then carefully acidified with 1 N HCl and the solid that precipitated was filtered, washed with water and dried under vacuo to yield the product. The compounds in the below table were prepared using this procedure and the starting material and base specified.

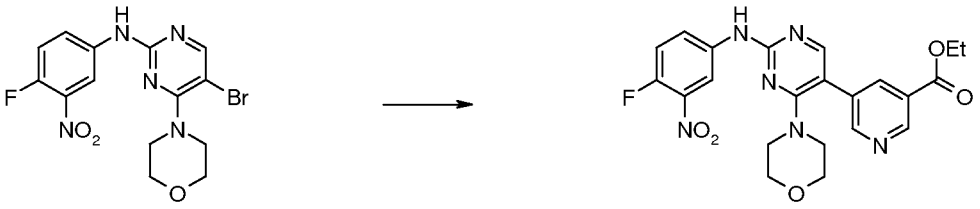
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
(E)-3-{3-[2-(3,5-Difluoro-4-methoxy-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid **Example 403**[f]		MS(ES): 469 (M+1) for $C_{24}H_{22}F_2N_4O_4$. 400 MHz, DMSO-d_6: δ 3.23-3.24 (m, 4H), 3.54-3.55 (m, 4H), 3.83 (s, 3H), 6.61 (d, J = 16.04 Hz, 1H), 7.46-7.56 (m, 2H), 7.59 (s, 1H), 7.63 (d, J = 15.84 Hz, 1H), 7.63 (s, 1H), 7.67 (s, 1H), 7.79 (s, 1H), 8.09 (s, 1H), 9.67 (br s, 1H), 12.44 (br s, 1H).	3-{3-[2-(3,5-Difluoro-4-methoxy-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 395**
(E)-3-{3-[2-(3,5-Difluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid **Example 404**[f]		MS(ES): 439 (M+1) for $C_{23}H_{20}F_2N_4O_3$. 400 MHz, DMSO-d_6: δ 3.24 (d, J = 4.08 Hz, 4H), 3.55 (t, J = 4.32 Hz, 4H), 6.61 (d, J = 16.00 Hz, 1H), 6.70 (t, J = 9.12 Hz, 1H), 7.46-7.55 (m, 4H), 7.63 (d, J = 16.20 Hz, 1H), 7.63 (s, 1H), 7.79 (s, 1H), 8.11 (s, 1H), 9.84 (s, 1H).	3-{3-[2-(3,5-Difluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 401**

(E)-3-{3-[2-(3,5-Dimethyl-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid **Example 405**[f]		MS(ES): 431 (M+1) for $C_{25}H_{26}N_4O_3$. 400 MHz, DMSO-d_6: δ 2.22 (s, 6H), 3.23 (br s, 4H), 3.55 (br s, 4H), 6.56 (s, 1H), 6.59 (d, *J* = 16.0 Hz, 1H), 7.40 (s, 2H), 7.42-7.47 (m, 2H), 7.48-7.50 (m, 1H), 7.54-7.58 (m, 1H), 7.73 (s, 1H), 8.04 (s, 1H), 9.26 (s, 1H).	3-{3-[2-(3,5-Dimethyl-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 402**
(E)-3-{3-[2-(3-Methoxy-5-tetrazol-1-yl-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid **Example 406**[g]		MS(ES): 501 (M+1) for $C_{25}H_{24}N_8O_4$ 400 MHz, DMSO-d_6: δ 3.27 (br s, 4H), 3.55 (br s, 4H), 3.84 (s, 3H), 6.61 (d, *J* = 16.04 Hz, 1H), 7.08 (br s, 1H), 7.46-7.53 (m, 3H), 7.60-7.64 (m, 2H), 7.79 (s, 1H), 8.11 (s, 1H), 8.28 (s, 1H), 9.82 (s, 1H), 10.08 (s, 1H), 12.44 (br s, 1H).	3-{3-[2-(3-Methoxy-5-tetrazol-1-yl-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 396**
(E)-3-{3-[2-(3-Cyano-5-fluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid **Example 407**[f]		MS(ES): 446 (M+1) for $C_{24}H_{20}FN_5O$. 400 MHz, DMSO-d_6: δ 3.25-3.26 (m, 4H), 3.54-3.55 (m, 4H), 6.60 (d, *J* = 16.00 Hz, 1H), 7.32 (dd, *J* = 1.32, 8.12 Hz, 1H), 7.45-7.51 (m, 2H), 7.56 (d, *J* = 16.04 Hz, 1H), 7.62 (d, *J* = 7.08 Hz, 1H), 7.76 (br s, 1H), 8.01-8.05 (m, 2H), 8.13 (s, 1H), 10.03 (br s, 1H).	3-{3-[2-(3-Cyano-5-fluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 397**
(E)-3-{3-[2-(3-Chloro-5-cyano-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid **Example 408**[f]		MS(ES): 462 (M+1) for $C_{24}H_{20}ClN_5O_3$. 400 MHz, DMSO-d_6 : δ 3.26 (d, *J* = 3.80 Hz, 4H), 3.56 (d, *J* = 3.80 Hz, 4H), 6.61 (d, *J* = 16.04 Hz, 1H), 7.46-7.53 (m, 3H), 7.61 (s, 1H), 7.65 (t, *J* = 3.56 Hz, 1H), 7.79 (s, 1H), 8.15 (t, *J* = 7.96 Hz, 2H), 8.26 (t, *J* = 1.84 Hz, 1H), 9.99 (s, 1H), 12.44 (br s, 1H).	3-{3-[2-(3-Chloro-5-cyano-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 398**

(E)-3-{3-[2-(3-Chloro-5-fluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid **Example 409**[f]		MS(ES): 454 (M+1) for $C_{23}H_{20}ClFN_4O_3$. 400 MHz, DMSO-d_6: δ 3.25 (br s, 4H), 3.55 (br s, 4H), 6.56 (d, *J* = 15.92 Hz, 1H), 6.90 (d, *J* = 8.08 Hz, 1H), 7.39-7.45 (m, 3H), 7.55 (m, 1H), 7.67-7.69 (m, 2H), 7.78 (m, 1H), 8.10 (s, 1H), 9.84 (s, 1H).	3-{3-[2-(3-Chloro-5-fluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 399**
(E)-3-{3-[2-(3-Fluoro-5-methoxy-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid **Example 410**[f]		MS(ES): 451 (M+1) for $C_{24}H_{23}FN_4O_4$. 400 MHz, DMSO-d_6: δ 3.24 (br s, 4H), 3.55 (br s, 4H), 3.74 (s, 3H), 6.36 (dd, *J* = 2.04, 10.86 Hz, 1H), 6.61 (d, *J* = 16.04 Hz, 1H), 7.28-7.32 (m, 2H), 7.46-7.54 (m, 2H), 7.61-7.65 (m, 2H), 7.79 (br s, 1H), 8.09 (br s, 1H), 9.59 (br s, 1H), 12.44 (br s, 1H).	3-{3-[2-(3-Fluoro-5-methoxy-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 400**

Base used in the reaction (f) NaOH (g) $Ba(OH)_2$

Example 411: 5-[2-(4-Fluoro-3-nitro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester

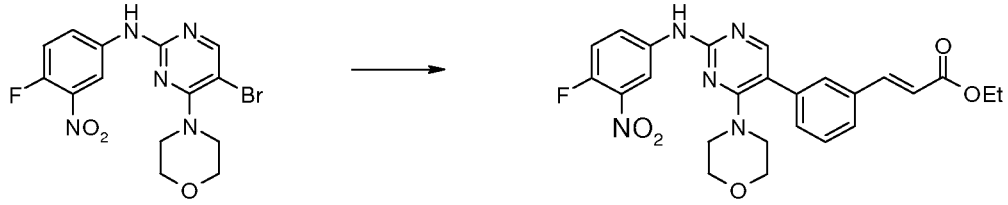


A suspension of 5-bromo-*N*-(4-fluoro-3-nitrophenyl)-4-morpholin-4-ylpyrimidin-2-amine **Intermediate 150** (0.87 mmol, 0.35 g), (4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-nicotinic acid ethyl ester (0.92 mmol, 0.25 g), tris(dibenzylideneacetone)dipalladium(0) (10 mol %, 0.087 mmol, 80 mg), XPHOS (30 mol %, 0.26 mmol, 125 mg) and sodium carbonate (0.87 mmol, 92 mg) in acetonitrile/water (20 mL : 5 mL) was degassed and heated to 90 °C for 30 min under inert atmosphere. The solvent was removed in vacuo and the crude mixture was taken in EtOAc (30 mL). It was then washed with water and brine. The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude material was purified by silica gel column chromatography. The product eluted with $CHCl_3$: MeOH (98 : 2) eluent mixture. The title compound was obtained (0.2 g).

MS (ES) : 469 (M+1) for $C_{22}H_{21}FN_6O_5$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.35 (t, *J* = 7.04 Hz, 3H), 3.24-3.26 (m, 4H), 3.55-3.58 (m, 4H), 4.37 (q, *J* = 7.08 Hz, 2H), 7.52 (dd, *J* = 9.16, 11.14 Hz, 1H), 7.90 (dt, *J* = 3.20, 6.10 Hz, 1H), 8.21 (s, 1H), 8.39 (t, *J* = 2.08 Hz, 1H), 8.94 (d, *J* = 2.24 Hz, 1H), 8.95-8.96 (m, 1H), 9.01 (d, *J* = 1.92 Hz, 1H), 10.04 (br s, 1H).

Example 412: 3-{3-[2-(4-Fluoro-3-nitro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester

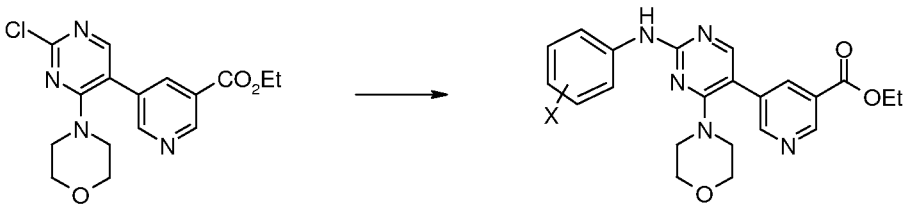


A suspension of 5-bromo-*N*-(4-fluoro-3-nitrophenyl)-4-morpholin-4-ylpyrimidin-2-amine **Intermediate 150** (0.87 mmol, 0.35 g), ethyl boronocinnamate (0.92 mmol, 0.203 g), tris(dibenzylideneacetone)dipalladium(0) (10 mol %, 0.087 mmol, 80 mg), XPHOS (30 mol %, 0.26 mmol, 125 mg) and sodium carbonate (0.87 mmol, 92 mg) in acetonitrile/water (20 mL : 5 mL) was degassed and heated to 90 °C for 30 min under inert atmosphere. The solvent was removed in vacuo and the crude mixture was taken in EtOAc (30 mL). It was then washed with water and brine. The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude material was purified by silica gel column chromatography. The product eluted with Hexane : Ethyl Acetate (90 : 10) eluent mixture. The title compound was obtained (0.2 g).

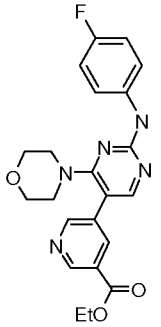
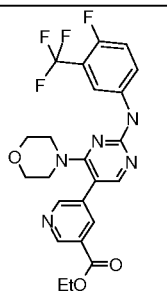
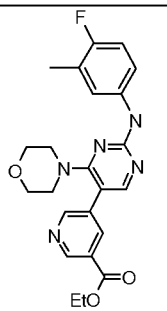
MS (ES) : 494 (M+1) for $C_{25}H_{24}FN_5O_5$.

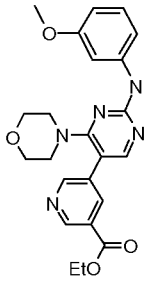
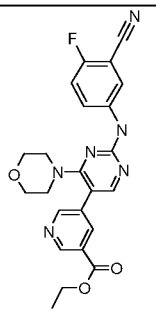
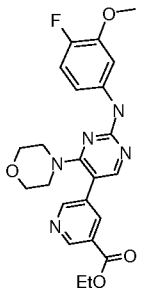
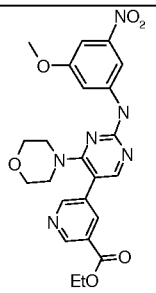
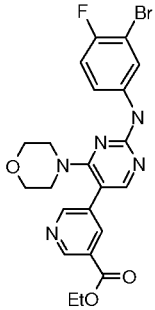
^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.25 (t, *J* = 7.08 Hz, 3H), 3.27-3.28 (m, 4H), 3.55-3.57 (m, 4H), 4.19 (q, *J* = 7.08 Hz, 2H), 6.73 (d, *J* = 16.04 Hz, 1H), 7.46-7.55 (m, 3H), 7.67 (d, *J* = 7.36 Hz, 1H), 7.69 (d, *J* = 16.08 Hz, 1H), 7.83 (s, 1H), 7.88-7.91 (m, 1H), 8.11 (s, 1H), 8.96 (dd, *J* = 2.80, 6.86 Hz, 1H), 9.94 (s, 1H).

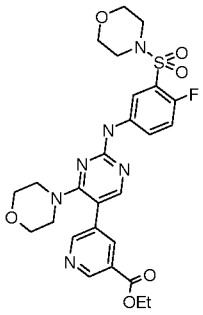
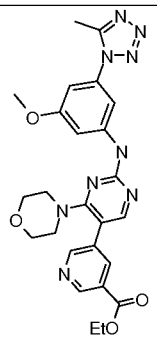
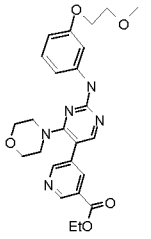
General procedure for the reaction of anilines with 5-(2-Chloro-4-morpholin-4-yl-pyrimidin-5-yl)-nicotinic acid ethyl ester (Intermediate 152)



To a suspension of 5-(2-Chloro-4-morpholin-4-yl-pyrimidin-5-yl)-nicotinic acid ethyl ester **Intermediate 152** (0.6 mmol, 1 eq.) taken in n-BuOH / acetonitrile / dioxane (10 mL) was added the corresponding aniline. The reaction mixture was then treated with 4 N HCl in dioxane (2 mL) and refluxed at 100 °C for 1.5 h. The reaction mixture was cooled to room temperature, diluted with diethyl ether, the solid filtered and dried to yield the corresponding nicotinic acid ethyl ester. The compounds in the table below were prepared using this general procedure and the starting material and solvent specified.

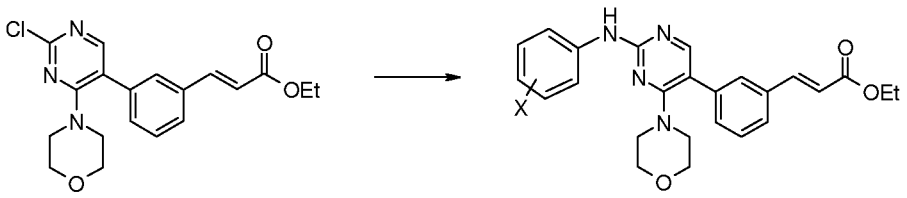
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 413[a]		MS(ES): 424 (M+1) for $C_{22}H_{22}FN_5O_3$. 400 MHz, DMSO-d_6: δ 1.36 (t, *J* = 7.20 Hz, 3H), 3.33 (br s, 4H), 3.54 (br s, 4H), 4.39 (q, *J* = 7.20 Hz, 2H), 7.23 (t, *J* = 8.80 Hz, 2H), 7.63-7.66 (m, 2H), 8.14 (s, 1H), 8.38 (t, *J* = 2.00 Hz, 1H), 8.92 (d, *J* = 2.00 Hz, 1H), 9.07 (d, *J* = 2.00 Hz, 1H), 10.20 (s, 1H) .	4-fluoro aniline
Example 414[b]		MS(ES): 492 (M+1) for $C_{23}H_{21}F_4N_5O_3$. 300 MHz, DMSO-d_6: δ 1.35 (t, *J* = 7.05 Hz, 3H), 3.35 (br s, 4H), 3.54 (br s, 4H), 4.38 (q, *J* = 6.99 Hz, 2H), 7.54 (t, *J* = 9.48 Hz, 1H), 7.84 (br s, 1H), 8.20 (s, 1H), 8.23 (d, *J* = 6.04 Hz, 1H), 8.40 (br s, 1H), 8.92 (br s, 1H), 9.07 (br s, 1H), 10.79 (br s, 1H).	4-fluoro-3-trifluoromethylaniline
Example 415[b]		MS(ES): 438 (M+1) for $C_{23}H_{24}FN_5O_3$. 400 MHz, DMSO-d_6: δ 1.35 (t, *J* = 7.08 Hz, 3H), 2.23 (s, 3H), 3.32 (br s, 4H), 3.54-3.56 (m, 4H), 4.38 (q, *J* = 7.12 Hz, 2H), 7.14 (t, *J* = 9.12 Hz, 1H), 7.40-7.44 (m, 1H), 7.54 (dd, *J* = 2.44, 6.92 Hz, 1H), 8.11 (s, 1H), 8.36 (t, *J* = 2.12 Hz, 1H), 8.90 (d, *J* = 2.20 Hz, 1H), 9.05 (d, *J* = 1.96 Hz, 1H), 10.20 (br s, 1H).	4-Fluoro-3-methyl-phenylamine

Example 416[b]		MS(ES): 436 (M+1) for $C_{23}H_{25}N_5O_4$. 300 MHz, DMSO-d_6: δ 1.34 (t, *J* = 7.05 Hz, 3H), 3.21 (br s, 4H), 3.55 (br s, 4H), 3.73 (s, 3H), 4.37 (q, *J* = 6.99 Hz, 2H), 6.51 (d, *J* = 8.82 Hz, 1H), 7.16 (t, *J* = 8.16 Hz, 1H), 7.27 (d, *J* = 7.35 Hz, 1H), 7.54 (s, 1H), 8.16 (s, 1H), 8.39 (s, 1H), 8.94 (s, 1H), 8.99 (s, 1H), 9.52 (s, 1H).	m-anisidine
Example 417[b]		MS(ES): 449 (M+1) for $C_{23}H_{21}FN_6O_3$. 400 MHz, $CDCl_3$: δ 1.45 (t, *J* = 7.12 Hz, 3H), 3.30-3.32 (m, 4H), 3.66-3.68 (m, 4H), 4.47 (q, *J* = 7.12 Hz, 2H), 7.16-7.21 (m, 2H), 7.65 (ddd, *J* = 2.88, 4.46, 9.09 Hz, 1H), 8.05 (br s, 1H), 8.20 (ddd, *J* = 2.80, 5.44 Hz, 1H), 8.39 (t, *J* = 2.12 Hz, 1H), 8.87 (br s, 1H), 9.19 (br s, 1H).	5-Amino-2-fluorobenzo nitrile
Example 418[b]		The compound was taken to the next step on the basis of Mass spectrum with 78% purity. MS(ES): 454 (M+1) for $C_{23}H_{24}FN_5O_4$.	4-Fluoro-3-methoxyanil ine
Example 419[c]		MS(ES): 481 (M+1) for $C_{23}H_{24}N_6O_6$. 400 MHz, DMSO-d_6: δ 1.35 (t, *J* = 7.08 Hz, 3H),3.40 (br s, 4H), 3.58 (br s, 4H), 3.89 (s, 3H), 4.38 (q, *J* = 7.12 Hz, 2H), 7.44 (t, *J* = 2.00 Hz, 1H), 7.61 (d, *J* = 2.00 Hz, 1H), 8.24 (d, *J* = 6.40 Hz, 1H), 8.44-8.46 (m, 2H), 8.96 (d, *J* = 2.00 Hz, 1H), 9.09 (d, *J* = 2.00 Hz, 1H), 10.85 (br s, 1H).	3-Methoxy-5-nitro aniline
Example 420[b]		MS(ES): 502 (M) and 504 (M+2) for $C_{22}H_{21}BrFN_5O_3$. 400 MHz, DMSO-d_6: δ 1.35 (t, *J* = 7.04 Hz, 3H), 3.22 (br s, 4H), 3.55 (br s, 4H), 4.37 (q, *J* = 7.12 Hz, 2H), 7.30 (t, *J* = 8.80 Hz, 1H), 7.63-7.66 (m, 1H), 8.18 (s, 1H), 8.30 (dd, *J* = 2.20, 6.32 Hz, 1H), 8.38 (br s, 1H), 8.93 (br s, 1H), 9.00 (br s, 1H), 9.73 (br s, 1H).	3-bromo-4-fluoro aniline

Example 421[b]		MS(ES): 573 (M+1) for $C_{26}H_{29}FN_6O_6S$. 400 MHz, DMSO-d_6: δ 1.35 (t, *J* = 7.08 Hz, 3H), 3.04 (br s, 4H), 3.31 (br s, 4H), 3.54-3.56 (m, 4H), 3.64-3.66 (m, 4H), 4.38 (q, *J* = 7.12 Hz, 2H), 7.50 (t, *J* = 9.32 Hz, 1H), 7.82-7.84 (m, 1H), 8.19 (s, 1H), 8.40 (t, *J* = 2.08 Hz, 1H), 8.50 (dd, *J* = 2.44, 5.68 Hz, 1H), 8.93 (d, *J* = 2.16 Hz, 1H), 9.05 (d, *J* = 1.96 Hz, 1H), 10.32 (br s, 1H).	4-Fluoro-3-(morpholine-4-sulfonyl)-phenylamine
Example 422[b]		MS(ES): 518 (M+1) for $C_{25}H_{27}N_9O_4$. 400 MHz, DMSO-d_6: δ 1.36 (t, *J* = 6.80 Hz, 3H), 2.61 (s, 3H), 3.23 (br s, 4H), 3.52-3.54 (m, 4H), 3.83 (s, 3H), 4.38 (q, *J* = 7.20 Hz, 2H), 6.88 (s, 1H), 7.63 (s, 1H), 7.79 (d, *J* = 1.60 Hz, 1H), 8.22 (s, 1H), 8.40 (s, 1H), 8.95 (d, *J* = 2.00 Hz, 1H), 9.02 (d, *J* = 2.00 Hz, 1H), 9.92 (s, 1H).	3-Methoxy-5-(5-methyl-tetrazol-1-yl)-phenylamine
Example 423[c]		MS(ES): 480 (M+1) for $C_{25}H_{29}N_5O_5$. 400 MHz, DMSO-d_6: δ 1.36 (t, *J* = 6.80 Hz, 3H), 3.32 (s, 3H), 3.44 (br s, 4H), 3.57 (br s, 4H), 3.66-3.69 (m, 2H), 4.09-4.11 (m, 3H), 4.40 (q, *J* = 7.20 Hz, 2H), 6.70-6.80 (m, 1H), 7.13 (d, *J* = 0.80 Hz, 1H), 7.26-7.32 (m, 2H), 8.19 (s, 1H), 8.40 (t, *J* = 2.00 Hz, 1H), 8.93 (d, *J* = 2.40 Hz, 1H), 9.10 (d, *J* = 2.00 Hz, 1H), 10.90 (br s, 1H).	3-(2-Methoxy-ethoxy)-phenylamine

Solvents used in the reaction (a) n-butanol (b) acetonitrile (c) dioxane

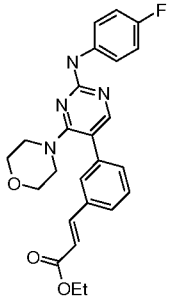
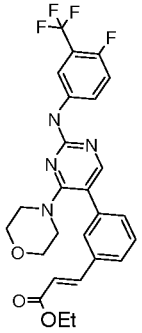
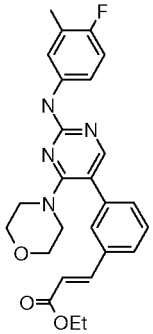
General procedure for the reaction of anilines with 3-[3-(2-Chloro-4-morpholin-4-yl-pyrimidin-5-yl)-phenyl]-acrylic acid ethyl ester (Intermediate 153)

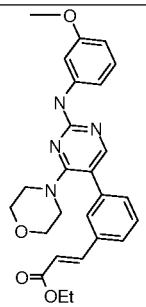
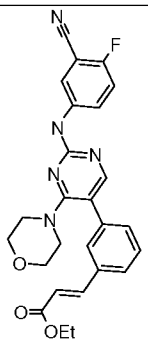
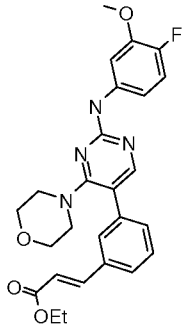
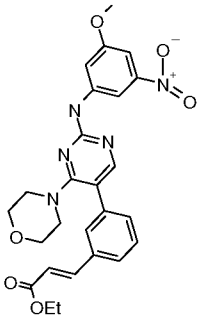


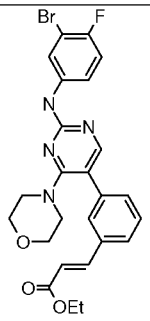
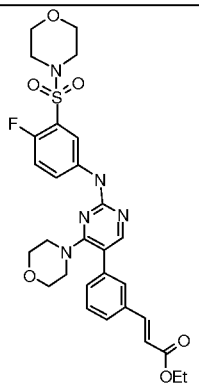
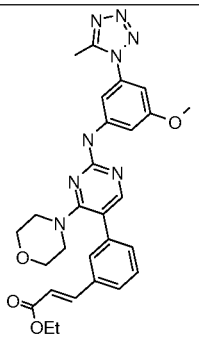
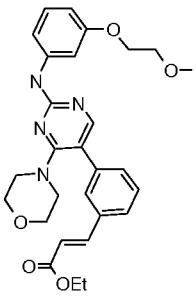
To a suspension of 3-[3-(2-Chloro-4-morpholin-4-yl-pyrimidin-5-yl)-phenyl]-acrylic acid ethyl ester **Intermediate 153** (1 eq.) taken in n-BuOH / acetonitrile / dioxane was added the

corresponding aniline. The reaction mixture was then treated with 4 N HCl in dioxane and refluxed at 100 ℃ for 1.5 h. The reaction mixture was cooled to room temperature, diluted with diethyl ether and the solid was filtered and dried to afford the corresponding cinnamic acid ethyl ester.

The compounds in the below table were prepared using this general procedure with the starting material and solvent specified.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 424[b]		MS(ES): 449.2 (M+1) for $C_{25}H_{25}FN_4O_3$. 300 MHz, DMSO-d_6 : δ 1.27 (t, *J* = 7.14 Hz, 3H), 3.20-3.25 (m, 4H), 3.50-3.55 (m, 4H), 4.20 (q, *J* = 7.17 Hz, 2H), 6.71 (d, *J* = 16.08 Hz, 1H), 7.07-7.13 (m, 2H), 7.45-7.55 (m, 3H), 7.60-7.80 (m, 4H), 8.04 (s, 1H), 9.42 (s, 1H).	4-fluoro aniline
Example 425[b]		MS(ES): 517 (M+1) for $C_{26}H_{24}F_4N_4O_3$. 300 MHz, DMSO-d_6: δ 1.25 (t, *J* = 7.05 Hz, 1H), 3.23-3.32 (m, 4H), 3.54-3.55 (m, 4H), 4.19 (q, *J* = 7.02 Hz, 2H), 6.72 (d, *J* = 16.05 Hz, 1H), 7.39-7.55 (m, 3H), 7.69 (d, *J* = 16.23 Hz, 1H), 7.66 (br s, 1H), 7.82 (s, 1H), 7.87 (br s, 1H), 8.09 (s, 1H), 8.44 (d, *J* = 4.29 Hz, 1H), 9.79 (s, 1H).	4-fluoro-3-trifluoromethylaniline
Example 426[b]		MS(ES): 463 (M+1) for $C_{26}H_{27}FN_4O_3$. 400 MHz, DMSO-d_6: δ 1.26 (t, *J* = 7.08 Hz, 3H), 2.07 (s, 3H), 3.32-3.48 (m, 4H), 3.50-3.70 (m, 4H), 4.20 (q, *J* = 7.12 Hz, 2H), 6.74 (d, *J* = 16.04 Hz, 1H), 7.17 (t, *J* = 9.04 Hz, 1H), 7.21-7.27 (m, 1H), 7.38-7.41 (m, 1H), 7.47-7.54 (m, 3H), 7.70 (d, *J* = 16.08 Hz, 1H), 7.74 (d, *J* = 7.36 Hz, 1H), 7.81 (br s, 1H), 7.99 (br s, 1H).	4-fluoro-3-methylaniline

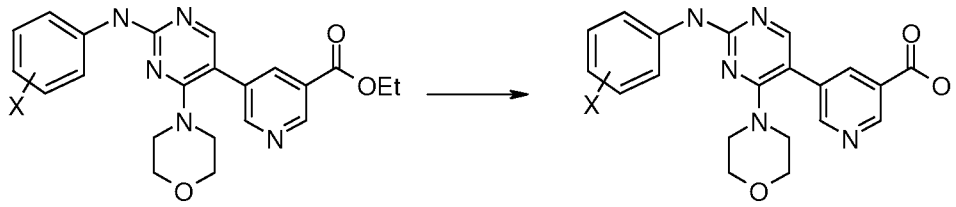
Example 427[b]		MS(ES): 461 (M+1) for $C_{26}H_{28}N_4O_4$. 300 MHz, DMSO-d_6: δ 1.25 (t, *J* = 7.05 Hz, 3H), 3.23 (br s, 4H), 3.54 (br s, 4H), 3.73 (s, 3H), 4.19 (q, *J* = 7.17 Hz, 2H), 6.49 (d, *J* = 8.16 Hz, 1H), 6.71 (d, *J* = 16.23 Hz, 1H), 7.14 (t, *J* = 7.86 Hz, 1H), 7.27 (d, *J* = 7.83 Hz, 1H), 7.49-7.66 (m, 3H), 7.72-7.82 (m, 2H), 7.99 (s, 1H), 8.06 (s, 1H), 8.30 (s, 1H).	m-anisidine
Example 428[b]		MS(ES): 474 (M+1) for $C_{26}H_{24}FN_5O_3$. 300 MHz, DMSO-d_6 : δ 1.25 (t, *J* = 7.05 Hz, 3H), 3.32 (br s, 4H), 3.55 (br s, 4H), 4.19 (q, *J* = 6.75 Hz, 2H), 6.73 (d, *J* = 16.11 Hz, 1H), 7.08 (s, 1H), 7.25 (br s, 1H), 7.41 (br s, 1H), 7.50-7.56 (m, 2H), 7.66-7.72 (m, 1H), 7.81 (s, 1H), 7.95 (br s, 1H), 8.07 (s, 1H), 8.22 (br s, 1H).	5-Amino-2-fluorobenzonitrile
Example 429[b]		MS(ES): 479 (M+1) for $C_{26}H_{27}FN_4O_4$. 400 MHz, DMSO-d_6: δ 1.26 (t, *J* = 7.08 Hz, 3H), 3.41 (br s, 4H), 3.50 (br s, 4H), 3.84 (s, 3H), 4.20 (q, *J* = 7.12 Hz, 2H), 6.75 (d, *J* = 16.04 Hz, 1H), 7.04-7.07 (m, 1H), 7.24 (dd, *J* = 8.80, 11.26 Hz, 1H), 7.48-7.55 (m, 3H), 7.72-7.76 (m, 1H), 7.82 (s, 1H), 8.01 (s, 1H), 10.39 (br s, 1H).	4-Fluoro-3-methoxyaniline
Example 430[c]		MS(ES): 506 (M+1) for $C_{26}H_{27}N_5O_6$. 400 MHz, DMSO-d_6 : δ 1.26 (t, *J* = 7.04 Hz, 3H), 3.28-3.29 (m, 4H), 3.55-3.57 (m, 4H), 3.85 (s, 3H), 4.19 (q, *J* = 7.12 Hz, 2H), 6.73 (d, *J* = 16.04 Hz, 1H), 7.29 (t, *J* = 2.20 Hz, 1H), 7.48 (t, *J* = 7.60 Hz, 1H), 7.55 (d, *J* = 7.80 Hz, 1H), 7.67-7.71 (m, 3H), 7.84 (br s, 1H), 8.13 (s, 1H), 8.61 (t, *J* = 1.88 Hz, 1H), 9.93 (br s, 1H).	3-Methoxy-5-nitro-phenylamine

Example 431[b]		MS(ES): 527 (M) and 529 (M+2) for $C_{25}H_{24}BrFN_4O_3$. 300 MHz, DMSO-d_6 : δ 1.25 (t, *J* = 6.99 Hz, 3H), 3.23 (br s, 4H), 3.55 (br s, 4H), 4.19 (q, *J* = 6.87 Hz, 2H), 6.71 (d, *J* = 16.11 Hz, 1H), 7.29 (t, *J* = 8.94 Hz, 1H), 7.47-7.54 (m, 2H), 7.55-7.65 (m, 2H), 7.69 (d, *J* = 16.32 Hz, 1H), 7.81 (s, 1H), 8.08 (s, 1H), 8.30 (dd, *J* = 2.28, 6.24 Hz, 1H), 9.62 (br s, 1H).	3-Bromo-4-fluoroaniline
Example 432[b]		MS(ES): 598 (M+1) for $C_{29}H_{32}FN_5O_6S$. 400 MHz, DMSO-d_6: δ 1.25 (t, *J* = 7.04 Hz, 3H), 3.04 (br s, 4H), 3.37 (br s, 4H), 3.55-3.56 (m, 4H), 3.63-3.66 (m, 4H), 4.19 (q, *J* = 7.04 Hz, 2H), 6.74 (d, *J* = 16.00 Hz, 1H), 7.49-7.54 (m, 3H), 7.69 (d, *J* = 16.04 Hz, 1H), 7.72 (br s, 1H), 7.79-7.80 (m, 1H), 7.82 (br s, 1H), 8.07 (s, 1H), 8.43-8.44 (m, 1H), 10.46 (br s, 1H).	4-Fluoro-3-(morpholine-4-sulfonyl)-phenylamine
Example 433[b]		MS(ES): 543 (M+1) for $C_{28}H_{30}N_8O_4$. 400 MHz, DMSO-d_6: δ 1.26 (t, *J* = 7.12 Hz, 3H), 2.60 (s, 3H), 3.22-3.24 (m, 4H), 3.51-3.53 (m, 4H), 3.82 (s, 3H), 4.20 (q, *J* = 7.12 Hz, 2H), 6.72 (d, *J* = 16.04 Hz, 1H), 6.85 (t, *J* = 2.12 Hz, 1H), 7.48 (t, *J* = 7.64 Hz, 1H), 7.54 (d, *J* = 7.08 Hz, 1H), 7.62 (t, *J* = 2.04 Hz, 1H), 7.67 (d, *J* = 7.48 Hz, 1H), 7.69 (d, *J* = 16.00 Hz, 1H), 7.78 (t, *J* = 1.84 Hz, 1H), 7.83 (s, 1H), 8.11 (s, 1H), 9.79 (s, 1H).	3-methoxy-5-(5-methyl-1H-tetrazol-1-yl)aniline
Example 434[c]		MS(ES): 505 (M+1) for $C_{28}H_{32}N_4O_5$. 400 MHz, DMSO-d_6: δ 1.27 (t, *J* = 7.20 Hz, 3H), 3.24 (br s, 4H), 3.32 (s, 3H), 3.55-3.56 (m, 4H), 3.67 (t, *J* = 3.60 Hz, 2H), 4.02-4.07 (m, 2H), 4.21 (q, *J* = 7.20 Hz, 2H), 6.51 (d, *J* = 8.40 Hz, 1H), 6.73 (d, *J* = 16.00 Hz, 1H), 7.16 (t, *J* = 8.00 Hz, 1H), 7.29 (d, *J* = 8.00 Hz, 1H), 7.51 (t, *J* = 7.60 Hz, 1H), 7.54-7.56 (m, 1H), 7.66 (s, 1H), 7.70 (d, *J* = 16.80 Hz, 1H), 7.80 (br s, 1H), 8.08 (s, 1H),	3-(2-methoxyethoxy)aniline

		8.32 (d, J = 1.20 Hz, 1H), 9.41 (br s, 1H).	

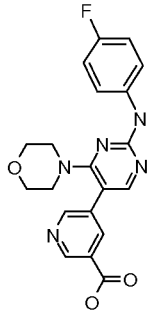
Solvents used in the reaction (a) n-butanol (b) acetonitrile (c) dioxane

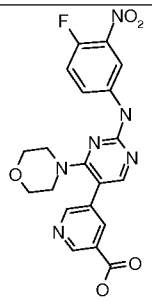
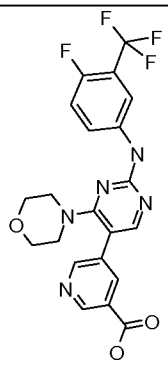
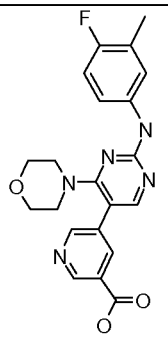
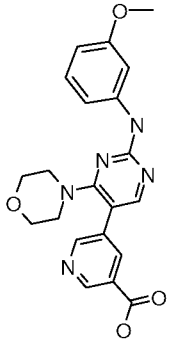
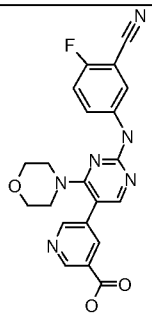
General procedure for the hydrolysis of pyridyl ester derivatives

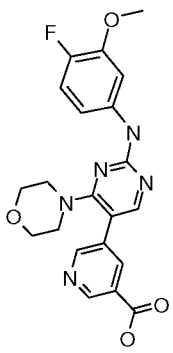
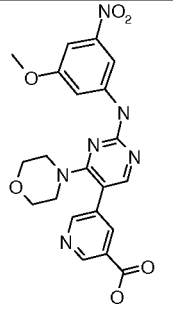
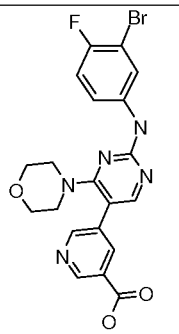
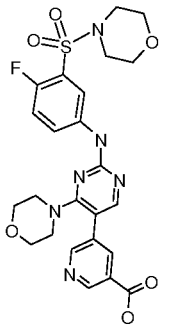
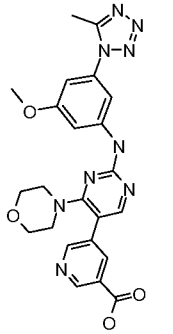


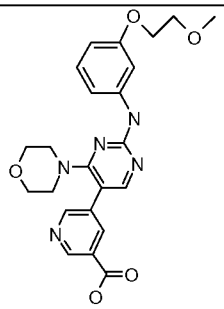
Ester compound (1 eq, 0.22 mmol) was dissolved in a mixture of tetrahydrofuran (1 mL) and water (1 mL) and treated with sodium hydroxide (35 mg, 1N, 0.88 mmol). The reaction was allowed to stir at room temperature for 1 hr. After completion of reaction, the reaction mixture was carefully acidified with 1 N HCl. The solid that precipitated was filtered off, washed with water and dried under vacuum.

The compounds in the below table were prepared using this general procedure and the specified starting material.

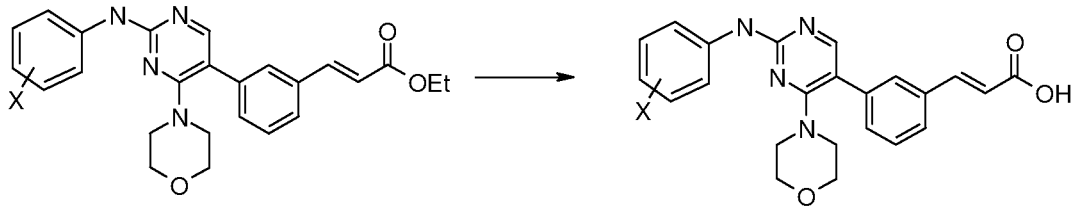
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 435		MS(ES): 396 (M+1) for $C_{20}H_{18}FN_5O_3$. 400 MHz, DMSO-d_6: δ 3.20-3.21 (m, 4H), 3.54-3.56 (m, 4H), 7.12 (t, J = 8.92 Hz, 2H), 7.73-7.77 (m, 2H), 8.13 (s, 1H), 8.34 (t, J = 1.96 Hz, 1H), 8.89 (d, J = 2.00 Hz, 1H), 8.98 (d, J = 1.68 Hz, 1H), 9.53 (s, 1H), 13.60 (br s, 1H).	5-[2-(4-Fluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester **Example 413**

Example 436		MS(ES): 441 (M+1) for $C_{20}H_{17}FN_6O_5$. 400 MHz, DMSO-d_6: δ 3.25-3.27 (m, 4H), 3.56-3.57 (m, 4H), 7.53 (dd, *J* = 9.24, 11.08 Hz, 1H), 7.90-7.92 (m, 1H), 8.20 (s, 1H), 8.35 (d, *J* = 1.92 Hz, 1H), 8.91-9.00 (m, 3H), 10.03 (s, 1H), 13.60 (br s, 1H).	5-[2-(4-Fluoro-3-nitro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester **Example 411**
Example 437		MS(ES): 464 (M+1) for $C_{21}H_{17}F_4N_5O_3$. 400 MHz, DMSO-d_6: δ 3.22-3.23 (m, 4H), 3.54-3.56 (m, 4H), 7.44 (t, *J* = 9.76 Hz, 1H), 7.89-7.92 (m, 1H), 8.18 (s, 1H), 8.35 (m, 1H), 8.43-8.44 (m, 1H), 8.91 (d, *J* = 2.04 Hz, 1H), 8.99 (d, *J* = 1.80 Hz, 1H), 9.89 (br s, 1H), 13.53 (br s, 1H).	5-[2-(4-Fluoro-3-trifluoromethyl-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester **Example 414**
Example 438		MS(ES): 410 (M+1) for $C_{21}H_{20}FN_5O_3$. 400 MHz, DMSO-d_6: δ 2.22 (s, 3H), 3.21-3.22 (m, 4H), 3.55-3.56 (m, 4H), 7.05 (t, *J* = 9.20 Hz, 1H), 7.54 (dd, *J* = 4.40, 8.20 Hz, 1H), 7.70 (dd, *J* = 2.40, 7.20 Hz, 1H), 8.14 (s, 1H), 8.35 (s, 1H), 8.91 (br s, 1H), 8.99 (br s, 1H), 9.49 (br s, 1H), 13.60 (br s, 1H).	5-[2-(4-Fluoro-3-methyl-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester **Example 415**
Example 439		MS(ES): 408 (M+1) for $C_{21}H_{21}N_5O_4$. 400 MHz, DMSO-d_6: δ 3.22 (br s, 4H), 3.55 (br s, 4H), 3.73 (s, 3H), 6.51 (d, *J* = 7.96 Hz, 1H), 7.16 (t, *J* = 8.12 Hz, 1H), 7.28 (d, *J* = 7.88 Hz, 1H), 7.54 (br s, 1H), 8.15 (br s, 1H), 8.35 (br s, 1H), 8.91 (br s, 1H), 8.98 (br s, 1H), 9.51 (br s, 1H), 13.6 (br s, 1H) .	5-[2-(3-Methoxy-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester **Example 416**
Example 440		MS(ES): 421 (M+1) for $C_{21}H_{17}FN_6O_3$. 400 MHz, DMSO-d_6: δ 3.22-3.23 (m, 4H), 3.53-3.56 (m, 4H), 7.47 (t, *J* = 9.24 Hz, 1H), 7.96-8.02 (m, 1H), 8.19 (s, 1H), 8.31-8.35 (m, 2H), 8.89 (d, *J* = 2.04 Hz, 1H), 8.99 (d, *J* = 1.76 Hz, 1H), 9.91 (s, 1H), 13.50 (br s, 1H).	5-[2-(3-Cyano-4-fluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester **Example 417**

Example 441		MS(ES): 426 (M+1) for $C_{21}H_{20}FN_5O_4$. 400 MHz, DMSO-d_6 : δ 3.22 (t, *J* = 4.08 Hz, 4H), 3.55 (t, *J* = 4.24 Hz, 4H), 3.83 (s, 3H), 7.10 (dd, *J* = 8.80, 11.24 Hz, 1H), 7.20 (t, *J* = 2.44 Hz, 1H), 7.76 (dd, *J* = 2.08, 7.96 Hz, 1H), 8.15 (s, 1H), 8.35 (d, *J* = 1.84 Hz, 1H), 8.90 (s, 1H), 8.98 (s, 1H), 9.52 (s, 1H), 13.50 (br s, 1H).	5-[2-(4-Fluoro-3-methoxy-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester **Example 418**
Example 442		MS(ES): 453 (M+1) for $C_{21}H_{20}N_6O_6$. 400 MHz, DMSO-d_6: δ 3.28-3.29 (m, 4H), 3.57-3.58 (m, 4H), 3.86 (s, 3H), 7.31 (s, 1H), 7.72 (s, 1H), 8.22 (s, 1H), 8.37 (s, 1H), 8.61 (s, 1H), 8.93 (d, *J* = 1.20 Hz, 1H), 9.01 (s, 1H), 10.04 (s, 1H), 13.58 (br s, 1H).	5-[2-(3-Methoxy-5-nitro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester **Example 419**
Example 443		MS(ES): 474 (M) and 476 (M+2) for $C_{20}H_{17}BrFN_5O_3$. 400 MHz, DMSO-d_6: δ 3.23-3.38 (m, 4H), 3.51-3.52 (m, 4H), 7.30 (t, *J* = 8.84 Hz, 1H), 7.63-7.67 (m, 1H), 8.17 (s, 1H), 8.30 (dd, *J* = 2.52, 6.40 Hz, 1H), 8.34 (d, *J* = 1.84 Hz, 1H), 8.90 (s, 1H), 8.99 (s, 1H), 9.72 (s, 1H), 13.50 (s, 1H).	5-[2-(3-Bromo-4-fluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-nicotinic acid ethyl ester **Example 420**
Example 444		MS(ES): 545 (M+1) for $C_{24}H_{25}FN_6O_6S$. 400 MHz, DMSO-d_6: δ 3.03 (br s, 4H), 3.24 (br s, 4H), 3.55 (br s, 4H), 3.65 (br s, 4H), 7.44 (t, *J* = 9.52 Hz, 1H), 7.83-7.85 (m, 1H), 8.17 (s, 1H), 8.34 (s, 1H), 8.59 (br s, 1H), 8.90 (s, 1H), 8.99 (s, 1H), 9.94 (s, 1H), 13.58 (br s, 1H).	5-{2-[4-Fluoro-3-(morpholine-4-sulfonyl)-phenylamino]-4-morpholin-4-yl-pyrimidin-5-yl}-nicotinic acid ethyl ester **Example 421**
Example 445		MS(ES): 490 (M+1) for $C_{23}H_{23}N_9O_4$. 400 MHz, DMSO-d_6: δ 2.60 (s, 3H), 3.22-3.23 (m, 4H), 3.52-3.54 (m, 4H), 3.82 (s, 3H), 6.86 (t, *J* = 1.88 Hz, 1H), 7.62 (s, 1H), 7.78 (s, 1H), 8.19 (s, 1H), 8.34 (t, *J* = 1.96 Hz, 1H), 8.90 (d, *J* = 2.00 Hz, 1H), 8.99 (d, *J* = 1.72 Hz, 1H), 9.88 (s, 1H), 13.60 (br s, 1H).	5-{2-[3-Methoxy-5-(5-methyl-tetrazol-1-yl)-phenylamino]-4-morpholin-4-yl-pyrimidin-5-yl}-nicotinic acid ethyl ester

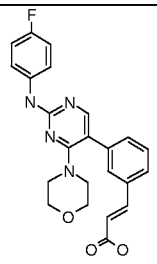
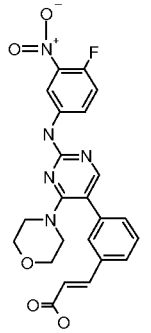
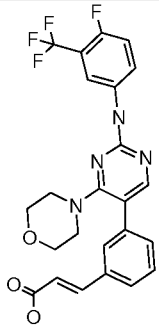
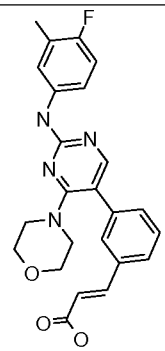
			Example 422
Example 446		MS(ES): 452 (M+1) for $C_{23}H_{25}N_5O_5$. 400 MHz, DMSO-d_6: δ 3.22-3.23 (m, 4H), 3.31 (s merged with solvent peak, 3H), 3.54-3.56 (m, 4H), 3.65 (t, *J* = 4.52 Hz, 2H), 4.05 (t, *J* = 4.84 Hz, 2H), 6.52 (dd, *J* = 2.24, 8.08 Hz, 1H), 7.13-7.17 (m, 1H), 7.28 (d, *J* = 8.04 Hz, 1H), 7.53 (s, 1H), 8.15 (s, 1H), 8.35 (t, *J* = 2.08 Hz, 1H), 8.90 (d, *J* = 2.16 Hz, 1H), 8.98 (d, *J* = 1.92 Hz, 1H), 9.51 (s, 1H), 13.52 (br s, 1H).	5-{2-[3-(2-Methoxy-ethoxy)-phenylamino]-4-morpholin-4-yl-pyrimidin-5-yl}-nicotinic acid ethyl ester **Example 423**

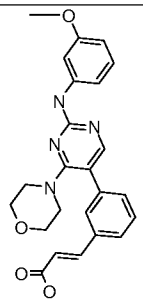
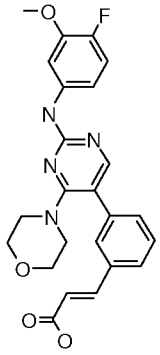
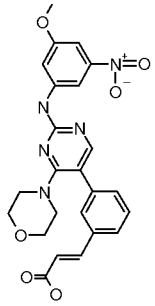
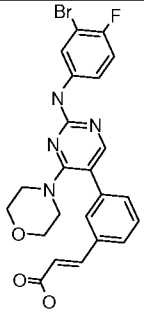
General procedure for the hydrolysis of cinnamyl ester derivatives

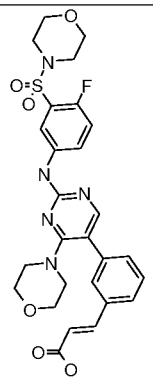
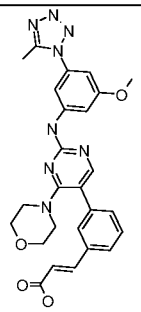
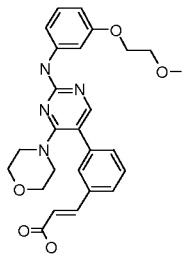


Ester compound (1 eq, 0.22 mmol) was dissolved in a mixture of tetrahydrofuran (1 mL) and water (1 mL) and treated with sodium hydroxide (35 mg, 1N, 0.88 mmol). The reaction was allowed to stir at room temperature for 1 hr. After completion of reaction, the reaction mixture was carefully acidified with 1 N HCl. The solid that precipitated was filtered off, washed with water and dried under vacuum.

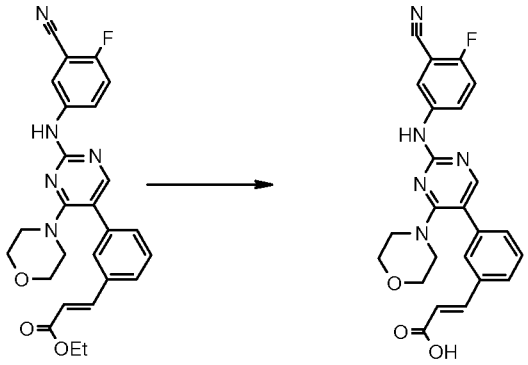
The compounds in the below table were prepared using this general procedure and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 447		MS(ES): 421 (M+1) for $C_{23}H_{21}FN_4O_3$. 400 MHz, DMSO-d6: δ 3.21-3.22 (m, 4H), 3.53-3.54 (m, 4H), 6.61 (d, *J* = 15.92 Hz, 1H), 7.11 (t, *J* = 8.88 Hz, 2H), 7.44-7.48 (m, 2H), 7.54-7.60 (m, 2H), 7.74-7.77 (m, 3H), 8.04 (s, 1H), 9.42 (s, 1H).	3-{3-[2-(4-Fluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 424**
Example 448		MS(ES): 466 (M+1) for $C_{23}H_{20}FN_5O_5$. 400 MHz, DMSO-d_6: δ 3.27-3.28 (m, 4H), 3.55-3.57 (m, 4H), 6.62 (d, *J* = 16.08 Hz, 1H), 7.47-7.54 (m, 3H), 7.64-7.66 (m, 1H), 7.64 (d, *J* = 15.92 Hz, 1H), 7.80 (br s, 1H), 7.88-7.92 (m, 1H), 8.12 (s, 1H), 8.96 (dd, *J* = 2.76, 6.88 Hz, 1H), 9.94 (br s, 1H), 12.44 (br s, 1H).	3-{3-[2-(4-Fluoro-3-nitro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 412**
Example 449		MS(ES): 489 (M+1) for $C_{24}H_{20}F_4N_4O_3$. 400 MHz, $(CD_3)CO_2D$: δ 3.63 (br s, 4H), 3.74-3.76 (m, 4H), 6.68 (d, *J* = 16.20 Hz, 2H), 7.36 (t, *J* = 9.44 Hz, 1H), 7.54 (d, *J* = 7.24 Hz, 1H), 7.60 (t, *J* = 7.44 Hz, 1H), 7.73 (s, 1H), 7.73 (br s, 1H), 7.79-7.81 (m, 1H), 7.88 (d, *J* = 16.00 Hz, 1H), 8.08 (s, 1H), 8.33 (d, *J* = 5.08 Hz, 1H).	3-{3-[2-(4-Fluoro-3-trifluoromethyl-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 425**
Example 450		MS(ES): 435 (M+1) for $C_{24}H_{23}FN_4O_3$. 400 MHz, DMSO-d_6: δ 2.21 (s, 3H), 3.22-3.23 (m, 4H), 3.55-3.58 (m, 4H), 6.61 (d, *J* = 16.00 Hz, 1H), 7.04 (t, *J* = 9.20 Hz, 1H), 7.46-7.55 (m, 3H), 7.64 (d, *J* = 16.00 Hz, 1H), 7.64 (s, 1H), 7.70 (dd, *J* = 2.40, 6.80 Hz, 1H), 7.78 (br s, 1H), 8.05 (br s, 1H), 9.37 (br s, 1H), 12.40 (br s, 1H).	3-{3-[2-(4-Fluoro-3-methyl-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 426**

Example 451		MS(ES): 433 (M+1) for $C_{24}H_{24}N_4O_4$. 400 MHz, DMSO-d_6: δ 3.24 (br s, 4H), 3.55 (br s, 4H), 3.73 (s, 3H), 6.50 (d, *J* = 6.80 Hz, 1H), 6.61 (d, *J* = 16.04 Hz, 1H), 7.15 (t, *J* = 6.92 Hz, 1H), 7.27 (d, *J* = 5.20 Hz, 1H), 7.47-7.65 (m, 5H), 7.79 (br s, 1H), 8.06 (br s, 1H), 9.40 (br s, 1H), 12.42 (br s, 1H).	3-{3-[2-(3-Methoxy-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 427**
Example 452		MS(ES): 451 (M+1) for $C_{24}H_{23}FN_4O_4$. 400 MHz, DMSO-d6 : δ 3.21-3.27 (m, 4H), 3.52-3.58 (m, 4H), 3.83 (s, 3H), 6.61 (d, *J* = 16.00 Hz, 1H), 7.09 (dd, *J* = 8.88, 11.24 Hz, 1H), 7.18-7.20 (m, 1H), 7.45-7.53 (m, 2H), 7.62 (d, *J* = 15.92 Hz, 1H), 7.62 (d, *J* = 7.60 Hz, 1H), 7.75-7.78 (m, 2H), 8.06 (s, 1H), 9.41 (s, 1H), 12.50 (br s, 1H).	3-{3-[2-(4-Fluoro-3-methoxy-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 429**
Example 453		MS(ES): 478 (M+1) for $C_{24}H_{23}N_5O_6$. 400 MHz, DMSO-d_6: δ 3.32 (br s, 4H), 3.56 (br s, 4H), 3.85 (s, 3H), 6.55 (d, *J* = 15.92 Hz, 1H), 7.28 (t, *J* = 2.20 Hz, 1H), 7.32 (d, *J* = 15.96 Hz, 1H), 7.43 (m, 2H), 7.50-7.51 (m, 1H), 7.66 (s, 1H), 7.72 (d, *J* = 1.56 Hz, 1H), 8.10 (d, *J* = 2.60 Hz, 1H), 8.60 (br s, 1H), 9.93 (br s, 1H).	3-{3-[2-(3-Methoxy-5-nitro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 430**
Example 454		MS(ES): 499 (M) and 501 (M+2) for $C_{23}H_{20}BrFN_4O_3$. 400 MHz, DMSO-d_6: δ 3.25 (br s, 4H), 3.55 (br s, 4H), 6.61 (d, *J* = 16.08 Hz, 1H), 7.31 (t, *J* = 8.80 Hz, 1H), 7.48 (t, *J* = 7.44 Hz, 1H), 7.50 (br s, 1H), 7.63 (d, *J* = 15.96 Hz, 1H), 7.63-7.65 (m, 2H), 7.78 (br s, 1H), 8.07 (s, 1H), 8.27 (dd, *J* = 1.96, 6.18 Hz, 1H), 9.71 (br s, 1H).	3-{3-[2-(3-Bromo-4-fluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester **Example 431**

Example 455		MS(ES): 570 (M+1) for $C_{27}H_{28}FN_5O_6S$. 400 MHz, DMSO-d_6: δ 3.03 (br s, 4H), 3.26 (br s, 4H), 3.54-3.55 (m, 4H), 3.64-3.65 (m, 4H), 6.61 (d, *J* = 16.04 Hz, 1H), 7.43 (t, *J* = 9.20 Hz, 1H), 7.48-7.53 (m, 2H), 7.63 (d, *J* = 15.76 Hz, 1H), 7.63 (s, 1H), 7.79 (s, 1H), 7.82-7.85 (m, 1H), 8.09 (s, 1H), 8.60-8.61 (m, 1H), 9.85 (s, 1H), 12.44 (br s, 1H).	3-(3-{2-[4-Fluoro-3-(morpholine-4-sulfonyl)-phenylamino]-4-morpholin-4-yl-pyrimidin-5-yl}-phenyl)-acrylic acid ethyl ester **Example 432**
Example 456		MS(ES): 515 (M+1) for $C_{26}H_{26}N_8O_4$. 400 MHz, DMSO-d_6: δ 2.61 (s, 3H), 3.27 (br s, 4H), 3.52-3.53 (m, 4H), 3.83 (s, 3H), 6.62 (d, *J* = 16.00 Hz, 1H), 6.89 (s, 1H), 7.49-7.54 (m, 2H), 7.60-7.67 (m, 3H), 7.76-7.80 (m, 2H), 8.10 (s, 1H), 9.89 (s, 1H), 12.40 (br s, 1H).	3-(3-{2-[3-Methoxy-5-(5-methyl-tetrazol-1-yl)-phenylamino]-4-morpholin-4-yl-pyrimidin-5-yl}-phenyl)-acrylic acid ethyl ester **Example 433**
Example 457		MS(ES): 477 (M+1) for $C_{26}H_{28}N_4O_5$. 400 MHz, DMSO-d_6: δ 3.24-3.25 (m, 4H), 3.32 (s, 3H), 3.55-3.55 (m, 4H), 3.66 (t, *J* = 4.40 Hz, 2H), 4.06 (t, *J* = 4.80 Hz, 2H), 6.50 (dd, *J* = 2.00, 8.00 Hz, 1H), 6.61 (d, *J* = 16.00 Hz, 1H), 7.15 (t, *J* = 8.40 Hz, 1H), 7.29 (d, *J* = 8.00 Hz, 1H), 7.45-7.53 (m, 2H), 7.55-7.63 (m, 3H), 7.78 (s, 1H), 8.08 (s, 1H), 9.41 (br s, 1H).	3-(3-{2-[3-(2-Methoxy-ethoxy)-phenylamino]-4-morpholin-4-yl-pyrimidin-5-yl}-phenyl)-acrylic acid ethyl ester **Example 434**

Example 458: (E)-3-(3-(2-(3-cyano-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)phenyl)acrylic acid



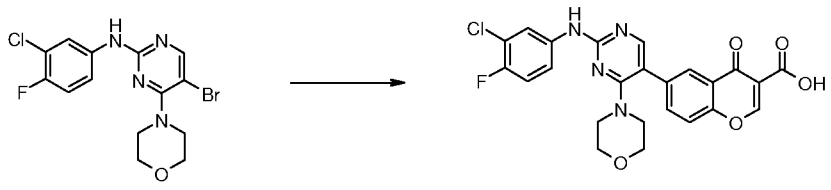
To 3-{3-[2-(3-Cyano-4-fluoro-phenylamino)-4-morpholin-4-yl-pyrimidin-5-yl]-phenyl}-acrylic acid ethyl ester (**Example 428**) (0.12 g, 0.25 mmol) in THF (1 mL) and water (0.2 mL), sodium hydroxide (0.5 mmol, 20 mg) was added and the mixture was heated at 60 °C overnight. The reaction mixture was then acidified using 1.5 N HCl and the solid obtained was filtered, washed with water and dried. LCMS analysis indicated that the solid was a 17 :3 mixture of the title compound and the corresponding carboxamide resulting from nitrile hydrolysis. A pure sample of the title compound was produced by converting the carboxamide to the nitrile using the procedure below.

The mixture obtained as above (0.07 g) was taken in $POCl_3$ (1 mL) and heated at 100 °C for 3 h. The reaction mixture was cooled and concentrated under vacuo. Crushed ice was then added to the slurry to obtain an off-white solid, which was filtered, further washed with water and dried to give the pure title compound (0.06 g).

MS(ES): 446 (M+1) for $C_{24}H_{20}FN_5O_3$.

400 MHz, DMSO-d_6: δ 3.34 (br s, 4H), 3.55 (br s, 4H), 6.63 (d, J = 16.04 Hz, 1H), 7.49-7.56 (m, 3H), 7.64 (d, J = 16.04 Hz, 1H), 7.69 (d, J = 6.72 Hz, 1H), 7.78 (s, 1H), 7.95 (br s, 1H), 8.06 (s, 1H), 8.21 (m, 1H), 10.36 (br s, 1H).

Example 459: 6-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)-4-oxo-4H-chromene-3-carboxylic acid



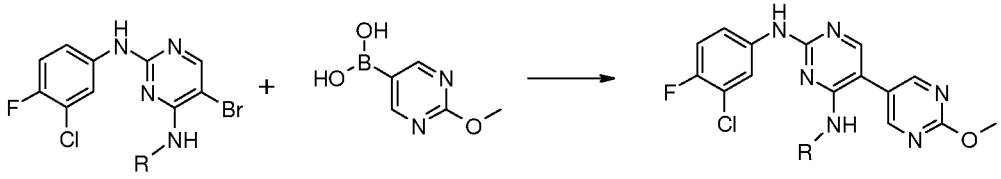
A suspension of 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-morpholin-4-ylpyrimidin-2-amine [**Intermediate 146**] (0.56 mmol, 220 mg), 2:1 mixture of boronic acid and pinacol boronate, **Intermediate 155** (52 mg), tris(dibenzylideneacetone)dipalladium(0) (10 mol%, 0.054 mmol, 52 mg), 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (30 mol%, 0.17 mmol, 81 mg) and sodium carbonate (0.56 mmol, 60 mg) in 4:1 acetonitrile-water (10 mL) was degassed and then heated to 90 °C for 30 minutes. Solvent was removed in vacuo, resulting residue was redissolved in ethyl acetate (20 mL), filtered through a bed of celite and washed with water (2x10 mL). The filtrate was then acidified with 1.5N HCl, and the precipitate formed was filtered, washed with water and dried to yield the title compound as a brown solid (0.16 mmol, 80 mg, 29 %).

MS(ES): 497 (M+1) for $C_{24}H_{18}ClFN_4O_5$.

400 MHz, DMSO-d_6 : δ 3.23 (br s, 4H), 3.55 (br s, 4H), 7.25-7.30 (m, 1H), 7.40 (t, *J* = 8.96 Hz, 1H), 7.54-7.58 (m, 1H), 7.62 (d, *J* = 8.24 Hz, 1H), 7.91-7.93 (m, 1H), 7.97-8.00 (m, 2H), 9.92 (s, 1H), 9.98 (br s, 1H).

Example 460: N^2-(3-chloro-4-fluorophenyl)-2'-methoxy-N^4-[2-(pyridin-3-yl)ethyl]-5,5'-bipyrimidine-2,4-diamine

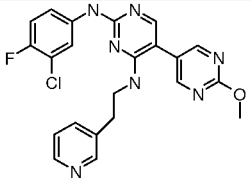
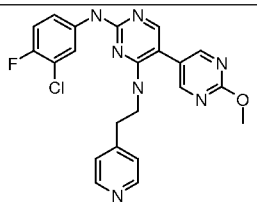
Example 461: N^2-(3-chloro-4-fluorophenyl)-2'-methoxy-N^4-[2-(pyridin-4-yl)ethyl]-5,5'-bipyrimidine-2,4-diamine



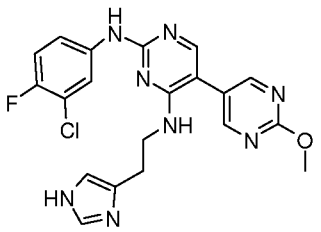
A suspension of 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[alkylamino]pyrimidin-2-amine (1 eq), (2-methoxypyrimidin-5-yl)boronic acid (1.05 eq),

tris(dibenzylideneacetone)dipalladium(0) (10 mol%), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (30 mol%) and sodium carbonate (1.1 eq) in acetonitrile/water (4:1) was heated to 90 °C for 30 minutes. The reaction mixture was diluted with ethyl acetate (25 mL); organic layer was separated, dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel column chromatography using chloroform:methanol (9:1) as an eluent to afford the product.

The compounds in the below table were prepared using this method and the specified starting material.

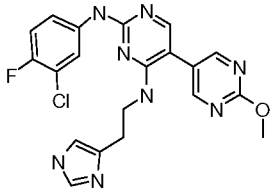
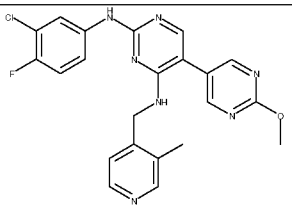
Compound	Structure	Mass and ^{1}H NMR data	SM
Example 460	 N^2-(3-chloro-4-fluorophenyl)-2'-methoxy-N^4-[2-(pyridin-3-yl)ethyl]-5,5'-bipyrimidine-2,4-diamine	MS(ES): 452 (M+1) for $C_{22}H_{19}ClFN_7O$ 400 MHz, DMSO-d_6: δ 2.89-2.91 (t, *J* = 7.04 Hz, 2H), 3.58 (q, *J*= 6.72 Hz, 2H), 3.94 (s, 3H), 7.01 (t, *J* = 5.28 Hz, 1H), 7.25-7.32 (m, 2H), 7.61 (d, *J* = 6.92 Hz, 2H), 7.79 (s, 1H), 8.20 (dd, *J* = 2.52, 6.90 Hz, 1H), 8.40-8.43 (m, 2H), 8.48 (s, 2H), 9.43 (s, 1H).	**Intermediate 45** 5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-[2-(pyridin-3-yl)ethyl]pyrimidine-2,4-diamine
Example 461	 N^2-(3-chloro-4-fluorophenyl)-2'-methoxy-N^4-[2-(pyridin-4-yl)ethyl]-5,5'-bipyrimidine-2,4-diamine	MS(ES): 452 (M+1) for $C_{22}H_{19}ClFN_7O$. 400 MHz, DMSO-d_6: δ 2.90 (t, *J* = 7.2 Hz, 2H), 3.60 (q, J = 6.40 Hz, 2H), 3.96 (s, 3H), 7.02 (t, *J* = 6.00 Hz, 1H), 7.23-7.30 (m, 3H), 7.59-7.63 (m, 1H), 7.80 (s, 1H), 8.21 (dd, *J* = 2.40, 7.00 Hz, 1H), 8.46 (d, *J* = 6.00 Hz, 2H), 8.50 (s, 2H), 9.45 (s, 1H).	**Intermediate 46** 5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-[2-(pyridin-4-yl)ethyl]pyrimidine-2,4-diamine

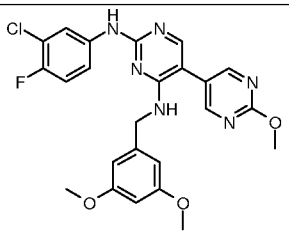
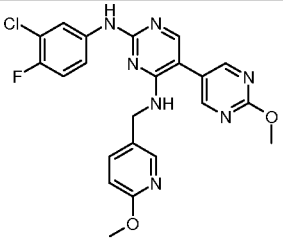
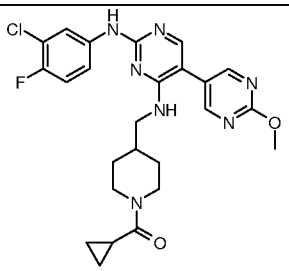
Example 462: N^2-(3-chloro-4-fluorophenyl)-N^4-[2-(1*H*-imidazol-4-yl)ethyl]-2'-methoxy-5,5'-bipyrimidine-2,4-diamine

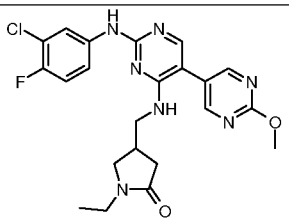
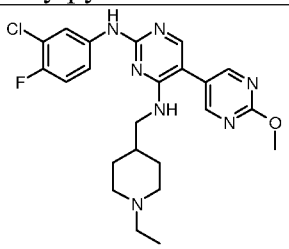
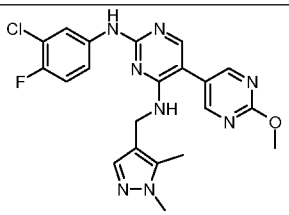
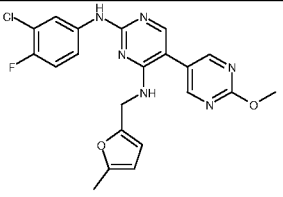


To a suspension of NaH (2.2 mmol, 60% dispersion in oil) in NMP, 2-(1H-Imidazol-4-yl)-ethylamine (1 eq) was added and stirred for 30 min. *N*-(3-chloro-4-fluorophenyl)-2'-methoxy-4-(methylsulfonyl)-5,5'-bipyrimidin-2-amine **Intermediate 156** (1eq) in NMP was added to the reaction mixture drop wise and stirred at RT for overnight. Water was added to the reaction mixture; the solid thus obtained was filtered and purified by column chromatography using chloroform-methanol to yield the title compound.

The compounds in the below table were prepared using this method and the specified starting material.

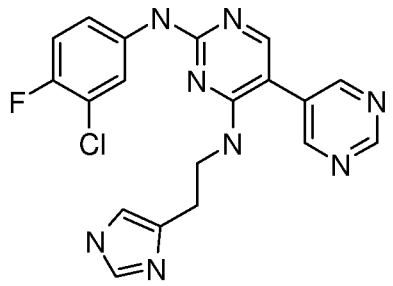
Compound	Structure	Mass and ^{1}H NMR data	SM
Example 462	 N^2-(3-chloro-4-fluorophenyl)-N^4-[2-(1*H*-imidazol-4-yl)ethyl]-2'-methoxy-5,5'-bipyrimidine-2,4-diamine	MS(ES): 441 (M+1) for $C_{20}H_{18}ClFN_8O$. 400 MHz, DMSO-d_6: δ 2.70-2.90 (m, 2H), 3.56-3.57 (m, 2H), 3.95 (s, 3H), 6.81 (br s, 1H), 7.07 (br s, 1H), 7.25 (t, *J* = 9.12 Hz, 1H), 7.51 (s, 1H), 7.70 (d, *J* = 7.00 Hz, 1H), 7.78 (s, 1H), 8.16 (dd, *J* = 2.52, 6.88 Hz, 1H), 8.52 (d, *J* = 5.72 Hz, 2H), 9.43 (s, 1H), 11.81 (br s, 1H).	2-(1H-Imidazol-4-yl)-ethylamine
Example 463	 N2-(3-chloro-4-fluorophenyl)-2'-methoxy-N4-((3-methylpyridin-4-yl)methyl)-5,5'-bipyrimidine-2,4-	MS(ES): 452(M+1) for $C_{22}H_{19}ClFN_7O$. 400 MHz, DMSO-d_6: δ 2.29 (s, 3 H) 3.96 (s, 4 H) 4.50 (m, 2 H) 7.16 (mm, 2 H) 7.37 (mm, 2 H) 7.85 (mm, 2 H) 8.34 (mm, 2 H) 8.68 (s, 2 H) 9.37 (s, 1 H)	(3-methylpyridin-4-yl)methanamine

	diamine		
Example 464	 N2-(3-chloro-4-fluorophenyl)-N4-(3,5-dimethoxybenzyl)-2'-methoxy-5,5'-bipyrimidine-2,4-diamine	MS(ES): 497(M+1) for $C_{24}H_{22}ClFN_6O_3$. 400 MHz, DMSO-d_6: δ 3.66 (s, 6 H) 3.96 (s, 3 H) 4.49 (m, 2 H) 6.33 (s, 1 H) 6.46 (s, 2 H) 7.23 (t, 1 H) 7.53 (m, 1 H) 7.65 (m, 1 H) 7.83 (s, 1 H) 8.03 (m, 1 H) 8.59 (s, 2 H) 9.59 (s, 1 H)	3,5-dimethoxybenzylamine
Example 465	 N2-(3-chloro-4-fluorophenyl)-2'-methoxy-N4-((6-methoxypyridin-3-yl)methyl)-5,5'-bipyrimidine-2,4-diamine	MS(ES): 468(M+1) for $C_{22}H_{19}ClFN_7O_2$. 400 MHz, DMSO-d_6: δ 3.78 (s, 3 H) 3.95 (m, 3 H) 4.48 (m, 2 H) 6.75 (d, 1 H) 7.26 (t, 1 H) 7.55 (mm, 2 H) 7.67 (d, 1 H) 7.82 (s, 1 H) 8.07 (m, 1 H) 8.13 (s, 1 H) 8.58 (s, 2 H) 9.48 (s, 1 H)	(6-methoxypyridin-3-yl)methanamine
Example 466	 (4-((2-(3-chloro-4-fluorophenylamino)-2'-methoxy-5,5'-bipyrimidin-4-ylamino)methyl)piperidin-1-yl)(cyclopropyl)methanone	MS(ES): 512(M+1) for $C_{25}H_{27}ClFN_7O_2$. 400 MHz, DMSO-d_6: δ 0.66 (m, 4 H) 0.99 (m, 2 H) 1.75 (m, 2 H) 1.93 (m, 2 H) 3.01 (s, 1 H) 3.26 (mm, 4 H) 3.99 (s, 3 H) 4.31 (m, 2 H) 7.11 (m, 1 H) 7.29 (t, 1 H) 7.55 (m, 1 H) 7.77 (s, 1 H) 8.24 (m, 1 H) 8.55 (s, 2 H) 9.49 (s, 1 H)	(4-(aminomethyl)piperidin-1-yl)(cyclopropyl)methanone

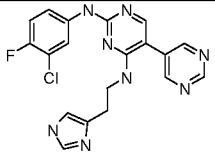
Example 467	 4-((2-(3-chloro-4-fluorophenylamino)-2'-methoxy-5,5'-bipyrimidin-4-ylamino)methyl)-1-ethylpyrrolidin-2-one	MS(ES): 472(M+1) for $C_{22}H_{23}ClFN_7O_2$. 400 MHz, DMSO-d_6: δ 0.96 (t, 3 H) 2.06 (m, 1 H) 2.36 (m, 1 H) 2.71 (m, 1 H) 3.14 (m, 3 H) 3.43 (m, 3 H) 3.96 (s, 3 H) 7.14 (s, 1 H) 7.29 (t, 1 H) 7.56 (m, 1 H) 7.79 (s, 1 H) 8.22 (m, 1 H) 8.55 (s, 2 H) 9.48 (s, 1 H)	4-(aminomethyl)-1-ethylpyrrolidin-2-one
Example 468	 N2-(3-chloro-4-fluorophenyl)-N4-((1-ethylpiperidin-4-yl)methyl)-2'-methoxy-5,5'-bipyrimidine-2,4-diamine	MS(ES): 472(M+1) for $C_{23}H_{27}ClFN_7O$. 400 MHz, DMSO-d_6: δ 0.95 (t, 3 H) 1.14 (m, 2 H) 1.65 (mm, 4 H) 2.24 (q, 2 H) 2.82 (m, 2 H) 3.21 (bs, 2 H) 3.95 (s, 3 H) 6.92 (m, 1 H) 7.27 (t, 1 H) 7.58 (m, 1 H) 7.74 (s, 1 H) 8.24 (m, 1 H) 8.53 (s, 2 H) 9.41 (s, 1 H)	(1-ethylpiperidin-4-yl)methanamine
Example 469	 N2-(3-chloro-4-fluorophenyl)-N4-((1,5-dimethyl-1H-pyrazol-4-yl)methyl)-2'-methoxy-5,5'-bipyrimidine-2,4-diamine	MS(ES): 455(M+1) for $C_{21}H_{20}ClFN_8O$. 400 MHz, DMSO-d_6: δ 2.17 (s, 3 H) 3.64 (s, 3 H) 3.94 (s, 4 H) 4.32 (m, 2 H) 7.17 (bs, 1 H) 7.28 (m, 2 H) 7.63 (m, 1 H) 7.77 (s, 1 H) 8.17 (m, 1 H) 8.51 (m, 2 H) 9.42 (s, 1 H)	(1,5-dimethyl-1H-pyrazol-4-yl)methanamine
Example 470	 N2-(3-chloro-4-fluorophenyl)-2'-	MS(ES): 441(M+1) for $C_{21}H_{18}ClFN_6O_2$. 400 MHz, DMSO-d_6: δ 2.19 (s, 3 H) 3.96 (s, 3 H) 4.46 (d, 2 H) 5.96 (s, 1 H) 6.09 (s, 1 H) 7.36 (t, 1 H) 7.55 (m, 1 H) 7.88 (s, 1 H) 8.06 (m, 2 H) 8.56 (s, 2 H) 10.14 (s, 1	(5-methylfuran-2-yl)methanamine

	methoxy-N4-((5-methylfuran-2-yl)methyl)-5,5'-bipyrimidine-2,4-diamine	H)	

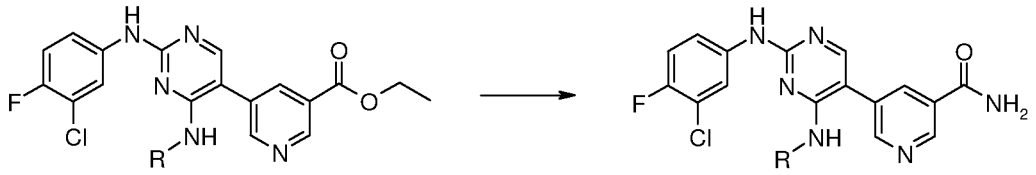
Example 471: N^2-(3-chloro-4-fluorophenyl)-N^4-[2-(1*H*-imidazol-4-yl)ethyl]-5,5'-bipyrimidine-2,4-diamine



To a suspension of NaH (2.2 mmol, 60% dispersion in oil) in DMF, 2-(1H-Imidazol-4-yl)-ethylamine (1 eq) was added and stirred for 30 minutes. N-(3-chloro-4-fluorophenyl)-4-methylsulfonyl-5-pyrimidin-5-ylpyrimidin-2-amine **Intermediate 123** (1 eq) in DMF was added to the reaction mixture drop wise and stirred at room temperature 16 hours. The reaction mixture was added to water and stirred for 15 min. The precipitated solid was filtered, washed with water and dried to afford the crude product. It was further purified by flash chromatography using chloroform:methanol (9:1) to get the pure product.

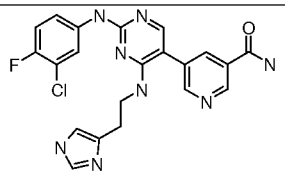
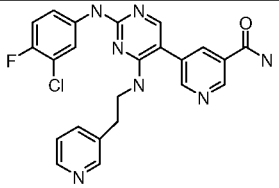
Compound	Structure	Mass and ^{1}H NMR data	SM
Example 471	 N^2-(3-chloro-4-fluorophenyl)-N^4-[2-(1*H*-imidazol-4-yl)ethyl]-5,5'-bipyrimidine-2,4-diamine	MS(ES): 411 (M+1) for $C_{19}H_{16}ClFN_8$. 400 MHz, DMSO-d_6: δ 2.70-2.90 (m, 2H), 3.56-3.61 (m, 2H), 6.85 (br s, 1H), 7.07 (br s, 1H), 7.25 (t, J = 9.12 Hz, 1H), 7.51 (s, 1H), 7.72 (br s, 1H), 7.86 (s, 1H), 8.16 (dd, J = 2.52, 6.88 Hz, 1H), 8.77 (s, 2H), 9.15 (s, 1H), 9.49 (s, 1H), 11.8 (br s, 1H).	2-(1H-Imidazol-4-yl)-ethylamine

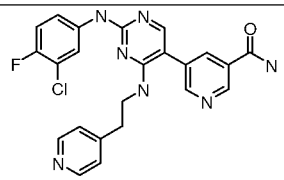
General procedure for conversion of pyridine carboxylic esters to carboxamide derivatives



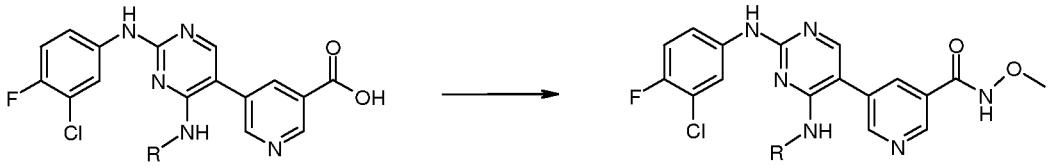
To a solution of ester (1 eq) in THF (2 mL) was added aqueous ammonia solution (20 mL) and the mixture was heated to 60 °C in a sealed tube for 16 -24 h. The reaction mixture was cooled to room temperature, the solid thus obtained was filtered, washed with water and dried to give product.

Compounds in the below table were prepared using this general procedure and the specified starting material.

Compound	Structure	Mass and ^{1}H NMR data	SM
Example 472	 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-imidazol-4-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxamide	MS(ES): 453 (M+1) for $C_{21}H_{18}ClFN_8O$ 400 MHz, DMSO-d_6: δ 2.80-2.83 (m, 2H), 3.59-3.64 (m, 2H), 6.83 (br s, 1H), 7.13 (br s, 1H), 7.27 (t, *J* = 9.20 Hz, 1H), 7.50 (s, 1H), 7.65 (br s, 1H), 7.73-7.75 (m, 1H), 7.88 (s, 1H), 8.15-8.18 (m, 2H), 8.21-8.22 (m, 1H), 8.67 (d, *J* = 1.20 Hz, 1H), 8.98 (d, *J* = 2.00 Hz, 1H), 9.47 (s, 1H), 11.82 (br s, 1H).	**Example 154** ethyl 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-imidazol-4-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylate
Example 473	 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(pyridin-3-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxamide	MS(ES): 464 (M+1) for $C_{23}H_{19}ClFN_7O$ 400 MHz, DMSO-d_6: δ 2.91 (t, *J* = 7.20 Hz, 2H), 3.61-3.63 (m, 2H), 7.26-7.33 (m, 2H), 7.62-7.66 (m, 3H), 7.88 (s, 1H), 8.16 (s, 2H), 8.21 (dd, *J* = 2.40, 6.80 Hz, 1H), 8.41-8.45 (m, 2H), 8.62 (d, *J* = 1.60 Hz, 1H), 8.98 (d, *J* = 2.00 Hz, 1H), 9.48 (s, 1H).	**Example 102** ethyl 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(pyridin-3-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylate

Example 474	 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(pyridin-4-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxamide	MS(ES): 464 (M+1) for $C_{23}H_{19}ClFN_7O$. 400 MHz, DMSO-d_6: δ 2.99 (t, *J* = 7.00 Hz, 2H), 3.75 (t, *J* = 7.20 Hz, 2H), 7.15 (t, *J* = 9.00 Hz, 1H), 7.28 (dd, *J* = 1.44, 4.60 Hz, 2H), 7.47 (ddd, *J* = 2.72, 4.10, 8.99 Hz, 1H), 7.81 (s, 1H), 8.07 (dd, *J* = 2.64, 6.74 Hz, 1H), 8.23-8.24 (m, 1H), 8.39 (dd, *J* = 1.52, 4.56 Hz, 2H), 8.65 (d, *J* = 2.12 Hz, 1H), 8.98 (d, *J* = 2.12 Hz, 1H).	**Example 103** ethyl 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(pyridin-4-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylate

Synthesis of *N*-methoxy carboxamides from carboxylic acids



Method A:

To a mixture of (**Example 257**) (1eq), triethylamine (3 eq) and methoxylamine hydrochloride (1.2 eq) in DMF was added HOBt (5 mol %), EDCI (1.2 eq) slowly at 0 °C. The reaction mixture was slowly raised to room temperature and stirred for overnight. Water was added and the precipitate thus formed was filtered and dried to yield **Example 475**.

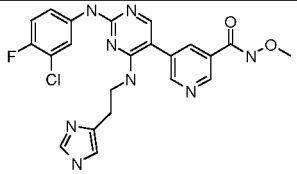
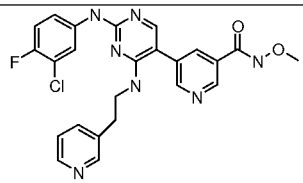
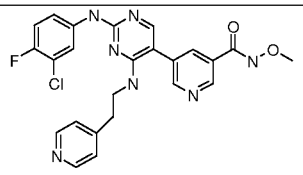
Method B:

To a mixture of **(Example 229)** (1eq), triethylamine (4 eq) and methoxylamine hydrochloride (1.2 eq) in EtOAc:DCM (1:1) was added T3P (50%, 1.5 eq) slowly at 0 °C. The reaction mixture was slowly raised to room temperature and stirred for overnight. Reaction mixture was then diluted with dichloromethane (12 mL), washed the dichloromethane solution successively with water (2x50 mL), 10% aq sodium bicarbonate solution (50 mL) and brine. The organic layer was dried over sodium sulphate, filtered, concentrated and dried to yield **Example 476.**

Method C:

To a mixture of (**Example 230**) (1eq), triethylamine (3.5 eq) and methoxylamine hydrochloride (1.0 eq) in DMF was added BOP (1.2 eq) slowly at 0 °C. The reaction mixture was slowly raised to room temperature and stirred for 3-4 h. Water was added followed by extraction with EtOAc. The organic layer was dried over sodium sulphate, filtered and concentrated. The resulting residue was purified by silica gel column chromatography using chloroform:methanol (9:1) as an eluent to afford **Example 477.**

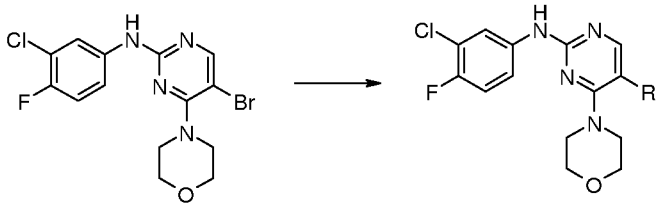
The compounds in the below table were prepared following the methods described above as indicated with the starting material listed.

Compound	Structure	Mass and ^{1}H NMR data	SM
Example 475[a]	 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-imidazol-4-yl)ethyl]amino}pyrimidin-5-yl)-*N*-methoxypyridine-3-carboxamide	MS (ES): 481 (M-1) for $C_{22}H_{20}ClFN_8O_2$. 400 MHz, DMSO-d_6 : δ 2.80 (br s, 2H), 3.60-3.61 (m, 2H), 3.74 (s, 3H), 6.84 (br s, 1H), 7.13 (br s, 1H), 7.26 (t, *J* = 9.44 Hz, 1H), 7.50 (s, 1H), 7.73 (br s, 1H), 7.87 (s, 1H), 8.09 (s, 1H), 8.15 (d, *J* = 6.24 Hz, 1H), 8.69 (s, 1H), 8.86 (s, 1H), 9.48 (s, 1H), 12.00 (br s, 2H).	**Example 257** 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(1*H*-imidazol-4-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylic acid
Example 476[b]	 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(pyridin-3-yl)ethyl]amino}pyrimidin-5-yl)-*N*-methoxypyridine-3-carboxamide	MS(ES): 492 (M-1) for $C_{24}H_{21}ClFN_7O_2$. 400 MHz, DMSO-d_6 : δ 2.91-2.93 (m, 2H), 3.61-3.63 (m, 2H), 3.76 (s, 3H), 7.04 (t, *J* = 5.20 Hz, 1H), 7.27-7.33 (m, 2H), 7.62-7.65 (m, 2H), 7.88 (s, 1H), 8.03 (s, 1H), 8.21 (dd, *J* = 1.20, 7.40 Hz, 1H), 8.43 (br s, 2H), 8.65 (s, 1H), 8.87 (s, 1H), 9.49 (s, 1H), 11.96 (br s, 1H).	**Example 229** 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(pyridin-3-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylic acid
Example 477[c]		MS(ES): 494 (M+1) for $C_{24}H_{21}ClFN_7O_2$. 400 MHz, DMSO-d_6: δ 2.90 (t, *J* = 6.72 Hz, 2H), 3.60-3.65 (m, 2H), 3.74 (s, 3H), 7.02 (t, *J* =	**Example 230** 5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-

	5-(2-[(3-chloro-4-fluorophenyl)amino]-4-{[2-(pyridin-4-yl)ethyl]amino}pyrimidin-5-yl)-*N*-methoxypyridine-3-carboxamide	5.68 Hz, 1H), 7.23 (d, *J* = 5.60 Hz, 2H), 7.27 (t, *J* = 9.08 Hz, 1H), 7.59-7.63 (m, 1H), 7.87 (s, 1H), 8.03 (s, 1H), 8.19 (dd, *J* = 2.56, 6.86 Hz, 1H), 8.45 (d, *J* = 5.76 Hz, 2H), 8.64 (s, 1H), 8.86 (d, *J* = 1.72 Hz, 1H), 9.48 (s, 1H), 11.96 (br s, 1H).	(pyridin-4-yl)ethyl]amino}pyrimidin-5-yl)pyridine-3-carboxylic acid

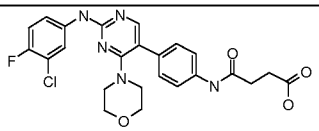
(a) Method A (b) Method B (c) Method C

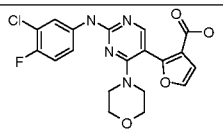
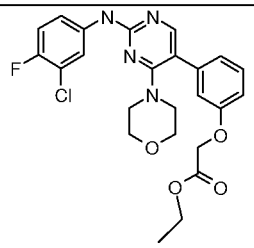
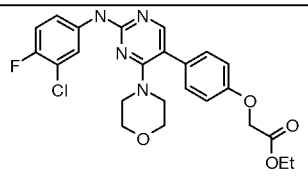
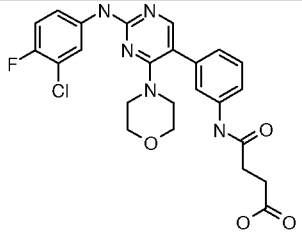
General procedure for Aryl-aryl coupling reaction using Intermediate 146

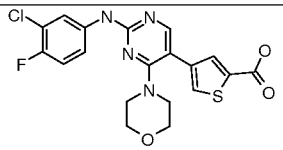
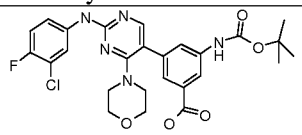
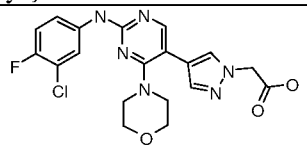
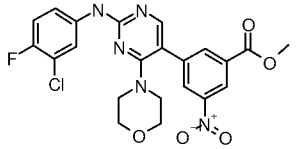
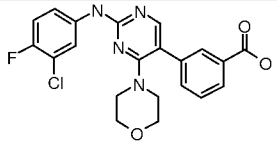


A suspension of **Intermediate 146** (1 eq), boronic acid (1.05 eq), tris(dibenzylideneacetone)dipalladium(0) (10 mol%), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (30 mol%) and sodium carbonate (2 eq) in acetonitrile/water (4:1) was heated to 90 °C for 30 minutes. The reaction mixture was diluted with ethyl acetate; organic layer was separated, dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel column chromatography using chloroform:methanol (9:1) as an eluent to afford the product.

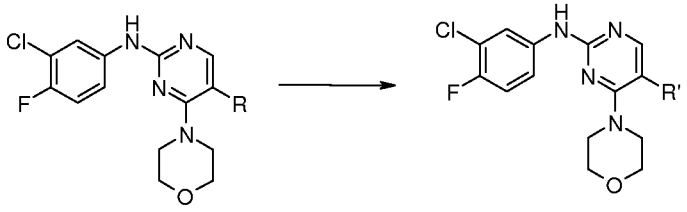
The compounds in the below table were prepared using this general method and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 478	 4-[(4-{2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidin-5-yl}phenyl)amino]-4-oxobutanoic acid	MS(ES): 500 (M+1) for $C_{24}H_{23}ClFN_5O_4$. 400 MHz, AcOH : δ 1.42 (s, 4H), 2.03-2.07 (m, 4H), 2.37 (t, *J* = 4.96 Hz, 4H), 5.88 (t, *J* = 9.00 Hz, 1H), 6.13 (d, *J* = 8.52 Hz, 2H), 6.20 (ddd, *J* = 2.72, 4.02, 8.95 Hz, 1H), 6.38 (d, *J* = 8.60 Hz, 2H), 6.66 (br s, 1H), 6.78 (dd, *J* = 2.68, 6.74 Hz, 1H).	4-oxo-4-{[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amino}butanoic acid

Example 479	 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidin-5-yl}furan-3-carboxylic acid	MS(ES): 419 (M+1) for $C_{19}H_{16}ClFN_4O_4$. 400 MHz, DMSO-d_6 : δ 3.24 (t, *J* = 4.56 Hz, 4H), 3.57 (t, *J* = 4.92 Hz, 4H), 6.80 (d, *J* = 1.92 Hz, 1H), 7.33 (t, *J* = 9.12 Hz, 1H), 7.61 (ddd, *J* = 2.76, 4.20, 9.05 Hz, 1H), 7.78 (d, *J* = 1.84 Hz, 1H), 8.07 (dd, *J* = 5.48, 5.44 Hz, 1H), 8.10 (s, 1H), 9.68 (s, 1H).	2-(dihydroxyboranyl)furan-3-carboxylic acid
Example 480	 ethyl (3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidin-5-yl}phenoxy)acetate	MS(ES): 487 (M+1) for $C_{24}H_{24}ClFN_4O_4$. 400 MHz, DMSO-d_6 : δ 1.20 (t, *J* = 7.08 Hz, 3H), 3.22 (t, *J* = 4.32 Hz, 4H), 3.55 (t, *J* = 4.84 Hz, 4H), 4.17 (q, *J* = 7.08 Hz, 2H), 4.82 (s, 2H), 6.87 (dd, *J* = 2.48, 8.04 Hz, 1H), 6.99 (t, *J* = 1.48 Hz, 1H), 7.06 (d, *J* = 7.72 Hz, 1H), 7.29-7.36 (m, 2H), 7.61 (ddd, *J* = 2.68, 4.16, 9.09 Hz, 1H), 8.01 (s, 1H), 8.14 (dd, *J* = 2.64, 6.88 Hz, 1H), 9.60 (s, 1H).	ethyl [3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]acetate
Example 481	 ethyl (4-{2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidin-5-yl}phenoxy)acetate	MS(ES): 459 (M+1) for $C_{22}H_{20}ClFN_4O_4$. 400 MHz, DMSO-d_6: δ 1.21 (t, *J* = 7.08 Hz, 3H), 3.22 (d, *J* = 3.88 Hz, 4H), 3.55 (t, *J* = 4.12 Hz, 4H), 4.17 (q, *J* = 7.04 Hz, 2H), 4.80 (s, 2H), 6.99 (d, *J* = 8.48 Hz, 2H), 7.31 (t, *J* = 9.04 Hz, 1H), 7.38 (d, *J* = 8.44 Hz, 2H), 7.60-7.63 (m, 1H), 7.97 (s, 1H), 8.14 (dd, *J* = 2.28, 6.80 Hz, 1H), 9.55 (s, 1H).	ethyl [4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]acetate
Example 482	 4-[(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidin-5-yl}phenyl)amino]-4-oxobutanoic acid	MS(ES): 500 (M+1) for $C_{24}H_{23}ClFN_5O_4$. 400 MHz, DMSO-d_6 : δ 2.49-2.53 (m, 2H), 2.55-2.57 (m, 2H), 3.22-3.26 (m, 4H), 3.54-3.58 (m, 4H), 7.11 (d, *J* = 7.56 Hz, 1H), 7.26-7.36 (m, 2H), 7.51 (d, *J* = 8.36 Hz, 1H), 7.60-7.63 (m, 1H), 7.72 (s, 1H), 7.97 (s, 1H), 8.13 (d, *J* = 6.76 Hz, 1H), 9.59 (s, 1H), 10.07 (s, 1H), 12.16 (br s, 1H).	4-oxo-4-{[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amino}butanoic acid

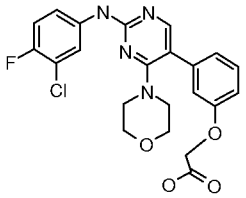
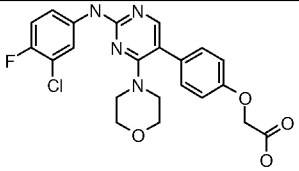
Example 483	 4-{2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidin-5-yl}thiophene-2-carboxylic acid	MS(ES): 433 (M-1) for $C_{19}H_{16}ClFN_4O_3S$. 400 MHz, DMSO-d_6 : δ 3.25 (t, *J* = 4.12 Hz, 4H), 3.55-3.60 (m, 4H), 7.32 (t, *J* = 9.04 Hz, 1H), 7.62 (dd, *J* = 3.04, 8.80 Hz, 1H), 7.88 (s, 1H), 7.92 (s, 1H), 8.12-8.17 (m, 1H), 8.31 (s, 1H), 9.66 (s, 1H), 13.30 (br s, 1H).	4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylic acid
Example 484	 3-[(*tert*-butoxycarbonyl)amino]-5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidin-5-yl}benzoic acid	MS(ES): 544 (M+1) for $C_{26}H_{27}ClFN_5O_5$. 400 MHz, DMSO-d_6: δ 1.49 (s, 9H), 3.23 (br s, 4H), 3.57 (br s, 4H), 7.33 (t, J = 9.12 Hz, 1H), 7.62-7.64 (m, 2H), 7.76 (br s, 1H), 8.02 (s, 1H), 8.10 (s, 1H), 8.13 (dd, J = 2.52, 6.92 Hz, 1H), 9.67 (dd, J = 8.76, Hz, 2H), 13.03 (br s, 1H).	3-[(*tert*-butoxycarbonyl)amino]-5-(dihydroxyboranyl)benzoic acid
Example 485	 (4-{2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidin-5-yl}-1*H*-pyrazol-1-yl)acetic acid	MS(ES): 433 (M+1) for $C_{19}H_{18}ClFN_6O_3$. 400 MHz, DMSO-d_6 : δ 3.26 (t, *J* = 4.24 Hz, 4H), 3.65 (t, *J* = 4.72 Hz, 4H), 4.98 (s, 2H), 7.30 (t, *J* = 9.12 Hz, 1H), 7.59-7.63 (m, 1H), 7.70 (s, 1H), 7.97 (s, 1H), 8.13 (s, 1H), 8.15 (d, *J* = 2.60 Hz, 1H), 9.57 (s, 1H), 13.08 (br s, 1H).	ethyl [4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl]acetate
Example 486	 methyl 3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidin-5-yl}-5-nitrobenzoate	MS(ES): 488.2 (M+1) for $C_{22}H_{19}ClFN_5O_5$. 400 MHz, DMSO-d_6 : δ 3.22 (t, *J* = 4.08 Hz, 4H), 3.55 (t, *J* = 4.52 Hz, 4H), 3.94 (s, 3H), 7.34 (t, *J* = 9.12 Hz, 1H), 7.63 (ddd, *J* = 2.76, 4.16, 9.09 Hz, 1H), 8.13 (dd, *J* = 2.60, 6.88 Hz, 1H), 8.23 (s, 1H), 8.44 (t, *J* = 1.48 Hz, 1H), 8.51 (t, *J* = 2.08 Hz, 1H), 8.56 (t, *J* = 1.76 Hz, 1H), 9.80 (s, 1H).	methyl 3-nitro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate
Example 487	 3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidin-5-yl}benzoic acid	MS(ES): 429 (M+1) for $C_{21}H_{18}ClFN_4O_3$. 400 MHz, DMSO-d_6: δ 3.21 (br s, 4H), 3.55 (br s, 4H), 7.32 (t, J = 9.04 Hz, 1H), 7.56 (t, J = 7.36 Hz, 1H), 7.62-7.64 (m, 1H), 7.71 (d, J = 7.68 Hz, 1H), 7.87 (d, J = 7.84 Hz, 1H), 8.04 (br s, 1H), 8.08 (br s, 1H), 8.14 (d, J = 4.88 Hz, 1H), 9.65 (s, 1H), 13.12 (br s, 1H).	3-(dihydroxyboranyl)benzoic acid

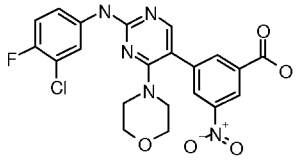
General procedure for hydrolysis of carboxylic acid ester derivatives



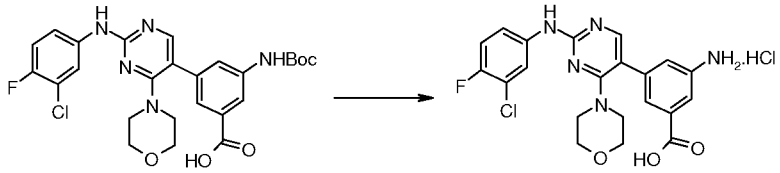
Starting ester (1eq, 0.22 mmol) was dissolved in a mixture of tetrahydrofuran (1 mL) and water (1 mL) and treated with 1 N sodium hydroxide (4 eq, 0.88 mmol) and allowed to stir at room temperature for 16 hours. Reaction mixture was then carefully acidified with 1 N HCl and the precipitate formed was filtered, washed with water and dried to yield the product.

The compounds in the below table were prepared using this general method and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 488	 (3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidin-5-yl}phenoxy)acetic acid	MS(ES): 459 (M+1) for $C_{22}H_{20}ClFN_4O_4$. 400 MHz, DMSO-d_6: δ 3.20-3.25 (m, 4H), 3.55-3.60 (m, 4H), 4.43 (s, 2H), 6.80 (d, J = 7.64 Hz, 1H), 6.91 (s, 1H), 6.98 (d, J = 7.64 Hz, 1H), 7.27-7.33 (m, 2H), 7.61-7.64 (m, 1H), 7.99 (s, 1H), 8.13 (dd, J = 2.32, 6.88 Hz, 1H), 9.58 (s, 1H).	**Example 480** ethyl (3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidin-5-yl}phenoxy)acetate
Example 489	 (4-{2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidin-5-yl}phenoxy)acetic acid	MS(ES): 459.2 (M+1) for $C_{22}H_{20}ClFN_4O_4$. 400 MHz, DMSO-d_6: δ 3.25 (br s, 4H), 3.55 (br s, 4H), 4.70 (s, 2H), 6.98 (d, J = 7.88 Hz, 2H), 7.31-7.38 (m, 3H), 7.55-7.65 (m, 1H), 7.96 (s, 1H), 8.09 (d, J = 4.92 Hz, 2H), 9.71 (s, 1H), 13.04 (br s, 1H).	**Example 481** ethyl (4-{2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidin-5-

			yl}phenoxy) acetate
Example 490	 3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidin-5-yl}-5-nitrobenzoic acid	MS(ES): 474 (M+1) for $C_{21}H_{17}ClFN_5O_5$. 400 MHz, DMSO-d_6: δ 3.23 (br s, 4H), 3.56 (br s, 4H), 7.33 (t, J = 9.04 Hz, 1H), 7.63-7.65 (m, 1H), 8.14 (d, J = 6.64 Hz, 1H), 8.20 (s, 1H), 8.41 (br s, 2H), 8.52 (br s, 1H), 9.76 (br s, 1H).	**Example 486** methyl 3-{2-[(3-chloro-4-fluorophenyl) amino]-4-(morpholin-4-yl) pyrimidin-5-yl}-5-nitrobenzoate

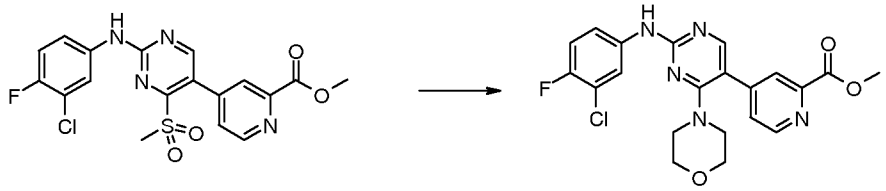
Example 491: 3-amino-5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidin-5-yl}benzoic acid



To 3-(tert-butoxycarbonylamino)-5-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)benzoic acid, **Example 484** (0.25 mmol, 110 mg), HCl in dioxane (4 mL) was added and the mixture was stirred at room temperature for 16 hours. The solvent was evaporated and the residue was triturated with diethyl ether. The solid thus obtained was dried to yield the title compound. MS (ES): 444 (M+1) for $C_{21}H_{19}ClFN_5O_3$.

400 MHz, DMSO-d_6: δ 3.38 (br s, 4H), 3.58 (br s, 4H), 7.09 (s, 1H), 7.40-7.45 (m, 3H), 7.52-7.56 (m, 1H), 7.95 (dd, J = 2.32, 6.66 Hz, 1H), 7.99 (s, 1H), 10.50 (br s, 1H).

Example 492: methyl 4-{2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidin-5-yl}pyridine-2-carboxylate

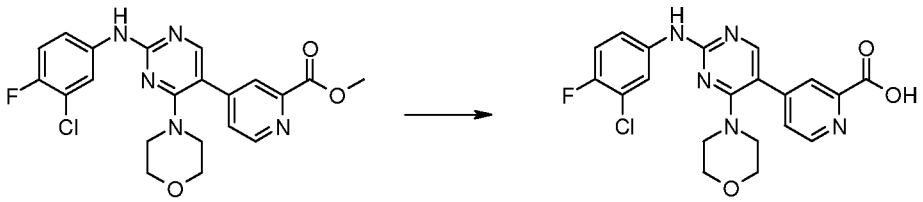


To a mixture of methyl 4-{2-[(3-chloro-4-fluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}pyridine-2-carboxylate (**Intermediate 157**), 0.23 mmol, 0.1 g) and morpholine (0.28 mmol, 24 mg) in NMP (2.5 mL), was added DIPEA (0.28 mmol, 36 mg) and heated to 90 °C for 1 h. Water (3 mL) was added to the reaction mixture and the solid thus formed was filtered and dried to yield the title compound.

MS(ES): 444 (M+1) for $C_{21}H_{19}ClFN_5O_3$

400 MHz, DMSO-d_6: δ 3.24 (t, J = 4.16 Hz, 4H), 3.59 (t, J = 4.20 Hz, 4H), 3.90 (s, 3H), 7.34 (t, J = 9.08 Hz, 1H), 7.61-7.62 (m, 1H), 7.77 (d, J = 3.60 Hz, 1H), 8.13 (dd, J = 2.52, 6.68 Hz, 1H), 8.17 (br s, 1H), 8.24 (s, 1H), 8.72 (d, J = 5.00 Hz, 1H), 9.81 (br s, 1H).

Example 493: 4-{2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidin-5-yl}pyridine-2-carboxylic acid

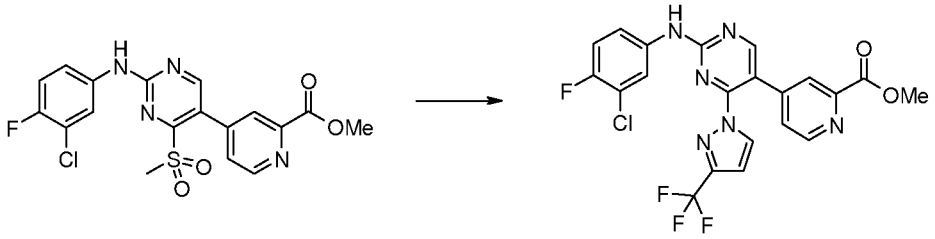


Methyl 4-{2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidin-5-yl}pyridine-2-carboxylate **Example 492**, 0.23 mmol, 0.1 g) was dissolved in tetrahydrofuran (1 mL) and treated with aq.1 N sodium hydroxide (0.11 mmol, 4 mg) and allowed to stir at room temperature for 1 h. After completion of the reaction, the mixture was then carefully acidified with 1 N HCl and the precipitate formed was filtered, washed with water and dried to yield the title compound.

MS(ES): 428 (M-1) for $C_{20}H_{17}ClFN_5O_3$.

400 MHz, DMSO-d_6: δ 3.25 (br s, 4H), 3.60 (br s, 4H), 7.35 (t, J = 9.20 Hz, 1H), 7.63-7.65 (m, 1H), 7.75 (d, J = 3.60 Hz, 1H), 8.14 (dd, J = 2.00, 6.40 Hz, 1H), 8.18 (s, 1H), 8.24 (s, 1H), 8.71 (s, 1H), 9.81 (br s, 1H).

Example 494: methyl 4-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-2-carboxylate

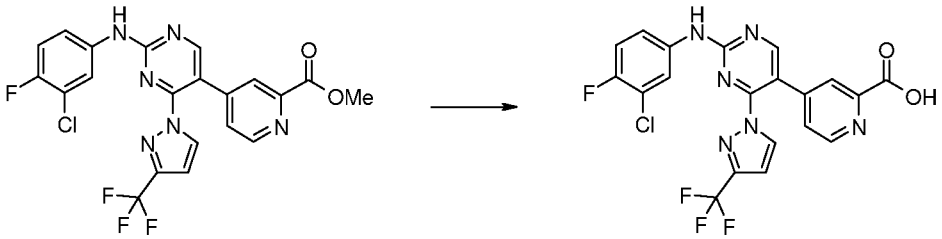


A suspension of sodium hydride (2 eq, 0.23 mmol, 5.5 mg) in NMP was cooled to 0 °C and a solution of 3-(trifluoromethyl)-1*H*-pyrazole (2.2 eq, 0.13 mmol, 17 mg) in NMP (1 mL) was added slowly and the reaction mixture was gradually allowed to attain room temperature. The mixture was then stirred for 30 min at room temperature. It was recooled to 0 °C and a solution of methyl 4-{2-[(3-chloro-4-fluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}pyridine-2-carboxylate (**Intermediate 157,** 0.114 mmol, 50 mg) in DMSO (1 mL) was added slowly to the reaction mixture and stirred for 4 h. The reaction mixture was poured into ice-water (6 mL), and filtered and dried to yield the title compound.

MS(ES):493 (M+1) for $C_{21}H_{13}ClF_4N_6O_2$.

400 MHz, DMSO-d_6: δ 3.85 (s, 3H), 7.08 (d, J = 2.40 Hz, 1H), 7.44 (t, J = 9.20 Hz, 1H), 7.52 (br s, 1H), 7.71-7.75 (m, 1H), 7.76 (s, 1H), 8.07 (dd, J = 2.40, 6.80 Hz, 1H), 8.55 (s, 1H), 8.68 (d, J = 5.20 Hz, 1H), 8.85 (s, 1H), 10.54 (br s, 1H).

Example 495: 4-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-2-carboxylic acid

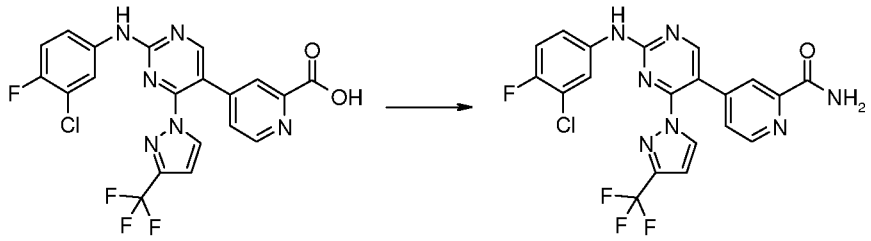


To methyl 4-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-2-carboxylate **Example 494** (0.32 mmol, 0.16 g) taken in

tetrahydrofuran (1 mL) and water (1 mL), was added Lithium hydroxide monohydrate (0.64 mmol, 28 mg) at 0 °C and was gradually allowed to attain room temperature over a period of 1 h. After completion of the reaction, the mixture was then carefully acidified with 1 N HCl and the precipitate formed was filtered, washed with water and dried to yield the title compound.

MS(ES): 479 (M+1) for $C_{20}H_{11}ClF_4N_6O_2$ (Taken to the next step on the basis of LCMS).

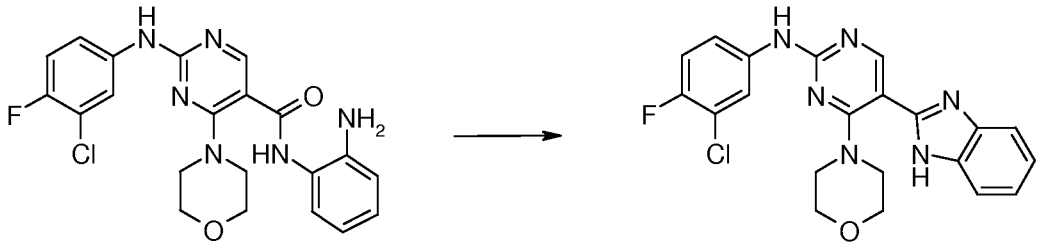
Example 496: 4-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-2-carboxamide



To a solution of 4-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-2-carboxylic acid, **Example 495** (0.38 mmol, 180 mg, 1 eq), pyridine (0.38 mmol, 30 mg, 1 eq) and di-*tert*-butyl dicarbonate (0.48 mmol, 107 mg, 1.3 eq) in DMSO (5 mL), was added ammonium hydrogencarbonate (0.48 mmol, 39 mg 1.26 eq) and the mixture stirred for 24 h at ambient temperature. After completion of the reaction, the reaction mixture was poured into crushed ice. The solid that was formed was filtered off and further purified by column chromatography.

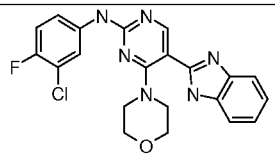
MS(ES): 478 (M+1) for $C_{20}H_{12}ClF_4N_7O$.

Example 497: 5-(1*H*-benzimidazol-2-yl)-*N*-(3-chloro-4-fluorophenyl)-4-(morpholin-4-yl)pyrimidin-2-amine

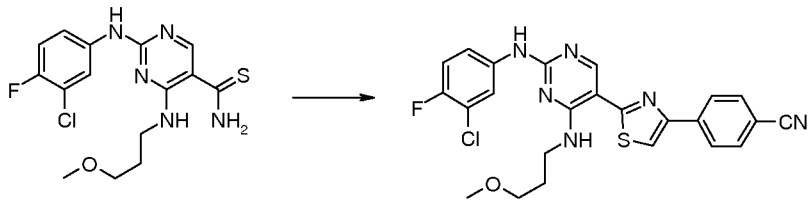


N-(2-aminophenyl)-2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidine-5-carboxamide **Intermediate 161** (0.16 mmol, 70 mg) was dissolved in acetic acid (3 mL) and the reaction mixture was heated at 90 °C for 8 h. The solid that had precipitated out was filtered.

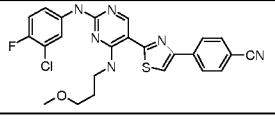
The filtrate was basified with NaOH and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4 and further purified by column chromatography using methanol: chloroform (2: 98) to yield 10 mg of the title compound as a white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 497	 5-(1*H*-benzimidazol-2-yl)-*N*-(3-chloro-4-fluorophenyl)-4-(morpholin-4-yl)pyrimidin-2-amine	MS(ES): 425 (M+1) for $C_{21}H_{18}ClFN_6O$. 400 MHz, DMSO-d_6: δ 3.29-3.32 (m, 4H), 3.60-3.63 (m, 4H), 7.14-7.21 (m, 2H), 7.35 (t, J = 9.08 Hz, 1H), 7.48-7.50 (m, 1H), 7.61-7.64 (m, 2H), 8.11 (dd, J = 2.40, 6.90 Hz, 1H), 8.38 (s, 1H), 9.78 (s, 1H), 12.49 (s, 1H).	**Intermediate 161** *N*-(2-aminophenyl)-2-[(3-chloro-4-fluorophenyl)amino]-4-(morpholin-4-yl)pyrimidine-5-carboxamide

Example 498: 4-(2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-1,3-thiazol-4-yl)benzonitrile

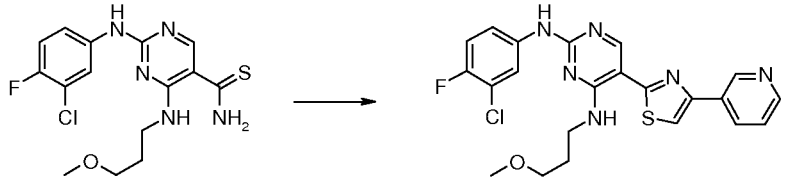


To a suspension of 2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidine-5-carbothioamide (**Intermediate 159**, 0.14 mmol, 50 mg) and magnesium sulphate (0.14 mmol, 16 mg) in dry acetone (2 mL) under nitrogen atmosphere, was added 4-cyanophenacyl bromide (0.14 mmol, 33 mg). The resulting mixture was stirred at reflux temperature for 3 h, concentrated and purified by silica gel column chromatography (60- 120 mesh) using ethyl acetate/hexanes as eluent to afford the title compound (23 mg).

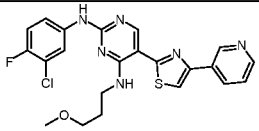
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 498		MS(ES): 495 (M+1) for $C_{24}H_{20}ClFN_6OS$ 400 MHz, DMSO-d_6: δ 1.96	4-cyanophenacyl bromide

	4-(2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-1,3-thiazol-4-yl)benzonitrile	(t, J = 6.28 Hz, 2H), 3.22 (s, 3H), 3.49 (t, J = 6.00 Hz, 2H), 3.69 (q, J = 6.40 Hz, 2H), 7.33 (t, J = 9.08 Hz, 1H), 7.63-7.64 (m, 1H), 7.95 (d, J = 8.40 Hz, 2H), 8.17 (d, J = 8.40 Hz, 2H), 8.25 (dd, J = 2.40, 6.80 Hz, 1H), 8.32 (s, 1H), 8.59 (s, 1H), 9.27 (t, J = 4.40 Hz, 1H), 9.86 (br s, 1H).	and **Intermediate 159**

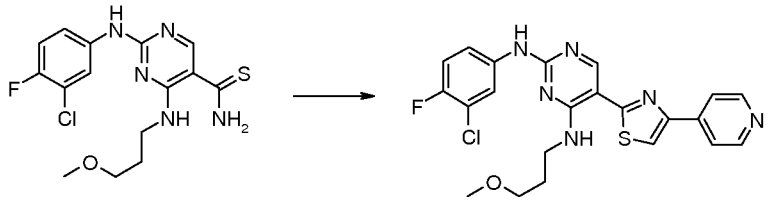
Example 499: N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)-5-[4-(pyridin-3-yl)-1,3-thiazol-2-yl]pyrimidine-2,4-diamine



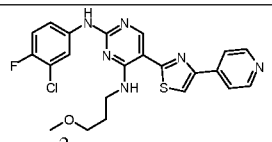
To a solution of 2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidine-5-carbothioamide (**Intermediate 159**), 0.54 mmol, 200 mg) in ethanol (2 mL) was added 3-bromoacetylpyridine hydrobromide (0.59 mmol, 0.167 g) and triethylamine (0.5 mmol, 50 mg). The resulting mixture was subjected to microwave irradiation at 150 °C for 2 h. The precipitated solid was filtered, washed with water and dried to afford the crude product. It was further purified by silica gel column chromatography (60-120 mesh) to afford the title compound (40 mg).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 499	 N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)-5-[4-(pyridin-3-yl)-1,3-thiazol-2-yl]pyrimidine-2,4-diamine	MS(ES): 471 (M+1) for $C_{22}H_{20}ClFN_6OS$. 400 MHz, DMSO-d_6: δ 1.94-1.95 (m, 2H), 3.22 (s, 3H), 3.50 (t, J = 6.04 Hz, 2H), 3.70 (q, J = 6.60 Hz, 2H), 7.33 (t, J = 9.12 Hz, 1H), 7.52 (q, J = 4.72 Hz, 1H), 7.64-7.68 (m, 1H), 8.22 (s, 1H), 8.26 (dd, J = 2.48, 6.88 Hz, 1H), 8.34 (d, J = 7.88 Hz, 1H), 8.57-8.60 (m, 2H), 9.22 (d, J = 1.76 Hz, 1H), 9.31 (t, J = 5.40 Hz, 1H), 9.86 (br s, 1H).	3-bromoacetylpyridine hydrobromide and **Intermediate 159**

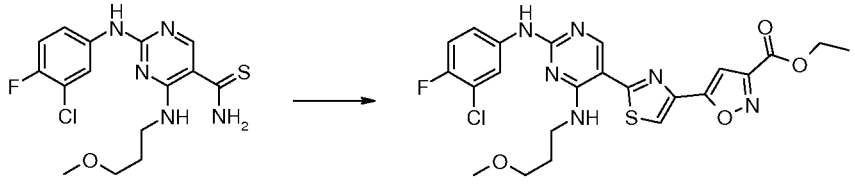
Example 500: N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)-5-[4-(pyridin-4-yl)-1,3-thiazol-2-yl]pyrimidine-2,4-diamine



To a suspension of 2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidine-5-carbothioamide (**Intermediate 159**), 0.22 mmol, 80 mg) in DMF (2 mL), was added 4-bromoacetylpyridine hydrobromide (0.23 mmol, 65 mg) and warmed to 80 °C for 3 h. After completion of the reaction, as monitored by TLC, the reaction mixture was quenched with water. The solid that precipitated out was filtered. It was further stirred with acetonitrile, filtered and dried to afford the title compound (60 mg).

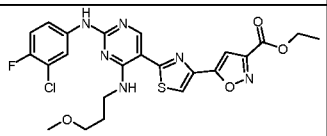
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 500	 N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)-5-[4-(pyridin-4-yl)-1,3-thiazol-2-yl]pyrimidine-2,4-diamine	MS(ES): 471 (M+1) for $C_{22}H_{20}ClFN_6OS$. 400 MHz, DMSO-d_6: δ 1.97 (t, J = 6.44 Hz, 2H), 3.23 (s, 3H), 3.50 (t, J = 6.04 Hz, 2H), 3.71 (q, J = 6.48 Hz, 2H), 7.34 (t, J = 9.08 Hz, 1H), 7.64-7.67 (m, 1H), 8.20-8.21 (m, 2H), 8.25 (dd, J = 2.40, 6.82 Hz, 1H), 8.62 (s, 2H), 8.81-8.82 (m, 2H), 9.22 (br t, 1H), 9.90 (br s, 1H).	4-bromoacetylpyridine hydrobromide and **Intermediate 159**

Example 501: ethyl 5-(2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-1,3-thiazol-4-yl)isoxazole-3-carboxylate

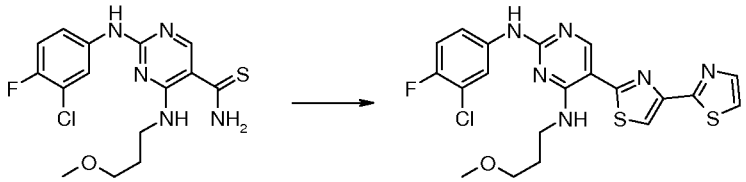


To a suspension of 2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidine-5-carbothioamide (**Intermediate 159**, 0.54 mmol, 200 mg) and magnesium sulfate heptahydrate

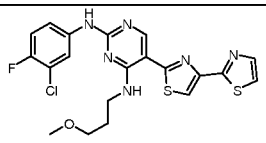
(0.65 mmol, 160 mg) in dry acetone (2 mL) under nitrogen atmosphere, was added ethyl 5-(bromoacetyl)-1,2-oxazole-3-carboxylate (0.59 mmol, 155 mg). The resulting mixture was stirred at reflux temperature for 3 hours, concentrated and purified by silica gel column chromatography (60- 120 mesh; product eluted at 1% MeOH/$CHCl_3$) as eluent to afford the title compound (64 mg).

Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 501	 ethyl 5-(2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-1,3-thiazol-4-yl)isoxazole-3-carboxylate	MS(ES): 533 (M+1) for $C_{23}H_{22}ClFN_6O_4S$. 400 MHz, DMSO-d_6: δ 1.35 (t, J = 7.08 Hz, 3H), 1.92-1.95 (m, 2H), 3.22 (s, 3H), 3.51 (t, J = 6.08 Hz, 2H), 3.69 (q, J = 6.48 Hz, 2H), 4.41 (q, J = 7.08 Hz, 2H), 7.33 (t, J = 9.12 Hz, 1H), 7.46 (s, 1H), 7.64-7.68 (m, 1H), 8.23 (dd, J = 2.68, 6.88 Hz, 1H), 8.39 (s, 1H), 8.63 (s, 1H), 9.17 (t, J = 5.28 Hz, 1H), 9.89 (br s, 1H).	ethyl 5-(bromoacetyl)-1,2-oxazole-3-carboxylate and **Intermediate 159**

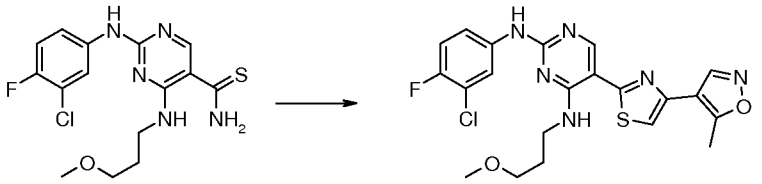
Example 502: 5-(2,4'-bi-1,3-thiazol-2'-yl)-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)pyrimidine-2,4-diamine



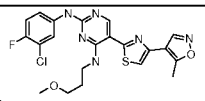
To a suspension of 2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidine-5-carbothioamide (**Intermediate 159**), 0.14 mmol, 50 mg) in DMF (2 mL), was added 2-bromo-1-(1,3-thiazol-2-yl)ethanone (0.13 mmol, 27 mg) and warmed to 100 °C for 3 h. The reaction mixture was quenched with water. The solid that precipitated out was filtered, washed with acetonitrile and dried to afford the title compound (35 mg).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 502	 5-(2,4'-bi-1,3-thiazol-2'-yl)-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)pyrimidine-2,4-diamine	MS(ES): 477 (M+1) for $C_{20}H_{18}ClFN_6OS_2$. 400 MHz, DMSO-d_6: δ 1.97-2.00 (m, 2H), 3.25 (s, 3H), 3.53 (t, J = 6.00 Hz, 2H), 3.67 (q, J = 6.80 Hz, 2H), 7.34 (t, J = 9.20 Hz, 1H), 7.63-7.67 (m, 1H), 7.86 (d, J = 3.20 Hz, 1H), 7.96 (d, J = 3.20 Hz, 1H), 8.18 (s, 1H), 8.28 (dd, J = 2.00, 6.80 Hz, 1H), 8.63 (s, 1H), 9.17 (br t, 1H), 9.92 (br s, 1H).	2-bromo-1-(1,3-thiazol-2-yl)ethanone and **Intermediate 159**

Example 503: N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)-5-[4-(5-methylisoxazol-4-yl)-1,3-thiazol-2-yl]pyrimidine-2,4-diamine

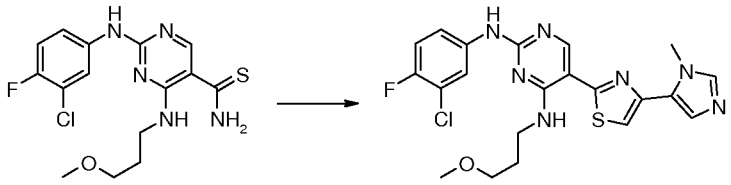


To a suspension of 2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidine-5-carbothioamide (**Intermediate 159**, 0.27 mmol, 100 mg) in DMF (2 mL), was added 2-bromo-1-(5-methylisoxazol-4-yl)ethanone (**Intermediate 164,** 0.2 mmol, 60 mg) and warmed to 80 °C for 3 h. The reaction mixture was quenched with water and the solid that precipitated out was filtered, washed with acetonitrile and dried to afford the title compound (35 mg).

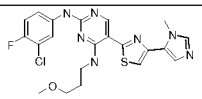
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 503	 N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)-	MS(ES): 475 (M+1) for $C_{21}H_{20}ClFN_6O_2S$. 400 MHz, DMSO-d_6: δ 1.90-1.94 (m, 2H), 2.72 (s, 3H), 3.19 (s, 3H), 3.43 (t, J = 6.00 Hz, 2H), 3.64 (q, J = 6.68 Hz,	**Intermediate 164** 2-bromo-1-(5-methylisoxazol-4-yl)ethanone

	5-[4-(5-methylisoxazol-4-yl)-1,3-thiazol-2-yl]pyrimidine-2,4-diamine	2H), 7.33 (t, *J* = 9.12 Hz, 1H), 7.64-7.64 (m, 1H), 7.81 (s, 1H), 8.22 (dd, *J* = 2.44, 6.84 Hz, 1H), 8.56 (s, 1H), 9.03 (s, 1H), 9.24 (br t, 1H), 9.89 (br s, 1H).	and **Intermediate 159**

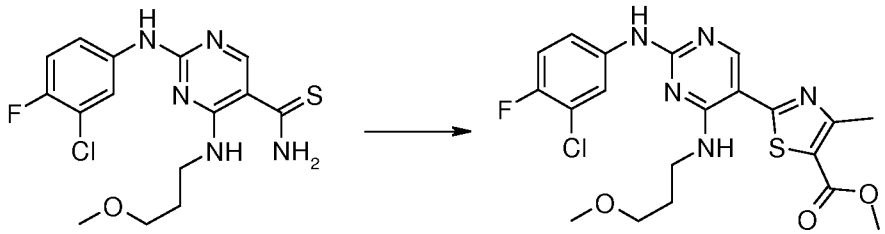
Example 504: N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)-5-[4-(1-methyl-1*H*-imidazol-5-yl)-1,3-thiazol-2-yl]pyrimidine-2,4-diamine



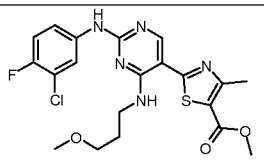
To a suspension of 2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidine-5-carbothioamide (**Intermediate 159**, 0.56 mmol, 206 mg,) in ethanol (5 mL), was added the mixture of 2-bromo-1-(1-methyl-1*H*-imidazol-5-yl)ethanone and 2,2-dibromo-1-(1-methyl-1*H*-imidazol-5-yl)ethanone (**Intermediate 165**, 1.12 mmol based on the former, 226 mg,) and warmed to 80 °C for 3 h. The reaction mixture was concentrated and subjected to purification by RP-HPLC (C18 column(19 x 250 mm, 7µm); using a binary solvent mixture of 20 mM NH_4OAc (A)/CH_3CN (B) (0-20 min: 10-60% B, 20-35 min: 60% B and 35-45 min: 60-100% B; flow rate of 15 mL/min; Separation was monitored at 210 and 254 nm) to give the title compound (98 mg).

Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 504	 N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)-5-[4-(1-methyl-1*H*-imidazol-5-yl)-1,3-thiazol-2-yl]pyrimidine-2,4-diamine	MS(ES): 474 (M+1) for $C_{21}H_{21}ClFN_7OS$. 400 MHz, CH_3COOD: δ 2.10 (m, 2H), 3.29 (s, 3H), 3.62 (t, *J* = 6.00 Hz, 2H), 3.85 (t, *J* = 6.80 Hz, 2H), 4.17 (s, 3H), 7.24 (t, *J* = 8.80 Hz, 1H), 7.59-7.63 (m, 1H), 7.98-8.00 (m, 2H), 8.15 (dd, *J* = 2.80, 6.60 Hz, 1H), 8.73 (s, 1H), 8.97 (br s, 1H).	**Intermediate 165** 2-bromo-1-(1-methyl-1*H*-imidazol-5-yl)ethanone and 2,2-dibromo-1-(1-methyl-1*H*-imidazol-5-yl)ethanone and **Intermediate 159**

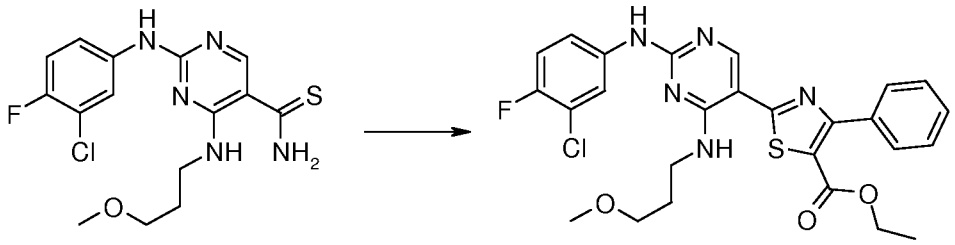
Example 505: methyl 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-methyl-1,3-thiazole-5-carboxylate



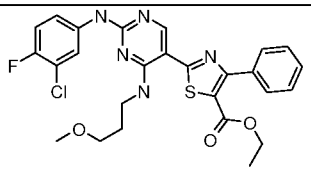
To a solution of 2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidine-5-carbothioamide (**Intermediate 159**, 200 mg, 0.5 mmol) in ethanol (1 mL) was added methyl-2-chloroacetoacetate (0.072 mL, 0.089 g, 0.6 mmol). The resulting mixture was subjected to microwave irradiation at 150 °C for 2 h. The precipitated solid was filtered, washed with water and dried to afford the crude product. It was further purified by silica gel column chromatography (60-120 mesh; product eluted at 20 % ethyl acetate/hexanes) as eluent to afford the title compound (40 mg).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 505	 methyl 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino] pyrimidin-5-yl}-4-methyl-1,3-thiazole-5-carboxylate	MS(ES): 466 (M+1) for $C_{20}H_{21}ClFN_5O_3S$. 400 MHz, DMSO-d_6: δ 1.88 (t, J = 6.40 Hz, 2H), 2.66 (s, 3H), 3.25 (s, 3H), 3.46 (t, J = 6.08 Hz, 2H), 3.61 (q, J = 6.80 Hz, 2H), 3.81 (s, 3H), 7.32 (t, J = 9.12 Hz, 1H), 7.64 (ddd, J = 2.72, 4.18, 9.06 Hz, 1H), 8.20 (dd, J = 2.48, 6.78 Hz, 1H), 8.58 (s, 1H), 9.33 (br s, 1H), 9.91 (br s, 1H).	methyl-2-chloroacetoacetate and **Intermediate 159**

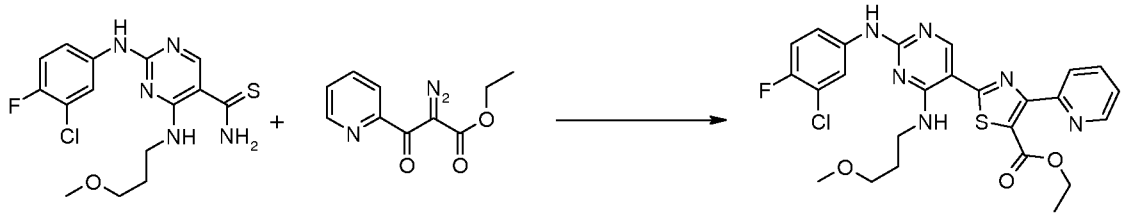
Example 506: ethyl 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-phenyl-1,3-thiazole-5-carboxylate



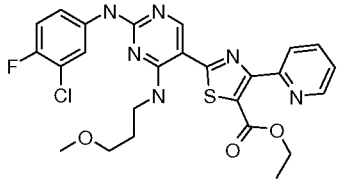
To a solution of 2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidine-5-carbothioamide (**Intermediate 159**, 100 mg, 0.27 mmol) in ethanol (10 mL) was added ethyl 2-bromo-3-oxo-3-phenylpropanoate (80 mg, 0.29 mmol). The resulting mixture was stirred overnight at RT. The solvent was removed *in vacuo* and the slurry taken in ethyl acetate was washed with water and brine. It was dried over sodium sulfate and further purified by silica gel column chromatography (60 - 120 mesh) using 1% MeOH/ $CHCl_3$ as eluent to afford the title compound (32 mg).

Compound	**Structure**	**Mass spectrum and ^{1}H NMR**	**SM**
Example 506	 ethyl 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino] pyrimidin-5-yl}-4-phenyl-1,3-thiazole-5-carboxylate	MS(ES): 542 (M+1) for $C_{26}H_{25}ClFN_5O_3S$. 400 MHz, DMSO-d_6: δ 1.21 (t, J = 7.00 Hz, 3H), 1.83 (q, J = 6.12 Hz, 2H), 3.10 (s, 3H), 3.39 (t, J = 6.00 Hz, 2H), 3.59 (q, J = 6.32 Hz, 2H), 4.22 (q, J = 7.20 Hz, 2H), 7.33 (t, J = 9.16 Hz, 1H), 7.47-7.48 (m, 3H), 7.63-7.65 (m, 1H), 7.77-7.78 (m, 2H), 8.22 (d, J = 4.52 Hz, 1H), 8.66 (s, 1H), 9.30 (br t, 1H), 9.98 (br s, 1H).	ethyl 2-bromo-3-oxo-3-phenylpropanoate and **Intermediate 159**

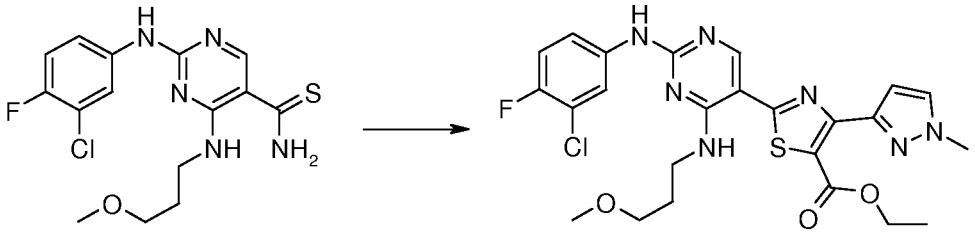
Example 507: ethyl 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-(pyridin-2-yl)-1,3-thiazole-5-carboxylate



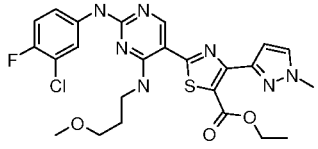
To 2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidine-5-carbothioamide (**Intermediate 159,** 1 mmol, 0.37 g) and [1-ethoxy-1,3-dioxo-3-(pyridin-2-yl)propan-2-ylidene]diazenium (**Intermediate 168**, 0.91 mmol, 200 mg) taken in dry toluene (5 mL), Copper(I) bromide dimethyl sulfide complex (0.76 mmol, 157 mg) was added and heated at 110 °C for 0.5 h. The reaction mixture was cooled to room temperature, quenched with water and extracted with ethyl acetate. The organic layer was washed with brine (50 mL x 2) and dried over sodium sulphate. The solvent was removed under vacuum to afford a solid, which was purified by silica gel column chromatography using chloroform: methanol (9:1) as eluent. It was further purified by RP-HPLC (Kromasil C18 column (50 x 250 mm, 10µm); using a binary solvent mixture of 20 mM NH_4OAc (A)/CH_3CN (B) (0-20 min: 10-80% B, 20-30 min: 80% B, flow rate of 40 mL/min; Separation was monitored at 210 nm and 254 nm) to give the title compound (42 mg).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 507	 ethyl 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-(pyridin-2-yl)-1,3-thiazole-5-carboxylate	MS(ES): 543 (M+1) for $C_{25}H_{24}ClFN_6O_3S$. 400 MHz, DMSO-d_6: δ 1.15 (t, J = 7.04 Hz, 3H), 1.82-1.84 (m, 2H), 3.10 (s, 3H), 3.40 (t, J = 6.12 Hz, 2H), 3.60 (q, J = 6.52 Hz, 2H), 4.20 (q, J = 7.16 Hz, 2H), 7.34 (t, J = 9.08 Hz, 1H), 7.46-7.49 (m, 1H), 7.63-7.64 (m, 1H), 7.85 (d, J = 7.80 Hz, 1H), 7.93 (dd, J = 1.72, 7.64, Hz, 1H), 8.22 (dd, J = 2.48, 6.80 Hz, 1H), 8.66 (s, 1H), 8.67 (s, 1H), 9.27 (br t, 1H), 9.98 (br s, 1H).	**Intermediate 168** [1-ethoxy-1,3-dioxo-3-(pyridin-2-yl)propan-2-ylidene]diazenium and **Intermediate 159**

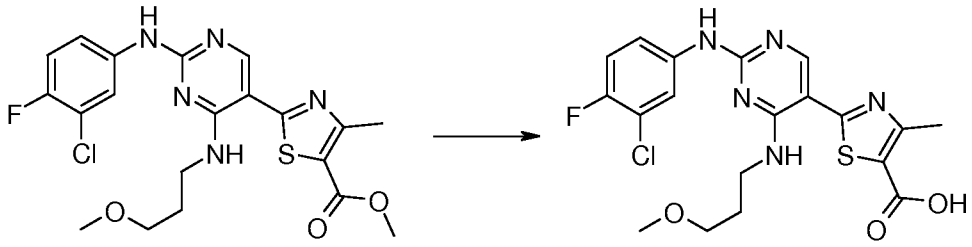
Example 508: ethyl 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-(1-methyl-1*H*-pyrazol-3-yl)-1,3-thiazole-5-carboxylate



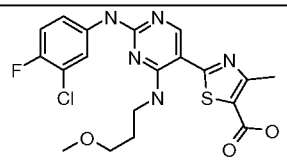
To a solution of 2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidine-5-carbothioamide (**Intermediate 159**, 95 mg, 0.25 mmol) in ethanol (10 mL) was added ethyl 2-chloro-3-(1-methyl-1*H*-pyrazol-3-yl)-3-oxopropanoate (**Intermediate 171**, 130 mg, 0.56 mmol). The resulting mixture was refluxed at 90 °C for 3 d. The solvent was removed *in vacuo* and the slurry was taken in ethyl acetate and washed with water and brine. The organic solution was dried over sodium sulfate and further purified by silica gel column chromatography (60 - 120 mesh) using 1% MeOH/ $CHCl_3$ as eluent to afford the title compound (24 mg).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 508	 ethyl 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-(1-methyl-1*H*-pyrazol-3-yl)-1,3-thiazole-5-carboxylate	MS(ES): 546 (M+1) for $C_{24}H_{25}ClFN_7O_3S$. 400 MHz, DMSO-d_6: δ 1.29 (t, *J* = 7.20 Hz, 3H), 1.94 (m, *J* = 6.40 Hz, 2H), 3.21 (s, 3H), 3.53 (t, *J* = 6.00 Hz, 2H), 3.62 (q, *J* = 6.40 Hz, 2H), 3.94 (s, 3H), 4.29 (q, *J* = 6.80 Hz, 2H), 7.03 (d, *J* = 2.00 Hz, 1H), 7.35 (t, *J* = 8.80 Hz, 1H), 7.64-7.67 (m, 1H), 7.81 (d, *J* = 2.00 Hz, 1H), 8.25 (dd, *J* = 2.00, 6.40 Hz, 1H), 8.66 (s, 1H), 9.72 (br t, *J* = 4.80 Hz, 1H), 9.96 (br s, 1H).	**Intermediate 171** ethyl 2-chloro-3-(1-methyl-1*H*-pyrazol-3-yl)-3-oxopropanoate and **Intermediate 159**

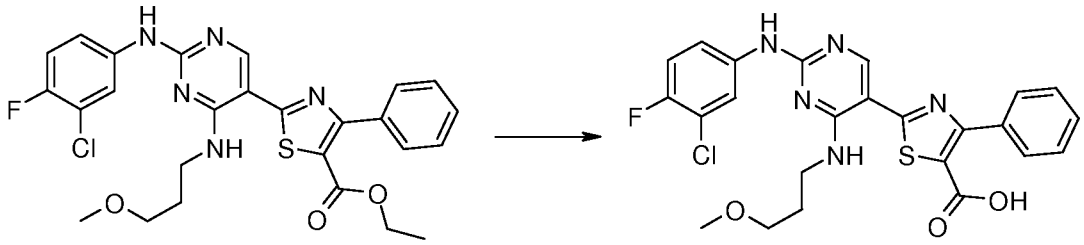
Example 509: 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-methyl-1,3-thiazole-5-carboxylic acid



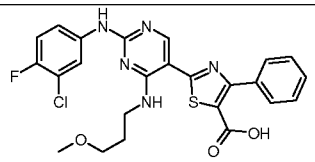
Example 505 (0.16 mmol 75 mg,) was dissolved in tetrahydrofuran (2 mL) and treated with 1 N aq. NaOH (0.6 mL). The reaction mixture was warmed to 60 °C for 24 h. The reaction mixture was concentrated and the aqueous layer carefully acidified with 1.5 N HCl. The solid that precipitated was filtered out, washed with water and dried under vacuum to yield the title compound (15 mg).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 509	 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-methyl-1,3-thiazole-5-carboxylic acid	MS(ES): 452 (M+1) for $C_{19}H_{19}ClFN_5O_3S$. 400 MHz, DMSO-d_6: δ 1.89 (t, J = 6.00 Hz, 2H), 2.66 (s, 3H), 3.27 (s, 3H), 3.47 (t, J = 5.60 Hz, 2H), 3.63 (d, J = 5.60 Hz, 2H), 7.34 (t, J = 8.80 Hz, 1H), 7.65 (d, J = 8.40 Hz, 1H), 8.22 (d, J = 6.40 Hz, 1H), 8.58 (s, 1H), 9.38 (br s, 1H), 9.91 (br s, 1H), 13.29 (br s, 1H).	**Example 505** methyl 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-methyl-1,3-thiazole-5-carboxylate

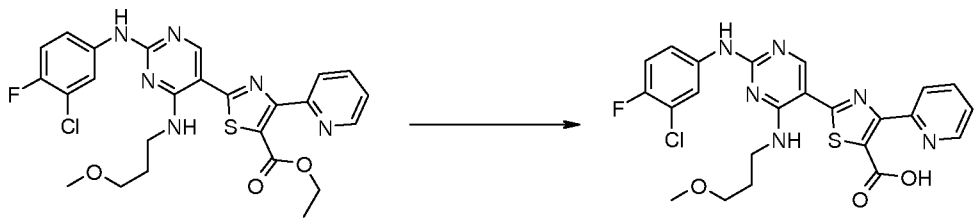
Example 510: 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-phenyl-1,3-thiazole-5-carboxylic acid



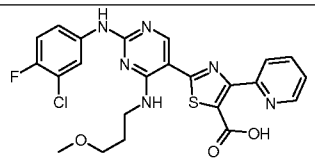
To a suspension of 150 mg of **Example 506** (0.28 mmol, 150 mg) taken in tetrahydrofuran (2.5 mL) and water (2.5 mL), Lithium hydroxide monohydrate (1.11 mmol, 46 mg) was added and the reaction was warmed overnight at 60 °C. After completion of reaction, the reaction mixture was concentrated and the aqueous layer was carefully acidified with 1.5 N HCl. The solid that precipitated was filtered out, washed with water and dried under vacuum to yield the title compound (110 mg).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 510	 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-phenyl-1,3-thiazole-5-carboxylic acid	MS(ES): 514 (M+1) for $C_{24}H_{21}ClFN_5O_3S$. 400 MHz, DMSO-d_6: δ 1.84 (t, J = 6.28 Hz, 2H), 3.11 (s, 3H), 3.40 (t, J = 6.00 Hz, 2H), 3.61 (t, J = 6.04 Hz, 2H), 7.34 (t, J = 9.12 Hz, 1H), 7.46-7.47 (m, 3H), 7.64-7.66 (m, 1H), 7.78-7.79 (m, 2H), 8.23 (d, J = 5.00 Hz, 1H), 8.65 (s, 1H), 9.33 (br t, 1H), 9.95 (br s, 1H), 13.50 (br s, 1H).	**Example 506** ethyl 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-phenyl-1,3-thiazole-5-carboxylate

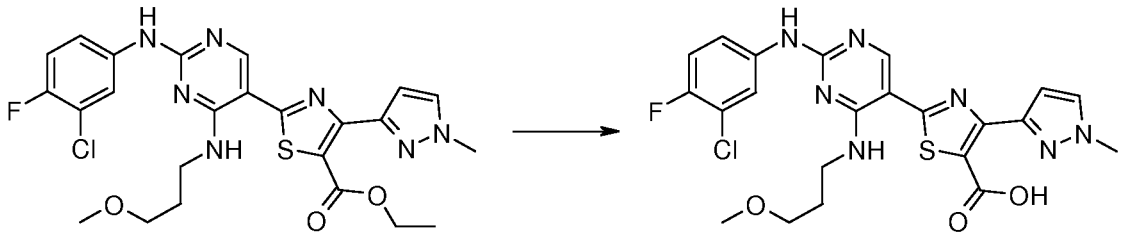
Example 511: 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-(pyridin-2-yl)-1,3-thiazole-5-carboxylic acid



To 40 mg of ethyl 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-(pyridin-2-yl)-1,3-thiazole-5-carboxylate (**Example 507**, 0.07 mmol) taken in THF (1 mL) and water (1 mL), was added Lithium hydroxide monohydrate (0.29 mmol, 12 mg) and the reaction was warmed overnight at 65 °C. The reaction mixture was concentrated then the aqueous layer was carefully acidified with 1.5 N HCl. The solid that precipitated was filtered out, washed with water and dried under vacuum to yield 18 mg of the title compound as a yellow powder.

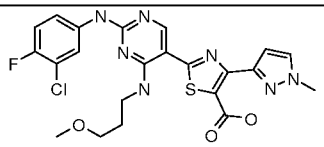
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 511	 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-(pyridin-2-yl)-1,3-thiazole-5-carboxylic acid	MS(ES): 515 (M+1) for $C_{23}H_{20}ClFN_6O_3S$. 400 MHz, DMSO-d_6: δ 1.98 (q, J = 6.40 Hz, 2H), 3.23 (s, 3H), 3.51 (t, J = 6.00 Hz, 2H), 3.71 (q, J = 5.60 Hz, 2H), 7.33 (t, J = 8.80 Hz, 1H), 7.64-7.66 (m, 1H), 7.80 (t, J = 6.40 Hz, 1H), 8.23 (d, J = 4.40 Hz, 1H), 8.38 (t, J = 7.20 Hz, 1H), 8.47 (d, J = 8.00 Hz, 1H), 8.66 (s, 1H), 8.85 (d, J = 5.20 Hz, 1H), 9.04 (br s, 1H), 9.98 (br s, 1H).	**Example 507** ethyl 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-(pyridin-2-yl)-1,3-thiazole-5-carboxylate

Example 512: 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-(1-methyl-1*H*-pyrazol-3-yl)-1,3-thiazole-5-carboxylic acid

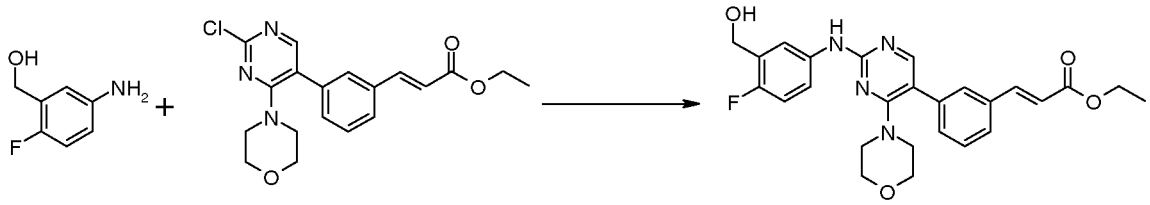


To 80 mg of ethyl 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-(1-methyl-1*H*-pyrazol-3-yl)-1,3-thiazole-5-carboxylate

(**Example 508**, 0.16 mmol) taken in THF (5 mL) was added Barium hydroxide monohydrate (0.44 mmol, 0.083 g) and water (5 mL). The reaction mixture was allowed to stir at RT overnight. After completion of the reaction, the mixture was then carefully acidified with 1.5 N HCl to pH=2 and the precipitate formed was filtered, washed with water and dried to yield the title compound (24 mg).

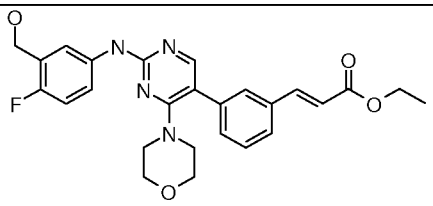
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 512	 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-(1-methyl-1*H*-pyrazol-3-yl)-1,3-thiazole-5-carboxylic acid	MS(ES): 518 (M+1) for $C_{22}H_{21}ClFN_7O_3S$. 400 MHz, DMSO-d_6: δ 1.95 (q, J = 6.40 Hz, 2H), 3.12 (s, 3H), 3.55 (t, J = 6.08 Hz, 2H), 3.60 (t, J = 5.52 Hz, 2H), 3.88 (s, 3H), 7.31 (t, J = 9.16 Hz, 1H), 7.44-7.45 (m, 1H), 7.63-7.65 (m, 2H), 8.25 (d, J = 6.68 Hz, 1H), 8.46 (s, 1H), 9.77 (s, 1H), 10.05 (br s, 1H).	**Example 508** ethyl 2-{2-[(3-chloro-4-fluorophenyl)amino]-4-[(3-methoxypropyl)amino]pyrimidin-5-yl}-4-(1-methyl-1*H*-pyrazol-3-yl)-1,3-thiazole-5-carboxylate

Example 513: ethyl (2*E*)-3-{3-[2-{[4-fluoro-3-(hydroxymethyl)phenyl]amino}-4-(morpholin-4-yl)pyrimidin-5-yl]phenyl}prop-2-enoate

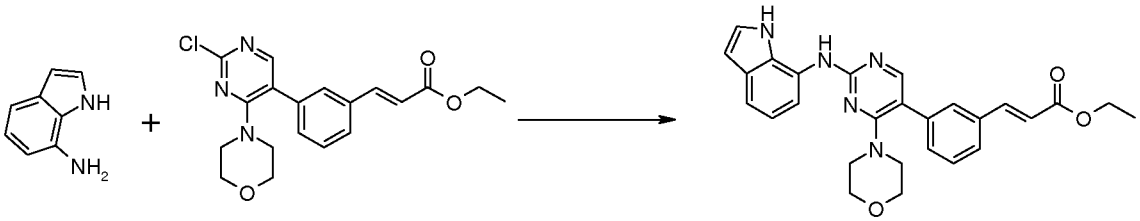


A suspension of (2*E*)-3-{3-[2-chloro-4-(morpholin-4-yl)pyrimidin-5-yl]phenyl}prop-2-enoate (**Intermediate 145**) (0.8 mmol, 0.30 g, 1 eq), (5-amino-2-fluorophenyl)methanol (0.88 mmol, 0.12 g, 1.1 eq), tris(dibenzyledeneacetone) dipalladium(0) (0.24 mmol, 0.22 g, 30 mol%), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (0.24 mmol, 0.11 g, 30 mol%) and sodium carbonate (0.8 mmol, 0.08 g, 1 eq) in acetonitrile/water (6 mL:2 mL) was heated to 90 °C for 30 minutes. The reaction mixture was concentrated and the residue was taken in ethyl acetate

(50 mL), washed with water (2x) and brine (1x). The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude compound was purified by silica gel column (60-120 mesh) chromatography using hexane: ethyl acetate (3:1) as an eluent to yield the title compound (0.190 g).

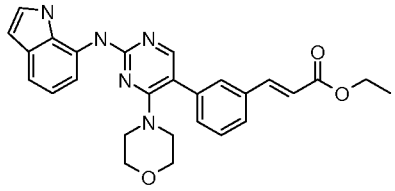
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 513	 ethyl (2*E*)-3-{3-[2-{[4-fluoro-3-(hydroxymethyl)phenyl]amino}-4-(morpholin-4-yl)pyrimidin-5-yl]phenyl}prop-2-enoate	MS(ES): 479 (M+1) for $C_{26}H_{27}FN_4O_4$. 300 MHz, DMSO-d_6: δ 1.25 (t, J = 7.14 Hz, 3H), 3.20 (m, 4H), 3.53 (m, 4H), 4.19 (q, J = 7.11 Hz, 2H), 4.57 (br s, 2H), 5.68 (br s, 1H), 6.72 (d, J = 16.11 Hz, 1H), 6.73-6.8 (m, 1H), 7.27 (t, J = 8.31 Hz, 1H), 7.45-7.54 (m, 2H), 7.69 (d, J = 16.29 Hz, 1H), 7.68 (br s, 1H), 7.81 (br s, 1H), 8.02 (d, J = 2.52 Hz, 1H), 8.06 (s, 1H), 8.90 (br s, 1H).	(5-amino-2-fluorophenyl)methanol and **Intermediate 145**

Example 514: ethyl (2*E*)-3-{3-[2-(1*H*-indol-7-ylamino)-4-(morpholin-4-yl)pyrimidin-5-yl]phenyl}prop-2-enoate

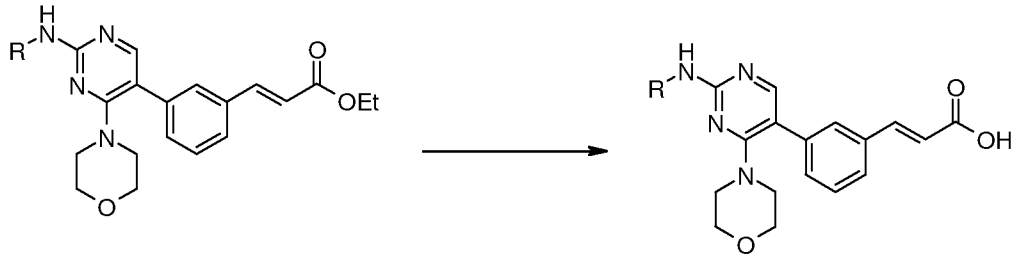


A suspension of (2*E*)-3-{3-[2-chloro-4-(morpholin-4-yl)pyrimidin-5-yl]phenyl}prop-2-enoate **(Intermediate 145)** (0.67 mmol, 0.25 g, 1 eq), 1*H*-indol-7-amine (0.8 mmol, 0.10 g, 1.2 eq), tris(dibenzyledeneacetone)dipalladium(0) (0.2 mmol, 0.184 g, 30 mol%), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (0.20 mmol, 0.1 g, 30 mol%) and sodium carbonate (0.7 mmol, 0.07 g, 1 eq) in acetonitrile/water (10 mL:2.5 mL) was heated to 90

°C for 30 minutes. The reaction mixture was concentrated and the residue was taken in ethyl acetate (50 mL), washed with water (2x) and brine (1x). The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude compound was purified by silica gel column (230-400 mesh) chromatography using chloroform: methanol (98:2) as an eluent to yield the title compound (0.17 g).

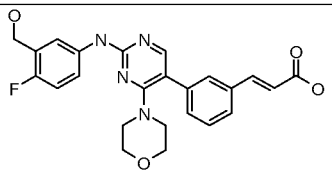
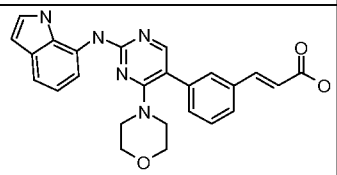
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 514	 ethyl (2*E*)-3-{3-[2-(1*H*-indol-7-ylamino)-4-(morpholin-4-yl)pyrimidin-5-yl]phenyl}prop-2-enoate	MS(ES): 470 (M+1) for $C_{27}H_{27}N_5O_3$. 400 MHz, DMSO-d_6: δ 1.26 (t, J = 7.08 Hz, 3H), 3.20 (br s, 4H), 3.52-3.53 (m, 4H), 4.20 (q, J = 7.04 Hz, 2H), 6.42 (br s, 1H), 6.72 (d, J = 16.04 Hz, 1H), 6.95 (t, J = 7.76 Hz, 1H), 7.22 (d, J = 7.80 Hz, 1H), 7.31 (t, J = 2.60 Hz, 1H), 7.48 (t, J = 7.60 Hz, 1H), 7.54 (d, J = 7.64 Hz, 1H), 7.66 (d, J = 7.88 Hz, 1H), 7.70 (d, J = 16.12 Hz, 1H), 7.77 (d, J = 7.60 Hz, 1H), 7.82 (br s, 1H), 8.07 (s, 1H), 9.05 (br s, 1H), 11.00 (br s, 1H).	1*H*-indol-7-amine and **Intermediate 145**

General procedure for hydrolysis of carboxylic acid ester to acid

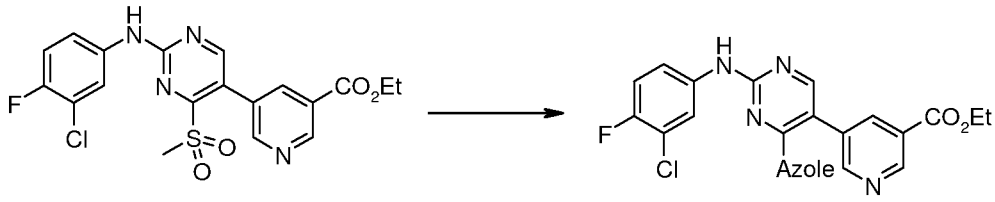


To ester derivative (1 eq) suspended in tetrahydrofuran (1 mL) was added 1 N aq. NaOH (4 eq) and stirred overnight at room temperature. After completion of reaction, the reaction mixture was carefully acidified with 1 N HCl and the solid that precipitated was filtered, washed with water and dried *in vacuo* to yield the desired carboxylic acid product.

The compounds in the below table were prepared using this method and the indicated starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 516	 (2*E*)-3-{3-[2-{[4-fluoro-3-(hydroxymethyl)phenyl]amino}-4-(morpholin-4-yl)pyrimidin-5-yl]phenyl}prop-2-enoic acid	MS(ES): 451 (M+1) for $C_{24}H_{23}FN_4O_4$ 400 MHz, DMSO-d_6: δ 3.22 (br s, 4H), 3.54 (br s, 4H), 4.59 (d, J = 3.60 Hz, 2H), 5.68 (br s, 1H), 6.61 (d, J = 16.00 Hz, 1H), 6.75-6.80 (m, 1H), 7.28 (t, J = 7.20 Hz, 1H), 7.47-7.53 (m, 2H), 7.62-7.66 (m, 2H), 7.79 (s, 1H), 8.05-8.08 (m, 2H), 8.90 (s, 1H), 12.44 (br s, 1H).	**Example 513** ethyl (2*E*)-3-{3-[2-{[4-fluoro-3-(hydroxymethyl)phenyl]amino}-4-(morpholin-4-yl)pyrimidin-5-yl]phenyl}prop-2-enoate
Example 517	 (2*E*)-3-{3-[2-(1*H*-indol-7-ylamino)-4-(morpholin-4-yl)pyrimidin-5-yl]phenyl}prop-2-enoic acid	MS(ES): 442 (M+1) for $C_{25}H_{23}N_5O_3$. 400 MHz, DMSO-d_6: δ 3.20 (br s, 4H), 3.53 (br s, 4H), 6.42 (br s, 1H), 6.61 (d, J = 16.08 Hz, 1H), 6.95 (t, J = 7.84 Hz, 1H), 7.22 (d, J = 7.72 Hz, 1H), 7.31 (br s, 1H), 7.47 (t, J = 7.52 Hz, 1H), 7.49-7.54 (m, 1H), 7.62 (br s, 1H), 7.65 (d, J = 8.08 Hz, 1H), 7.77 (d, J = 8.48 Hz, 1H), 7.78 (br s, 1H), 8.06 (br s, 1H), 9.05 (br s, 1H), 11.00 (br s, 1H), 12.42 (br s, 1H).	**Example 514** ethyl (2*E*)-3-{3-[2-(1*H*-indol-7-ylamino)-4-(morpholin-4-yl)pyrimidin-5-yl]phenyl}prop-2-enoate

General methods for the synthesis of ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(azol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylate



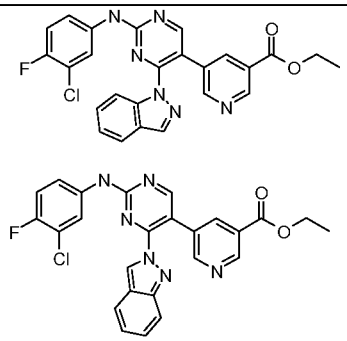
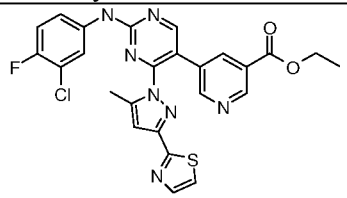
Method A:

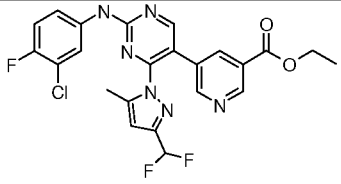
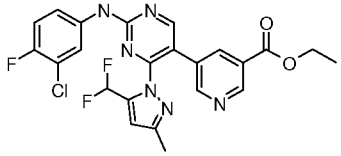
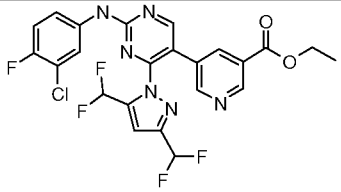
A solution of azole (2.2 eq) in DMF (1 mL) was added slowly to a suspension of sodium hydride (2.1 eq) in DMF (1 mL). The reaction mixture was stirred for 30 min at room temperature. A solution of ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(methylsulfonyl)pyrimidin-5-yl)nicotinate **Intermediate 124** (1 eq) in DMF (1 mL) was added slowly to the reaction mixture at 0 °C with stirring and allowed to warm to ambient temperature over 2.5 h. Water was added (~6 mL) and the solid formed was filtered and dried to yield the product.

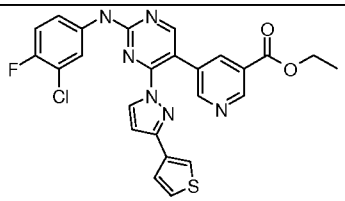
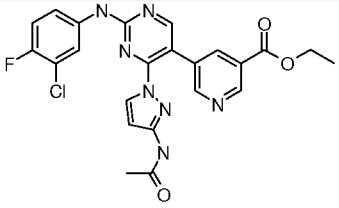
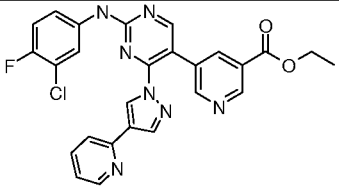
Method B:

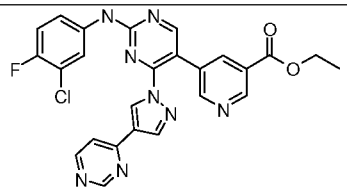
A solution of azole (2.2 eq) in DMSO (1 mL) was added slowly to a suspension of sodium hydride (2.1 eq) in DMSO (1 mL). The reaction mixture was stirred for 30 min at room temperature. A solution of **Intermediate 124** (1 eq) in DMSO (1 mL) was added slowly to the reaction mixture at 0 °C with stirring and allowed to warm to ambient temperature over 2.5 h. Water was added (~6 mL) and the solid formed was filtered and dried to yield the product.

The compounds in the below table were prepared using the methods described above as indicated and the starting material specified.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 519[a)]	 ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-indazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylate & ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-indazol-2-yl)pyrimidin-5-yl}pyridine-3-carboxylate	^{1}H NMR 400 MHz, DMSO-d_6: δ 1.23 (t, *J* = 7.15 Hz, 3H), 1.28 (t, *J* = 7.15 Hz, 3H), 4.24-4.34 (m, 4H), 7.09 (dd, *J* = 6.90, 8.16 Hz, 1H), 7.20-7.27 (m, 1H), 7.31-7.47 (m, 3H), 7.59 (t, *J* = 7.78 Hz, 1H), 7.62-7.70 (m, 1H), 7.74-7.87 (m, 3H), 8.03-8.10 (m, 3H), 8.14-8.17 (m, 1H), 8.16-8.21 (m, 2H), 8.45-8.52 (m, 1H), 8.56 (d, *J* = 2.26 Hz, 1H), 8.63 (d, *J* = 2.01 Hz, 1H), 8.71 (s, 1H), 8.86 (s, 1H), 8.95-9.01 (m, 3H), 10.26 (s, 1H), 10.47 (s, 1H).	1*H*-indazole
Example 520[c)]	 ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(1,3-thiazol-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 536 (M+1) for $C_{25}H_{19}ClFN_7O_2S$. 300 MHz, DMSO-d_6: δ 1.19 (t, *J* = 7.08 Hz, 3H), 2.5 (s, 3H, merges with DMSO peak),4.24 (q, *J* = 7.11 Hz, 2H), 6.77 (s, 1H), 7.42 (t, *J* = 9.03 Hz, 1H), 7.65-7.67 (m, 2H), 7.83 (d, *J* = 3.18 Hz, 1H), 7.95 (s, 1H), 8.09 (d, *J* = 6.51 Hz, 1H), 8.61 (s, 1H), 8.92 (s, 1H), 8.95 (s, 1H), 10.38 (br s, 1H).	2-(5-methyl-1*H*-pyrazol-3-yl)-1,3-thiazole

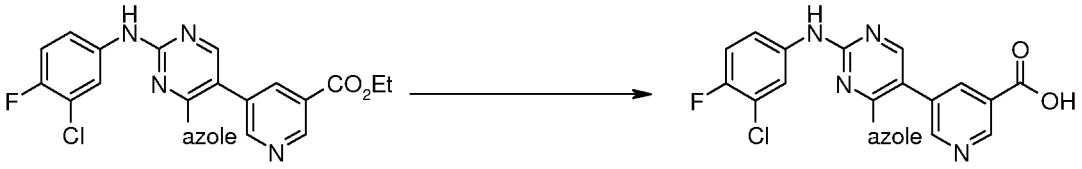
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 521[c)]	 ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(difluoromethyl)-5-methyl-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 503 (M+1) for $C_{23}H_{18}ClF_3N_6O_2$. 300 MHz, DMSO-d_6: δ 1.29 (t, *J* = 7.05 Hz, 3H), 2.41 (s, 3H), 4.30 (q, *J* = 7.05 Hz, 2H), 6.56 (s, 1H), 6.73 (t, *J* = 54.18 Hz, 1H), 7.42 (t, *J* = 9.15 Hz, 1H), 7.62-7.68 (m, 1H), 7.81 (t, *J* = 2.04 Hz, 1H), 8.06 (dd, *J* = 2.4, 6.6 Hz, 1H), 8.55 (d, *J* = 2.22 Hz, 1H), 8.96 (d, *J* = 1.92 Hz, 1H), 8.97 (s, 1H), 10.45 (br s, 1H).	3-(difluoromethyl)-5-methyl-1*H*-pyrazole
Example 522[c)]	 ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-(difluoromethyl)-3-methyl-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 503 (M+1) for $C_{23}H_{18}ClF_3N_6O_2$. 400 MHz, DMSO-d_6: δ 1.32 (t, *J* = 6.80 Hz, 3H), 1.98 (s, 3H), 4.34 (q, *J* = 7.20 Hz, 2H), 6.76 (s, 1H), 7.42 (t, *J* = 9.20 Hz, 1H), 7.60-7.64 (m, 1H), 7.96 (t, *J* = 2.00 Hz, 1H), 8.06 (d, *J* = 6.80 Hz, 1H), 8.58 (d, *J* = 2.40 Hz, 1H), 8.86 (s, 1H), 9.00 (d, *J* = 2.00 Hz, 1H), 10.26 (br s, 1H).	3-(difluoromethyl)-5-methyl-1*H*-pyrazole
Example 523[b)]	 ethyl 5-{4-[3,5-bis(difluoromethyl)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 539 (M+1) for $C_{23}H_{16}ClF_5N_6O_2$. 400 MHz, DMSO-d_6: δ 1.29 (t, *J* = 6.80 Hz, 3H), 4.31 (q, *J* = 7.20 Hz, 2H), 6.82 (t, *J* = 53.76 Hz, 1H), 7.25 (s, 1H), 7.40 (t, *J* = 9.20 Hz, 1H), 7.57 (t, *J* = 54.80 Hz, 1H), 7.62 (ddd, *J* = 2.80, 4.00, 9.10 Hz, 1H), 7.86 (t, *J* = 2.00 Hz, 1H), 8.03 (d, *J* = 4.40 Hz, 1H), 8.62 (d, *J* = 2.00 Hz, 1H), 8.97 (s, 1H), 8.99 (d, *J* = 2.00 Hz, 1H), 10.41 (br s, 1H).	3,5-bis(difluoromethyl)-1*H*-pyrazole

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 524[d]	 ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(thiophen-3-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 519 (M-1) for $C_{25}H_{18}ClFN_6O_2S$. 300 MHz, DMSO-d_6: δ 1.27 (t, J = 7.11 Hz, 3H), 4.32 (q, J = 6.54 Hz, 2H), 6.88 (d, J = 5.04 Hz, 1H), 6.97 (d, 1H), 7.43 (t, J = 9.24 Hz, 1H), 7.52 (m, 1H), 7.66 (br s, 1H), 7.72 (m, 1H), 8.07 (d, J = 4.23 Hz, 1H), 8.24 (br s, 1H), 8.51 (d, 1H), 8.64 (s, 1H), 8.76 (s, 1H), 9.07 (d, 1H), 10.28 (br s, 1H).	3-(thiophen-3-yl)-1*H*-pyrazole
Example 525[c]	 ethyl 5-{4-[3-(acetylamino)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 496 (M+1) for $C_{23}H_{19}ClFN_7O_3$. 300 MHz, DMSO-d_6: δ 1.30 (t, J = 7.08 Hz, 3H), 2.53 (s, 3H), 4.34 (q, J = 7.08 Hz, 2H), 6.85 (br d, 1H), 7.41 (t, J = 9.18 Hz, 1H), 7.72 (m, 1H), 8.04 (dd, J = 4.20 Hz, 1H), 8.09 (t, 1H), 8.34 (d, J = 2.61 Hz, 1H), 8.63 (d, J = 1.92 Hz, 1H), 8.65 (s, 1H), 9.01 (d, J = 1.92 Hz, 1H), 10.25 (br s, 1H), 10.28 (s, 1H).	N-(2H-Pyrazol-3-yl)-acetamide
Example 526[b]	 ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyridin-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 516 (M+1) for $C_{26}H_{19}ClFN_7O_2$. 400 MHz, DMSO-d_6: δ 1.30 (t, J = 6.80 Hz, 3H), 4.34 (q, J = 7.08 Hz, 2H), 7.30 (m, 1H), 7.44 (t, J = 9.20 Hz, 1H), 7.70-7.74 (m, 1H), 7.77-7.86 (m, 2H), 8.15 (dd, J = 2.80, 6.80 Hz, 1H), 8.18 (s, 2H), 8.59 (d, J = 4.00 Hz, 1H), 8.72-8.73 (m, 2H), 9.04 (s, 2H), 10.38 (s, 1H).	2-(1*H*-pyrazol-4-yl)pyridine

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 527[a)]	 ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyrimidin-4-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 515 (M-1) for $C_{25}H_{18}ClFN_8O_2$. 400 MHz, DMSO-d_6: δ 1.29 (t, *J* = 7.08 Hz, 3H), 4.33 (q, *J* = 7.08 Hz, 2H), 7.44 (t, *J* = 9.08 Hz, 1H), 7.70-7.74 (m, 1H), 7.88 (dd, *J* = 1.20, 5.24 Hz, 1H), 8.13 (dd, *J* = 2.60, 6.70 Hz, 1H), 8.17 (t, *J* = 2.00 Hz, 1H), 8.30 (s, 1H), 8.71 (d, *J* = 2.12 Hz, 1H), 8.77 (s, 1H), 8.80 (d, *J* = 5.32 Hz, 1H), 9.03 (d, *J* = 1.88 Hz, 1H), 9.15 (d, *J* = 1.08 Hz, 1H), 9.20 (s, 1H), 10.41 (br s, 1H).	4-(1*H*-pyrazol-4-yl)pyrimidine

(a) Method A (b) Method A, overnight (c) Method B (d) Method B, 125 °C, 4 h

General method for the synthesis of 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(azol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylic acid



Method C:

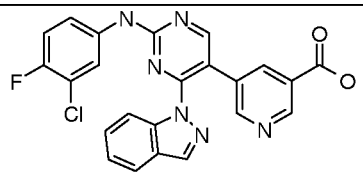
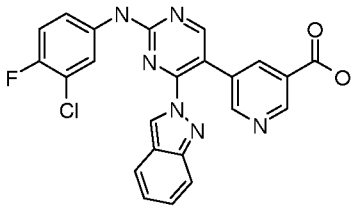
A solution of ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(azol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylate derivative (1 eq) in a mixture of tetrahydrofuran (1 mL) and water (1 mL) was treated with 1 N aq. sodium hydroxide (4 eq) and allowed to stir at room temperature for 3-8 h. After completion of the reaction, the mixture was carefully acidified with 1 N HCl and the precipitate formed was filtered, washed with water and dried to yieldthe product.

Method D:

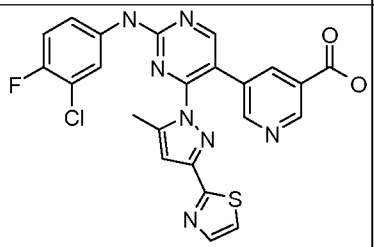
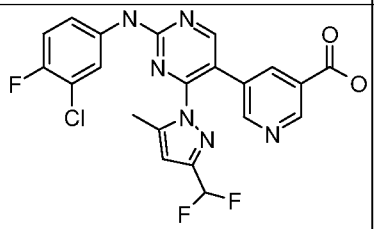
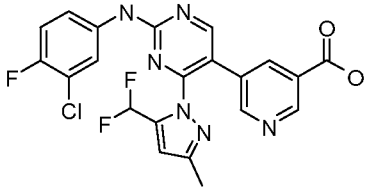
A solution of ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(azol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylate derivative (1 eq) in a mixture of dioxane (1 mL) and water (1 mL) was treated with 1 N aq. Barium hydroxide (2 eq) and allowed to stir at room temperature for 2-8 h. After

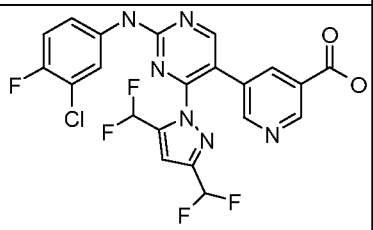
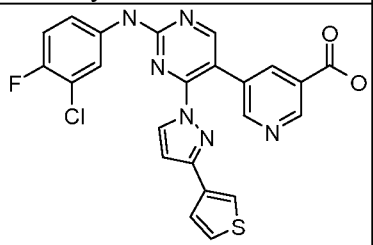
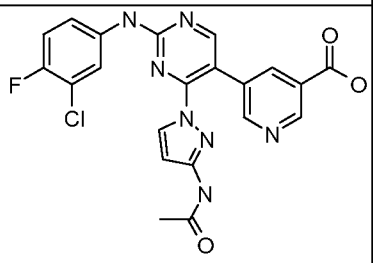
completion of the reaction, the mixture was carefully acidified with 1 N HCl and the precipitate formed was filtered, washed with water, dried to yield the product.

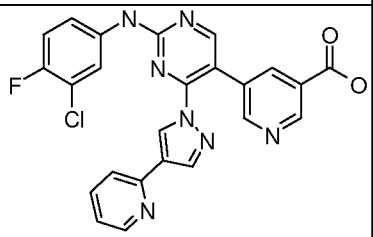
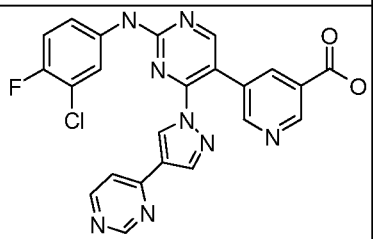
The compounds in the below table were prepared using the methods described above as indicated and the starting material specified.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 528[b)]	  5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-indazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylic acid & 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-indazol-2-yl)pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 459 (M-1) for $C_{23}H_{14}ClFN_6O_2$. 400 MHz, DMSO-d_6: δ 7.10 (t, J = 6.80 Hz, 1H), 7.25 (t, J = 8.80 Hz, 1H), 7.35-7.47 (m, 4H), 7.60 (t, J = 7.20 Hz, 1H), 7.66-7.68 (m, 1H), 7.81 (d, J = 8.40 Hz, 2H), 7.85 (d, J = 7.60 Hz, 1H), 8.03-8.10 (m, 3H), 8.18 (s, 1H), 8.20 (d, J = 2.40 Hz, 1H), 8.49 (br d, 1H), 8.53 (d, J = 2.00 Hz, 1H), 8.63 (d, J = 2.00 Hz, 1H), 8.73 (s, 1H), 8.87 (s, 1H), 8.97-8.99 (m, 2H), 10.27 (br s, 1H), 10.48 (br s, 1H).	**Example 519** ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-indazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylate & ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-indazol-2-yl)pyrimidin-5-yl}pyridine-3-carboxylate

5

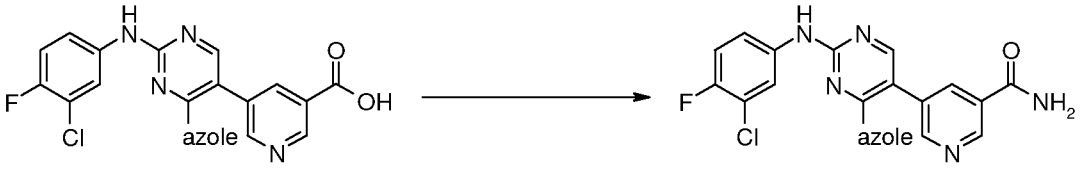
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 529[a)]	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(1,3-thiazol-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid.	MS(ES): 506 (M-1) for $C_{23}H_{15}ClFN_7O_2S$. 400 MHz, DMSO-d_6: δ 2.54 (s, 3H), 6.76 (s, 1H), 7.42 (t, *J* = 9.08 Hz, 1H), 7.63-7.68 (m, 2H), 7.82 (d, *J* = 3.20 Hz, 2H), 8.00 (t, *J* = 2.08 Hz, 1H), 8.09 (dd, *J* = 2.36, 6.74 Hz, 1H), 8.54 (d, *J* = 2.16 Hz, 1H), 8.90 (s, 1H), 8.93 (d, *J* = 1.88 Hz, 1H), 10.36 (s, 1H).	**Example 520** ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(1,3-thiazol-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 530[b)]	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(difluoromethyl)-5-methyl-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 475 (M+1) for $C_{21}H_{14}ClF_3N_6O_2$. 400 MHz, DMSO-d_6: δ 2.30 (s, 3H), 6.51 (s, 1H), 6.75 (t, *J* = 54.28 Hz, 1H), 7.39 (t, *J* = 9.08 Hz, 1H), 7.63-7.66 (m, 1H), 8.00-8.06 (m, 3H), 8.87 (s, 1H), 8.88 (br s, 1H), 10.39 (br s, 1H).	**Example 521** ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(difluoromethyl)-5-methyl-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 531 [b)]	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-(difluoromethyl)-3-methyl-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 475 (M+1) for $C_{21}H_{14}ClF_3N_6O_2$. 400 MHz, DMSO-d_6: δ 1.98 (s, 3H), 6.71 (s, 1H), 7.40 (t, *J* = 8.80 Hz, 1H), 7.59 (t, *J* = 54.40 Hz, 1H), 7.61-7.65 (m, 1H), 7.91 (br s, 1H), 8.05 (dd, *J* = 2.00, 6.60 Hz, 1H), 8.21 (br s, 1H), 8.77 (s, 1H), 8.90 (br s, 1H), 10.22 (br s, 1H).	**Example 522** ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-(difluoromethyl)-3-methyl-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 532[b)]	 5-{4-[3,5-bis(difluoromethyl)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 511 (M+1) for $C_{21}H_{12}ClF_5N_6O_2$. 400 MHz, DMSO-d_6: δ 6.82 (t, J = 53.76 Hz, 1H), 7.23 (s, 1H), 7.41 (t, J = 9.12 Hz, 1H), 7.57 (t, J = 55.52 Hz, 1H), 7.63-7.66 (m, 1H), 7.90 (s, 1H), 8.03 (d, J = 4.92 Hz, 1H), 8.39 (br s, 1H), 8.92 (s, 2H), 10.39 (br s, 1H).	**Example 523** ethyl 5-{4-[3,5-bis(difluoromethyl)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}pyridine-3-carboxylate
Example 533[c)]	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(thiophen-3-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 491 (M-1) for $C_{23}H_{14}ClFN_6O_2S$. 400 MHz, DMSO-d_6: δ 6.91 (d, J = 4.52 Hz, 1H), 6.95 (br s, 1H), 7.43 (t, J = 8.92 Hz, 1H), 7.52 (br s, 1H), 7.62 (br s, 1H), 7.73-7.75 (m, 1H), 8.09 (d, J = 5.20 Hz, 1H), 8.17 (br s, 1H), 8.47 (br s, 1H), 8.60 (s, 1H), 8.62 (s, 1H), 9.03 (s, 1H), 10.27 (s, 1H).	**Example 524** ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(thiophen-3-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 534[b)]	 5-{4-[3-(acetylamino)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 468 (M+1) for $C_{21}H_{15}ClFN_7O_3$. 400 MHz, DMSO-d_6: δ 1.92 (s, 3H), 6.83 (d, J = 2.20 Hz, 1H), 7.37 (t, J = 9.04 Hz, 1H), 7.71 (dd, J = 2.60, 8.36 Hz, 1H), 8.02-8.04 (m, 2H), 8.25 (br s, 1H), 8.33 (br s, 1H), 8.57 (br s, 1H), 8.93 (br s, 1H), 10.21 (br s, 1H), 10.42 (br s, 1H).	**Example 525** ethyl 5-{4-[3-(acetylamino)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}pyridine-3-carboxylate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 535 [a)]	 ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyridin-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 488 (M+1) for $C_{24}H_{15}ClFN_7O_2$. 400 MHz, DMSO-d_6: δ 7.28-7.29 (m, 1H), 7.43 (t, *J* = 9.08 Hz, 1H), 7.71 (ddd, *J* = 2.76, 4.14, 9.06 Hz, 1H), 7.78 (d, *J* = 7.88 Hz, 1H), 7.84 (td, *J* = 1.72, 10.72 Hz, 1H), 8.13 (d, *J* = 2.64 Hz, 1H), 8.15 (t, *J* = 1.92 Hz, 1H), 8.18 (s, 1H), 8.58 (d, *J* = 4.16 Hz, 1H), 8.69 (d, *J* = 2.20 Hz, 1H), 8.72 (s, 1H), 9.00 (d, *J* = 1.96 Hz, 1H), 9.03 (s, 1H), 10.36 (s, 1H), 13.45 (br s, 1H).	**Example 526** ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyridin-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 536[a)]	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyrimidin-4-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 487 (M-1) for $C_{23}H_{14}ClFN_8O_2$. 400 MHz, DMSO-d_6: δ 7.43 (t, *J* = 9.08 Hz, 1H), 7.70-7.74 (m, 1H), 7.88 (d, *J* = 5.28 Hz, 1H), 8.11-8.14 (m, 2H), 8.30 (s, 1H), 8.68 (d, *J* = 1.84 Hz, 1H), 8.76 (s, 1H), 8.80 (d, *J* = 5.24 Hz, 1H), 9.01 (d, *J* = 1.60 Hz, 1H), 9.15 (s, 1H), 9.20 (s, 1H), 10.40 (s, 1H), 13.49 (br s, 1H).	**Example 527** ethyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyrimidin-4-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

(a) Method C (b) Method D (c) Method D, THF-H_2O

General method for the synthesis of 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[azol-1-yl]pyrimidin-5-yl}pyridine-3-carboxamide



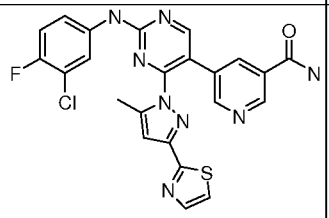
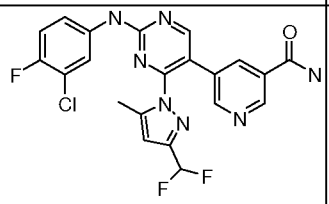
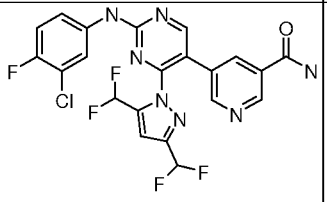
Method E:

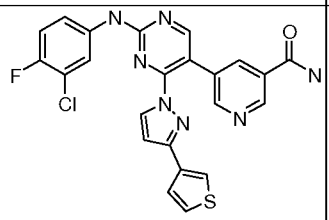
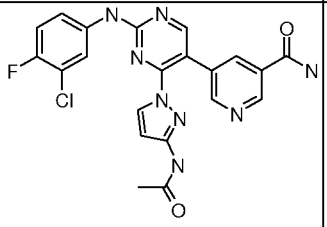
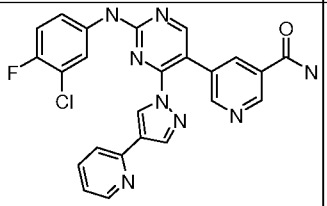
To a stirred solution of the carboxylic acid derivative (1 eq), pyridine (0.5 ml) and di-*tert*-butyl dicarbonate (1.3 eq) in dioxane (10-15 mL), ammonium hydrogencarbonate (1.26 eq) was added and the mixture was stirred for 4-16 h. The reaction mixture was then diluted with water (30-40 ml), stirred until precipitation was complete and the residue was then collected by filtration, washed with water, dried and further purified by column chromatography to give the product.

Method F:

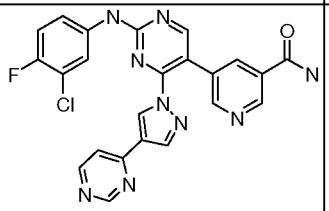
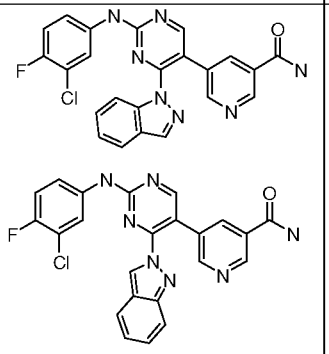
A solution of carboxylic acid derivative (1.02 mmol) taken in thionyl chloride (2 mL) was heated to 85 °C for 2 h. Thionyl chloride was then removed *in vacuo* and the solid obtained was quenched with a saturated solution of NH_3 in 1,4 dioxane (25 mL) and stirred for 20 min. The solid obtained was filtered and dried. The crude material was further purified by RP-HPLC to give the product.

The compounds in the below table were prepared using the methods described above as indicated and the starting material specified.

Compound	Structure	Mass and ^{1}H NMR data	SM
Example 537[d)]	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(1,3-thiazol-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxamide	MS(ES): 505 (M-1) for $C_{23}H_{16}ClFN_8OS$. 400 MHz, DMSO-d_6: δ 2.49 (s, 3H), 6.77 (br s, 1H), 7.43 (t, *J* = 9.08 Hz, 1H), 7.58 (br s, 1H), 7.64 (d, *J* = 3.20 Hz, 1H), 7.66-7.68 (m, 1H), 7.83 (d, *J* = 3.24 Hz, 1H), 8.09-8.13 (m, 3H), 8.31 (d, *J* = 2.08 Hz, 1H), 8.89 (d, *J* = 1.96 Hz, 1H), 8.91 (s, 1H).	**Example 529** 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(1,3-thiazol-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid
Example 538[a)]	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(difluoromethyl)-5-methyl-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxamide	MS(ES): 474 (M+1) for $C_{21}H_{15}ClF_3N_7O$. 400 MHz, DMSO-d_6: δ 2.41 (s, 3H), 6.56 (s, 1H), 6.73 (t, *J* = 54.16 Hz, 1H), 7.42 (t, *J* = 9.08 Hz, 1H), 7.61 (s, 1H), 7.65 (ddd, *J* = 2.72, 4.16, 9.03 Hz, 1H), 8.02 (t, *J* = 2.08 Hz, 1H), 8.07 (dd, *J* = 2.44, 6.62 Hz, 1H), 8.11 (s, 1H), 8.21 (d, *J* = 2.16 Hz, 1H), 8.90 (d, *J* = 1.96 Hz, 1H), 8.95 (s, 1H), 10.41 (s, 1H).	**Example 530** 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(difluoromethyl)-5-methyl-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid
Example 539[a)]	 5-{4-[3,5-bis(difluoromethyl)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}pyridine-3-carboxamide	MS(ES): 510 (M+1) for $C_{21}H_{13}ClF_5N_7O$. 400 MHz, DMSO-d_6: δ 6.82 (t, *J* = 53.76 Hz, 1H), 7.25 (s, 1H), 7.41 (t, *J* = 9.08 Hz, 1H), 7.58 (t, *J* = 53.68 Hz, 1H), 7.60-7.64 (m, 2H), 8.03 (br s, 1H), 8.04 (t, *J* = 2.08 Hz, 1H), 8.14 (br s, 1H), 8.30 (d, *J* = 2.08 Hz, 1H), 8.93 (d, *J* = 2.08 Hz, 1H), 8.94 (s, 1H), 10.40 (br s, 1H).	**Example 532** 5-{4-[3,5-bis(difluoromethyl)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}pyridine-3-carboxylic acid

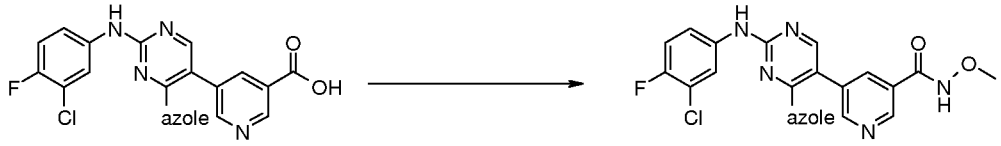
Compound	Structure	Mass and ^{1}H NMR data	SM
Example 540[a)]	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(thiophen-3-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxamide	MS(ES): 492 (M+1) for $C_{23}H_{15}ClFN_7OS$. 400 MHz, DMSO-d_6: δ 6.92 (dd, *J* = 1.08, 5.00 Hz, 1H), 6.97 (d, *J* = 2.72 Hz, 1H), 7.43 (t, *J* = 9.08 Hz, 1H), 7.52 (dd, *J* = 2.92, 4.96 Hz, 1H), 7.62 (br s, 1H), 7.66 (dd, *J* = 1.16, 2.86 Hz, 1H), 7.72-7.76 (m, 1H), 8.08 (dd, *J* = 2.48, 6.74 Hz, 1H), 8.17 (br s, 1H), 8.22 (t, *J* = 2.00 Hz, 1H), 8.50 (d, *J* = 2.68 Hz, 1H), 8.60 (br s, 1H), 8.64 (s, 1H), 9.01 (br s, 1H).	**Example 533** 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(thiophen-3-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid
Example 541[a)]	 5-{4-[3-(acetylamino)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}pyridine-3-carboxamide	MS(ES): 467 (M+1) for $C_{21}H_{16}ClFN_8O_2$. 400 MHz, DMSO-d_6: δ 1.94 (s, 3H), 6.88 (br s, 1H), 7.41 (t, *J* = 9.12 Hz, 1H), 7.62 (br s, 1H), 7.71-7.74 (m, 1H), 8.05 (d, *J* = 4.56 Hz, 1H), 8.14-8.15 (m, 2H), 8.33 (d, *J* = 2.16 Hz, 1H), 8.43 (br s, 1H), 8.66 (br s, 1H), 8.95 (br s, 1H), 10.28 (s, 1H), 10.33 (s, 1H).	**Example 534 (PE-032-019)** 5-{4-[3-(acetylamino)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}pyridine-3-carboxylic acid
Example 542[d)]	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyridin-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxamide	MS(ES): 487 (M+1) for $C_{24}H_{16}ClFN_8O$. 400 MHz, DMSO-d_6: δ 7.27 (t, *J* = 6.12 Hz, 1H), 7.43 (t, *J* = 9.12 Hz, 1H), 7.61 (br s, 1H), 7.70-7.73 (m, 1H), 7.77-7.84 (m, 2H), 8.13-8.18 (m, 4H), 8.54 (d, *J* = 1.96 Hz, 1H), 8.58 (d, *J* = 4.64 Hz, 1H), 8.72 (s, 1H), 8.95 (d, *J* = 1.84 Hz, 1H), 9.02 (s, 1H), 10.40 (br s, 1H).	**Example 535** 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyridin-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

5

Compound	Structure	Mass and ^{1}H NMR data	SM
Example 543[b]	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyrimidin-4-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxamide	MS(ES): 486 (M-1) and 973 (2M-1) for $C_{23}H_{15}ClFN_9O$. 400 MHz, DMSO-d_6: δ 7.43 (t, J = 9.08 Hz, 1H), 7.62 (br s, 1H), 7.71-7.73 (m, 1H), 7.89 (d, J = 5.12 Hz, 1H), 8.12-8.15 (m, 3H), 8.30 (s, 1H), 8.54 (br s, 1H), 8.76 (s, 1H), 8.80 (d, J = 5.16 Hz, 1H), 8.96 (br s, 1H), 9.14 (s, 1H), 9.20 (s, 1H), 10.41 (br s, 1H).	**Example 536** 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyrimidin-4-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid
Example 544[c]	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-indazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxamide & 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-indazol-2-yl)pyrimidin-5-yl}pyridine-3-carboxamide	MS(ES): 460 (M+1) for $C_{23}H_{15}ClFN_7O$. ^{1}H NMR 400 MHz, DMSO-d_6: δ 7.07-7.13 (m, 1H), 7.22-7.28 (m, 1H), 7.34-7.40 (m, 2H), 7.40-7.47 (m, 1H), 7.56-7.63 (m, 3H), 7.67 (d, J = 8.55 Hz, 1H), 7.76-7.83 (m, 1H), 7.86 (d, J = 7.93 Hz, 1H), 8.06-8.16 (m, 4H), 8.17-8.23 (m, 3H), 8.32 (d, J = 1.83 Hz, 1H), 8.47 (d, J = 1.83 Hz, 3H), 8.73 (s, 1H), 8.85-9.00 (m, 3H), 10.27 (s, 1H), 10.49 (s, 1H).	**Example 528** 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-indazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylic acid & 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-indazol-2-yl)pyrimidin-5-yl}pyridine-3-carboxylic acid

Solvents used in the reaction (a) Method E (b) Method E; Boc_2O(2.5 eq), Py (4 eq), NH_4HCO_3 (4 eq), DMF (c) Method E; DMSO (d) Method F

General method for the synthesis of 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[azol-1-yl]pyrimidin-5-yl}-*N*-methoxypyridine-3-carboxamide



Method G:

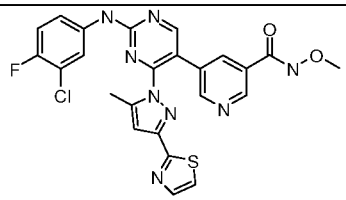
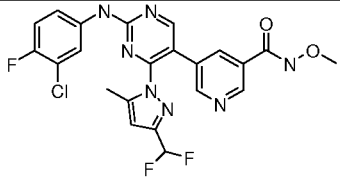
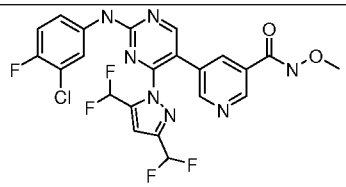
To a mixture of carboxylic acid derivative (1 eq), triethylamine (3 eq) and methoxylamine hydrochloride (2 eq) in DCM was added T3P (50% in EtOAc, 1.5 eq) slowly at 0 °C. The reaction mixture was slowly raised to room temperature and stirred overnight. The reaction mixture was then diluted with dichloromethane (12 mL) and washed successively with water, 10% aq sodium bicarbonate solution and brine. The organic layer was dried over sodium sulphate, filtered, concentrated and further purified by silica gel column chromatography to yield the product.

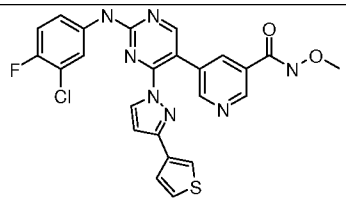
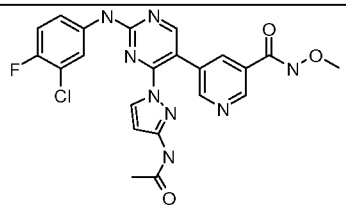
Method H:

To a mixture of carboxylic acid derivative (1 eq) and HATU (1.5 eq) in NMP, was added triethylamine (3 eq) and methoxylamine hydrochloride (1.2 eq) and the reaction mixture was stirred overnight. The reaction mixture was then diluted with water and the aqueous layer was extracted with EtOAc. The organic layer successively washed with 10% aq sodium bicarbonate solution and brine. The organic layer was dried over sodium sulphate, filtered, concentrated and further purified by silica gel column chromatography to yield the product.

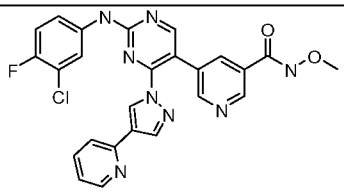
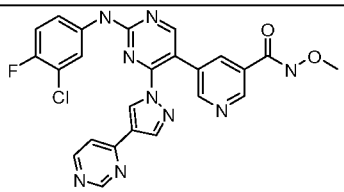
The compounds in the below table were prepared using the methods described above as indicated and the starting material specified.

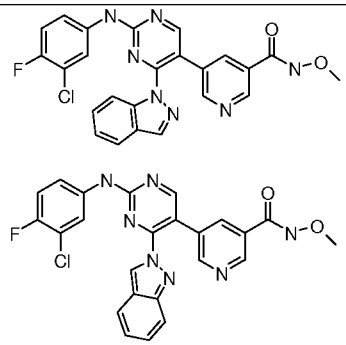
5

Compound	Structure	Mass and ^{1}H NMR data	SM
Example 545[a)]	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(1,3-thiazol-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-methoxypyridine-3-carboxamide	MS(ES): 537 (M+1) for $C_{24}H_{18}ClFN_8O_2S$. 400 MHz, DMSO-d_6: δ 2.51 (s, 3H), 3.67 (s, 3H), 6.77 (s, 1H), 7.43 (t, *J* = 9.12 Hz, 1H), 7.64-7.68 (m, 2H), 7.83 (d, *J* = 3.24 Hz, 1H), 7.99 (br s, 1H), 8.09 (dd, *J* = 2.36, 6.68 Hz, 1H), 8.35 (d, *J* = 1.88 Hz, 1H), 8.76 (d, *J* = 1.92 Hz, 1H), 8.90 (s, 1H), 10.39 (s, 1H), 11.92 (br s, 1H).	**Example 529** 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(1,3-thiazol-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid
Example 546[a)]	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(difluoromethyl)-5-methyl-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-methoxypyridine-3-carboxamide	MS(ES): 504 (M+1) for $C_{22}H_{17}ClF_3N_7O_2$. 400 MHz, DMSO-d_6: δ 2.41 (s, 3H), 3.71 (s, 3H), 6.57 (s, 1H), 6.73 (t, *J* = 54.12 Hz, 1H), 7.42 (t, *J* = 9.12 Hz, 1H), 7.64-7.66 (m, 1H), 7.88 (s, 1H), 8.06-8.07 (m, 1H), 8.26 (d, *J* = 1.56 Hz, 1H), 8.76 (d, *J* = 1.92 Hz, 1H), 8.95 (s, 1H), 10.46 (s, 1H), 11.95 (br s, 1H).	**Example 530** 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(difluoromethyl)-5-methyl-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid
Example 547[a)]	 5-{4-[3,5-bis(difluoromethyl)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}-*N*-methoxypyridine-3-carboxamide	MS(ES): 540 (M+1) for $C_{22}H_{15}ClF_5N_7O_2$. 400 MHz, DMSO-d_6: δ 3.71 (s, 3H), 6.82 (t, *J* = 54.04 Hz, 1H), 7.26 (s, 1H), 7.41 (t, *J* = 9.16 Hz, 1H), 7.59-7.72 (m, 2H), 7.93 (br s, 1H), 8.03 (br s, 1H), 8.35 (br s, 1H), 8.81 (br s, 1H), 8.94 (br s, 1H), 10.41 (br s, 1H), 11.98 (br s, 1H).	**Example 532** 5-{4-[3,5-bis(difluoromethyl)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}pyridine-3-carboxylic acid

Compound	Structure	Mass and ^{1}H NMR data	SM
Example 548[a)]	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(thiophen-3-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-methoxypyridine-3-carboxamide	MS(ES): 520 (M-1) for $C_{24}H_{17}ClFN_7O_2S$. 400 MHz, DMSO-d_6: δ 3.70 (s, 3H), 6.93 (dd, J = 1.04, 5.02 Hz, 1H), 6.98 (d, J = 2.68 Hz, 1H), 7.43 (t, J = 9.08 Hz, 1H), 7.52 (dd, J = 2.92, 4.96 Hz, 1H), 7.65 (dd, J = 1.08, 2.82 Hz, 1H), 7.72-7.76 (m, 1H), 8.08 (dd, J = 2.52, 6.74 Hz, 1H), 8.13 (br t, 1H), 8.51 (d, J = 2.72 Hz, 1H), 8.63 (br s, 2H), 8.89 (br s, 1H), 10.28 (s, 1H), 12.00 (br s, 1H).	**Example 533** 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(thiophen-3-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid
Example 549[b)]	 5-{4-[3-(acetylamino)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}-*N*-methoxypyridine-3-carboxamide	MS(ES): 497 (M+1) for $C_{22}H_{18}ClFN_8O_3$. 400 MHz, DMSO-d_6: δ 1.94 (s, 3H), 3.73 (s, 3H), 6.87 (d, J = 2.16 Hz, 1H), 7.41 (t, J = 9.12 Hz, 1H), 7.71-7.75 (m, 1H), 8.04-8.05 (m, 2H), 8.33 (d, J = 2.40 Hz, 1H), 8.45 (br s, 1H), 8.65 (s, 1H), 8.83 (br s, 1H), 10.28-10.31 (m, 2H), 11.96 (br s, 1H).	**Example 534** 5-{4-[3-(acetylamino)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}pyridine-3-carboxylic acid

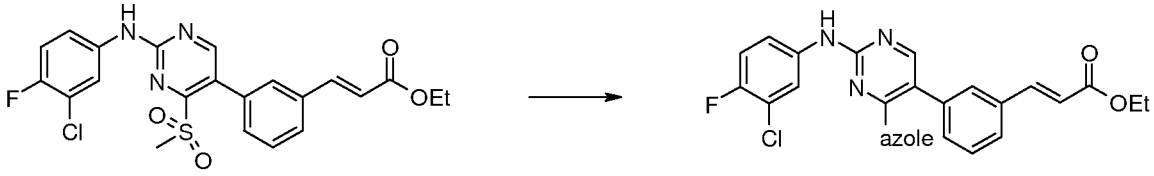
5

Compound	Structure	Mass and ^{1}H NMR data	SM
Example 550[b)]	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyridin-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-methoxypyridine-3-carboxamide	MS(ES): 517 (M+1) for $C_{25}H_{18}ClFN_8O_2$. 400 MHz, DMSO-d_6: δ 3.72 (s, 3H), 7.27 (t, J = 5.92 Hz, 1H), 7.44 (t, J = 9.16 Hz, 1H), 7.70-7.73 (m, 1H), 7.78 (d, J = 7.48 Hz, 1H), 7.84 (t, J = 7.32 Hz, 1H), 8.06 (br s, 1H), 8.14 (dd, J = 2.44, 6.78 Hz, 1H), 8.18 (s, 1H), 8.56-8.58 (m, 2H), 8.71 (s, 1H), 8.83 (s, 1H), 9.03 (s, 1H), 10.38 (s, 1H), 11.98 (br s, 1H).	**Example 535** 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyridin-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid
Example 551[a)]	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyrimidin-4-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-methoxypyridine-3-carboxamide	MS(ES): 518 (M+1) for $C_{24}H_{17}ClFN_9O_2$. 400 MHz, DMSO-d_6: δ 3.72 (s, 3H), 7.43 (t, J = 9.08 Hz, 1H), 7.71-7.74 (m, 1H), 7.89 (d, J = 4.76 Hz, 1H), 8.06 (s, 1H), 8.12 (dd, J = 2.48, 6.68 Hz, 1H), 8.30 (s, 1H), 8.56 (d, J = 1.52 Hz, 1H), 8.75 (s, 1H), 8.80-8.83 (m, 2H), 9.15 (s, 1H), 9.20 (s, 1H), 10.41 (s, 1H), 11.97 (s, 1H).	**Example 536** 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyrimidin-4-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

Compound	Structure	Mass and ^{1}H NMR data	SM
Example 552[a)]	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-indazol-1-yl)pyrimidin-5-yl}-*N*-methoxypyridine-3-carboxamide & 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-indazol-2-yl)pyrimidin-5-yl}-*N*-methoxypyridine-3-carboxamide	MS(ES): 490 (M+1) for $C_{24}H_{17}ClFN_7O_2$. ^{1}H NMR 400 MHz, DMSO-d_6: δ 3.71 (s, 6H), 7.07-7.13 (m, 1H), 7.22-7.28 (m, 1H), 7.34-7.40 (m, 2H), 7.41 (s, 1H), 7.41-7.48 (m, 1H), 7.57-7.63 (m, 1H), 7.63-7.69 (m, 1H), 7.80 (d, *J* = 8.80 Hz, 1H), 7.76-7.78 (m, 1H), 7.85 (d, *J* = 7.83 Hz, 1H), 7.98 (br s, 1H), 8.02-8.06 (m, 1H), 8.02-8.05 (m, 1H), 8.07 (br s, 1H), 8.18 (s, 1H), 8.19 (d, *J* = 2.45 Hz, 1H), 8.34 (d, *J* = 1.47 Hz, 1H), 8.48 (d, *J* = 1.71 Hz, 2H), 8.71 (s, 1H), 8.79 (s, 2H), 8.85 (s, 1H), 8.98 (s, 1H), 10.27 (s, 1H), 10.48 (s, 1H), 11.94 (br s, 1H).	**Example 528** 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-indazol-1-yl)pyrimidin-5-yl}pyridine-3-carboxylic acid & 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-indazol-2-yl)pyrimidin-5-yl}pyridine-3-carboxylic acid

(a) Method G (b) Method H

General method for the synthesis of ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(azol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoate



Method I:

A solution of azole (2.2 eq) in DMF (1 mL) was added slowly to a suspension of sodium hydride (2.1 eq) in DMF (1 mL). The reaction mixture was stirred for 30 min at room temperature. A solution of (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(methylsulfonyl)pyrimidin-5-yl)phenyl)acrylate **Intermediate 125** (1 eq) in DMF (1 mL) was added slowly to the reaction

mixture at 0 °C with stirring and allowed to warm to ambient temperature over 2.5 h. Water was added (~6 mL) and the solid formed was filtered, dried to yield the product.

Method J:

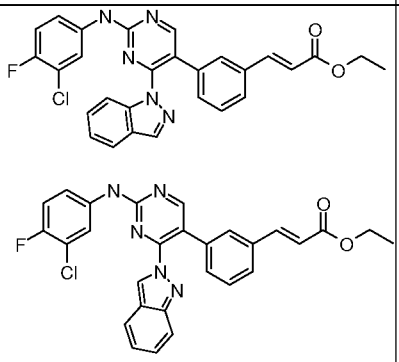
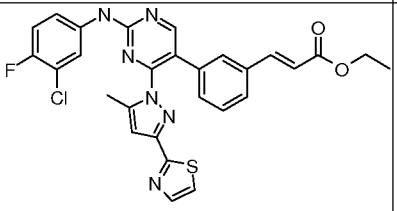
A solution of azole (2.2 eq) in DMSO (1 mL) was added slowly to a suspension of sodium hydride (2.1 eq) in DMSO (1 mL). The reaction mixture was stirred for 30 min at room temperature. A solution of (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(methylsulfonyl)pyrimidin-5-yl)phenyl)acrylate **Intermediate 125** (1 eq) in DMSO (1 mL) was added slowly to the reaction mixture at 0 °C with stirring and allowed to warm to ambient temperature over 2.5 h. Water was added (~6 mL) and the solid formed was filtered, dried to yield the product.

Method K:

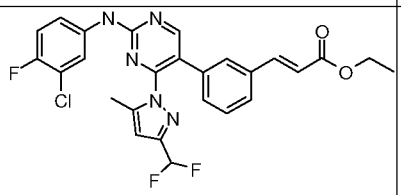
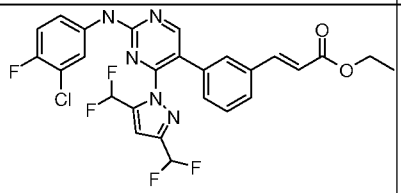
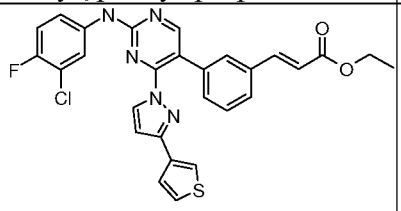
A suspension of azole (1.2 eq), potassium *tert*-butoxide (1.5 eq) and (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(methylsulfonyl)pyrimidin-5-yl)phenyl)acrylate **Intermediate 125** (1 eq) in DMSO (3 mL) was subjected to microwave irradiation at 130 °C for 1 h. After the reaction cooled to RT, the mixture was diluted with EtOAc, washed successively with water and brine. The organic layer was dried over sodium sulphate, filtered, concentrated and further purified by silica gel column chromatography to yield the product.

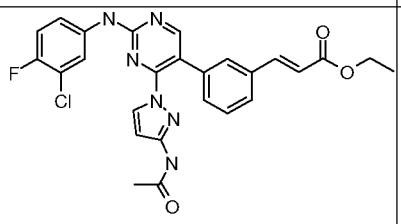
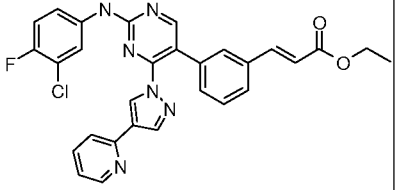
The compounds in the below table were prepared using the methods described above as indicated and the starting material specified.

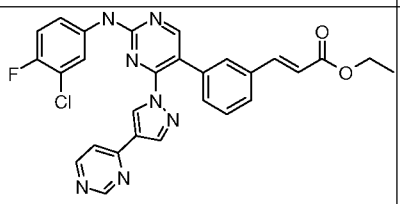
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Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 553[a)]	 ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-indazol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoate & ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-indazol-2-yl)pyrimidin-5-yl}phenyl)prop-2-enoate	^{1}H NMR 400 MHz, DMSO-d_6:: δ 1.24 (t, *J* = 7.03 Hz, 3H), 4.16 (d, *J* = 7.03 Hz, 2H), 6.51 (d, *J* = 16.06 Hz, 1H), 6.58 (d, *J* = 16.06 Hz, 1H), 7.00 (d, *J* = 7.03 Hz, 1H), 7.08 (t, *J* = 7.53 Hz, 2H), 7.21-7.48 (m, 8H), 7.52-7.68 (m, 6H), 7.72-7.79 (m, 2H), 7.83 (d, *J* = 7.28 Hz, 1H), 7.94 (s, 1H), 8.10 (dd, *J* = 6.90, 2.38 Hz, 1H), 8.17 (s, 1H), 8.17-8.21 (m, 1H), 8.28-8.34 (m, 1H), 8.73 (s, 1H), 8.80 (s, 1H), 8.87 (d, *J* = 1.00 Hz, 1H), 10.21 (s, 1H), 10.43 (s, 1H).	1*H*-indazole
Example 554[b)]	 ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(1,3-thiazol-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 561 (M+1) for $C_{28}H_{22}ClFN_6O_2S$. 300 MHz, DMSO-d_6: δ 1.22 (t, *J* = 6.90 Hz, 3H), 2.27 (s, 3H), 4.15 (q, *J* = 7.05 Hz, 2H), 6.56 (d, *J* = 16.05 Hz, 1H), 6.72 (s, 1H), 7.03 (d, *J* = 7.92 Hz, 1H), 7.32 (t, *J* = 7.32 Hz, 1H), 7.41 (t, *J* = 9.21 Hz, 1H), 7.53-7.66 (m, 5H), 7.83 (d, *J* = 3.15 Hz, 1H), 8.11 (d, *J* = 6.39 Hz, 1H), 8.92 (s, 1H), 10.39 (br s, 1H).	2-(5-methyl-1*H*-pyrazol-3-yl)-1,3-thiazole

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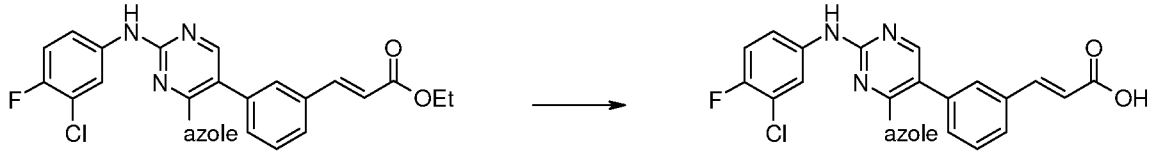
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 555[b)]	 ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(difluoromethyl)-5-methyl-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 528 (M+1) for $C_{26}H_{21}ClF_3N_5O_2$. 300 MHz, DMSO-d_6: δ 1.24 (t, *J* = 7.89 Hz, 3H), 2.20 (s, 3H), 4.18 (q, *J* = 7.44 Hz, 2H), 6.51 (s, 1H), 6.57 (d, *J* = 15.84 Hz, 1H), 6.82 (t, 1H), 6.97 (d, *J* = 7.86 Hz, 1H), 7.32 (t, *J* = 7.38 Hz, 1H), 7.41 (t, *J* = 9.18 Hz, 1H), 7.43 (br s, 1H), 7.56 (d, *J* = 16.11 Hz, 1H), 7.61-7.69 (m, 2H), 8.08 (dd, *J* = 8.76, Hz, 1H), 8.96 (s, 1H), 10.42 (s, 1H).	3-(difluoromethyl)-5-methyl-1*H*-pyrazole
Example 556[c)]	 ethyl (2*E*)-3-(3-{4-[3,5-bis(difluoromethyl)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}phenyl)prop-2-enoate	Taken to the next step on the basis of LCMS. MS(ES): 564 (M+1) for $C_{26}H_{19}ClF_5N_5O_2$. 91 % pure by LCMS.	3,5-bis(difluoromethyl)-1*H*-pyrazole
Example 557[b)]	 ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(thiophen-3-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 546 (M+1) for $C_{28}H_{21}ClFN_5O_2S$. 400 MHz, DMSO-d_6: δ 1.23 (t, *J* = 7.04 Hz, 3H), 4.16 (q, *J* = 7.12 Hz, 2H), 6.64 (d, *J* = 16.04 Hz, 1H), 6.92 (d, *J* = 2.64 Hz, 1H), 6.98 (dd, *J* = 1.04, 5.00 Hz, 1H), 7.28 (d, *J* = 7.68 Hz, 1H), 7.41 (t, *J* = 7.92 Hz, 1H), 7.42 (t, *J* = 9.04 Hz, 1H), 7.50 (dd, *J* = 2.92, 5.00 Hz, 1H), 7.63-7.66 (m, 2H), 7.71-7.72 (m, 3H), 8.14 (dd, *J* = 2.60, 6.80 Hz, 1H), 8.32 (d, *J* = 2.68 Hz, 1H), 8.63 (s, 1H), 10.26 (s, 1H).	3-(thiophen-3-yl)-1*H*-pyrazole

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Exampe \558[a)]	 ethyl (2*E*)-3-(3-{4-[3-(acetylamino)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 521 (M+1) for $C_{26}H_{22}ClFN_6O_3$. 400 MHz, DMSO-d_6: δ 1.26 (t, J = 7.20 Hz, 3H), 1.95 (s, 3H), 4.19 (q, J = 7.20 Hz, 2H), 6.66 (d, J = 16.00 Hz, 1H), 6.83 (d, J = 2.40 Hz, 1H), 7.11 (d, J = 7.60 Hz, 1H), 7.37 (t, J = 8.00 Hz, 1H), 7.40 (t, J = 8.80 Hz, 1H), 7.63-7.70 (m, 3H), 7.72-7.76 (m, 1H), 8.08 (dd, J = 2.80, 6.60 Hz, 1H), 8.15 (d, J = 2.40 Hz, 1H), 8.69 (s, 1H), 10.25 (s, 1H), 10.42 (s, 1H).	*N*-(1*H*-pyrazol-3-yl)acetamide
Example 559[a)]	 ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyridin-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 541 (M+1) for $C_{29}H_{22}ClFN_6O_2$. 400 MHz, DMSO-d_6: δ 1.24 (t, J = 7.2 Hz, 3H), 4.17 (q, J = 7.2 Hz, 2H), 6.64 (d, J = 16.4 Hz, 1H), 7.23 (t, J = 7.2 Hz, 1H), 7.27 (t, J = 6 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 9.6 Hz, 1H), 7.61-7.77 (m, 5H), 7.83 (t, J = 7.6 Hz, 1H), 8.16 (d, J = 6.8 Hz, 1H), 8.18 (s, 1H), 8.57 (d, J = 4.4 Hz, 1H), 8.73 (s, 1H), 8.91 (s, 1H), 10.32 (s, 1H).	2-(1*H*-pyrazol-4-yl)pyridine

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 560[a)]	 ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyrimidin-4-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 540 (M-1) for $C_{28}H_{21}ClFN_7O_2$. 400 MHz, DMSO-d_6: δ 1.23 (t, *J* = 7.04 Hz, 3H), 4.16 (q, *J* = 7.12 Hz, 2H), 6.62 (d, *J* = 16.04 Hz, 1H), 7.21 (d, *J* = 7.64 Hz, 1H), 7.38 (t, *J* = 7.64 Hz, 1H), 7.42 (t, *J* = 9.20 Hz, 1H), 7.62 (d, *J* = 16.16 Hz, 1H), 7.68 (br s, 2H), 7.71-7.74 (m, 1H), 7.87 (dd, *J* = 8.40, 1.72 Hz, 1H), 8.14 (dd, *J* = 2.64, 6.74 Hz, 1H), 8.30 (s, 1H), 8.77 (s, 1H), 8.79 (d, *J* = 5.32 Hz, 1H), 9.09 (s, 1H), 9.13 (s, 1H), 10.36 (br s, 1H).	4-(1*H*-pyrazol-4-yl)pyrimidine

(a) Method I (b) Method J (c) Method K

General method for the synthesis of (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[azol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid



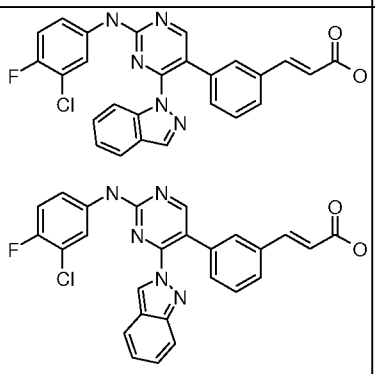
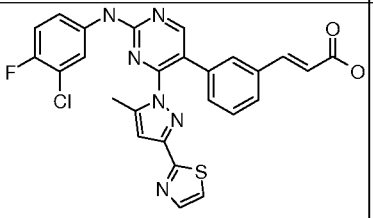
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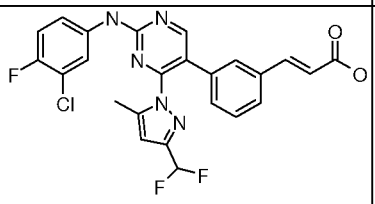
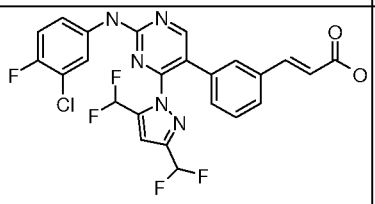
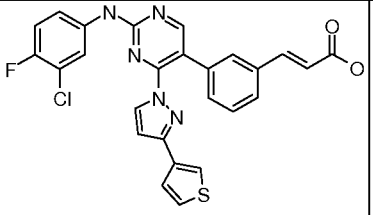
A solution of carboxylic ester derivative (1 eq) in a mixture of tetrahydrofuran (1 mL) and water (1 mL) was treated with 1 N aq. sodium hydroxide (4 eq) and allowed to stir at room temperature for 1 h. After completion of the reaction, the mixture was carefully acidified with 1 N HCl and the precipitate formed was filtered, washed with water and dried to the product.

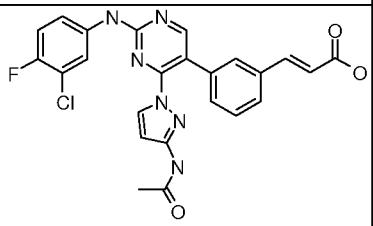
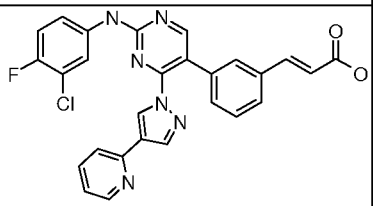
Method M:

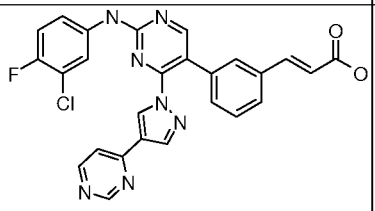
A solution of carboxylic ester derivative (1 eq) in a mixture of dioxane (1 mL) and water (1 mL) was treated with 1 N aq. Barium hydroxide (2 eq) and warmed to 60 °C for 3-10 h. After completion of the reaction, the mixture was carefully acidified with 1 N HCl and the precipitate formed was filtered, washed with water, dried to yield the product.

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Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 561[a)]	 (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-indazol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoic acid & (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-indazol-2-yl)pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 486 (M+1) for $C_{26}H_{17}ClFN_5O_2$. ^{1}H NMR 400 MHz, DMSO-d_6: δ 6.43 (d, *J* = 16.00 Hz, 1H), 6.47 (d, *J* = 15.81 Hz, 1H), 6.98 (d, *J* = 7.53 Hz, 1H), 7.07 (t, *J* = 7.65 Hz, 2H), 7.22-7.30 (m, 3H), 7.32 (d, *J* = 8.03 Hz, 1H), 7.36 (d, *J* = 4.77 Hz, 1H), 7.37-7.45 (m, 3H), 7.45-7.49 (m, 1H), 7.49-7.53 (m, 1H), 7.53-7.60 (m, 5H), 7.65 (dt, *J* = 3.36, 8.85 Hz, 1H), 7.73-7.79 (m, 2H), 7.83 (d, *J* = 7.78 Hz, 1H), 8.11 (dd, *J* = 2.51, 6.78, Hz, 1H), 8.17-8.21 (m, 1H), 8.31 (d, *J* = 8.28 Hz, 1H), 8.73 (s, 1H), 8.80 (s, 1H), 8.87 (s, 1H), 10.22 (s, 1H), 10.43 (s, 1H), 12.38 (br s, 1H).	**Example 553** ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(1*H*-indazol-1-yl)pyrimidin-5-yl}phenyl)prop-2-enoate & ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-(2*H*-indazol-2-yl)pyrimidin-5-yl}phenyl)prop-2-enoate
Example 562[a)]	 (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(1,3-thiazol-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 531 (M-1) for $C_{26}H_{18}ClFN_6O_2S$. 400 MHz, DMSO-d_6: δ 2.30 (s, 3H), 6.47 (d, *J* = 16.00 Hz, 1H), 6.72 (s, 1H), 7.02 (d, *J* = 7.92 Hz, 1H), 7.31 (t, *J* = 7.68 Hz, 1H), 7.41 (t, *J* = 9.12 Hz, 1H), 7.50 (d, *J* = 16.00 Hz, 1H), 7.55-7.56 (m, 2H), 7.64-7.65 (m, 2H), 7.83 (d, *J* = 3.24 Hz, 1H), 8.09 (dd, *J* = 38.52, 24.74 Hz, 1H), 8.91 (s, 1H), 10.37 (s, 1H), 12.37 (br s, 1H).	**Example 554** ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(1,3-thiazol-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate

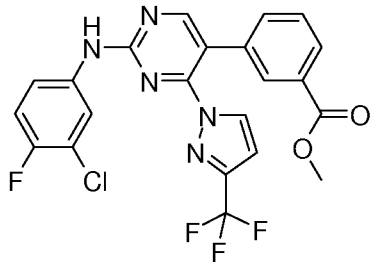
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 563[b)]	 (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(difluoromethyl)-5-methyl-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 500 (M+1) for $C_{24}H_{17}ClF_3N_5O_2$. 400 MHz, DMSO-d_6: δ 2.02 (s, 3H), 6.46 (d, *J* = 16.00 Hz, 1H), 6.52 (br s, 1H), 6.82 (t, *J* = 54.20 Hz, 1H), 6.99 (d, *J* = 7.80 Hz, 1H), 7.33 (t, *J* = 7.76 Hz, 1H), 7.37 (br s, 1H), 7.41 (t, *J* = 9.16 Hz, 1H), 7.49 (d, *J* = 16.00 Hz, 1H), 7.59 (d, *J* = 7.80 Hz, 1H), 7.64-7.68 (m, 1H), 8.08 (dd, *J* = 1.88, 6.54 Hz, 1H), 8.95 (s, 1H), 10.42 (s, 1H), 12.46 (br s, 1H).	**Example 555** ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(difluoromethyl)-5-methyl-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate
Example 564[b)]	 (2*E*)-3-(3-{4-[3,5-bis(difluoromethyl)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 536 (M+1) for $C_{24}H_{15}ClF_5N_5O_2$. 400 MHz, DMSO-d_6: δ 6.47 (d, *J* = 15.84 Hz, 1H), 6.86 (t, *J* = 53.76 Hz, 1H), 6.97 (m, 1H), 7.23 (br s, 1H), 7.43 (m, 5H), 7.62 (br s, 2H), 8.05 (br s, 1H), 8.95 (s, 1H), 10.40 (br s, 1H), 12.44 (br s, 1H).	**Example 556** ethyl (2*E*)-3-(3-{4-[3,5-bis(difluoromethyl)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}phenyl)prop-2-enoate
Example 565[c)]	 (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(thiophen-3-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 518 (M+1) for $C_{26}H_{17}ClFN_5O_2S$. 400 MHz, DMSO-d_6: δ 6.52 (d, *J* = 16.00 Hz, 1H), 6.92 (d, *J* = 2.40 Hz, 1H), 7.01 (d, *J* = 4.80 Hz, 1H), 7.26 (d, *J* = 7.60 Hz, 1H), 7.39-7.45 (m, 2H), 7.51-7.55 (m, 2H), 7.65-7.68 (m, 3H), 7.72-7.76 (m, 1H), 8.15 (dd, *J* = 2.40, 6.80 Hz, 1H), 8.32 (d, *J* = 2.80 Hz, 1H), 8.63 (br s, 1H), 10.3 (br s, 1H).	**Example 557** ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(thiophen-3-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 566[a)]	 (2*E*)-3-(3-{4-[3-(acetylamino)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 493 (M+1) for $C_{24}H_{18}ClFN_6O_3$. 400 MHz, DMSO-d_6: δ 1.95 (s, 3H), 6.53 (d, *J* = 15.60 Hz, 1H), 6.83 (d, *J* = 2.40 Hz, 1H), 7.06 (d, *J* = 7.20 Hz, 1H), 7.34 (t, *J* = 7.60 Hz, 1H), 7.40 (t, *J* = 9.20 Hz, 1H), 7.45 (d, *J* = 16.00 Hz, 1H), 7.56 (s, 1H), 7.58 (br s, 1H), 7.73-7.76 (m, 1H), 8.08 (dd, *J* = 2.40, 6.80 Hz, 1H), 8.13 (d, *J* = 2.40 Hz, 1H), 8.68 (br s, 1H), 10.24 (s, 1H), 10.43 (s, 1H).	**Example 558** ethyl (2*E*)-3-(3-{4-[3-(acetylamino)-1*H*-pyrazol-1-yl]-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl}phenyl)prop-2-enoate
Example 567[a)]	 (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyridin-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 511 (M-1) for $C_{27}H_{18}ClFN_6O_2$. 400 MHz, DMSO-d_6: δ 6.52 (d, *J* = 16.00 Hz, 1H), 7.20 (d, *J* = 7.44 Hz, 1H), 7.25 (t, *J* = 6.20 Hz, 1H), 7.37 (t, *J* = 7.64 Hz, 1H), 7.41 (t, *J* = 9.28 Hz, 1H), 7.57 (d, *J* = 15.96 Hz, 1H), 7.62 (d, *J* = 7.64 Hz, 1H), 7.65 (s, 1H), 7.69-7.76 (m, 2H), 7.82 (t, *J* = 7.60 Hz, 1H), 8.15 (dd, *J* = 2.48, 6.72 Hz, 1H), 8.18 (s, 1H), 8.56 (d, *J* = 4.20 Hz, 1H), 8.71 (s, 1H), 8.90 (s, 1H), 10.31 (s, 1H), 12.40 (br s, 1H).	**Example 559** ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyridin-2-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 568[a)]	 (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyrimidin-4-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid.	MS(ES): 512 (M-1) for $C_{26}H_{17}ClFN_7O_2$. 400 MHz, DMSO-d_6: δ 6.51 (d, *J* = 16.00 Hz, 1H), 7.19 (d, *J* = 7.76 Hz, 1H), 7.36 (t, *J* = 7.64 Hz, 1H), 7.41 (t, *J* = 9.12 Hz, 1H), 7.56 (d, *J* = 16.00 Hz, 1H), 7.61 (s, 1H), 7.64 (br s, 1H), 7.70-7.74 (m, 1H), 7.85-7.86 (m, 1H), 8.13 (dd, *J* = 2.56, 6.76 Hz, 1H), 8.30 (s, 1H), 8.75 (s, 1H), 8.78 (d, *J* = 5.32 Hz, 1H), 9.08 (s, 1H), 9.12 (s, 1H), 10.35 (s, 1H), 12.38 (br s, 1H).	**Example 560** ethyl (2*E*)-3-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[4-(pyrimidin-4-yl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate.

(a) Method L (b) Method M(c) Method M, ambient temperature

Example 569: methyl 3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)benzoate

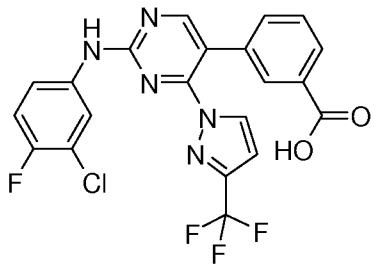


The title compound was prepared using the general method described above for **Example 1** using 3-(methoxycarbonyl)phenylboronic acid and **intermediate 115** as starting materials.

MS: ES+ 492 for $C_{22}H_{14}ClF_4N_5O_2$.

1H NMR (300 MHz, DMSO-D6) δ ppm 3.82 (s, 3 H), 6.99 (d, 1 H), 7.35 - 7.55 (m, 3 H), 7.64 - 7.76 (m, 2 H), 7.91 (d, 1 H), 8.09 (dd, 1 H), 8.40 (s, 1 H), 8.80 (s, 1 H), 10.43 (s, 1 H).

Example 570: 3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)benzoic acid

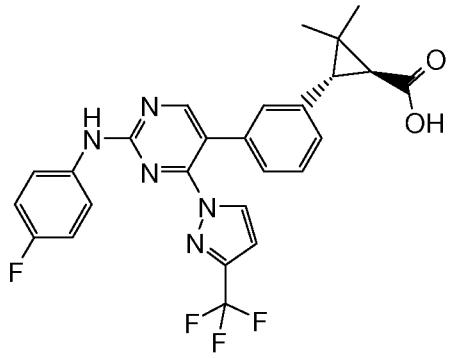


The title compound was prepared using the general method described above for Example **214** using 1N sodium hydroxide (2 equivalents), dioxane : THF (1:1) as solvent and (**Example 569** as a starting material.

MS: ES+ 478 for $C_{21}H_{12}ClF_4N_5O_2$.

1H NMR (400 MHz, DMSO-D6) δ ppm 6.98 (d, 1 H), 7.37-7.51 (m, 3 H), 7.66 (s, 1 H), 7.69 - 7.76 (m, 1 H), 7.88 (d, 1 H), 8.10 (dd, 1 H), 8.39 (s, 1 H), 8.79 (s, 1 H), 10.40 (s, 1 H), 12.93 (s, 1 H).

Example 571: (1,3-*trans*)-3-(3-(2-(4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenyl)-2,2-dimethylcyclopropanecarboxylic acid



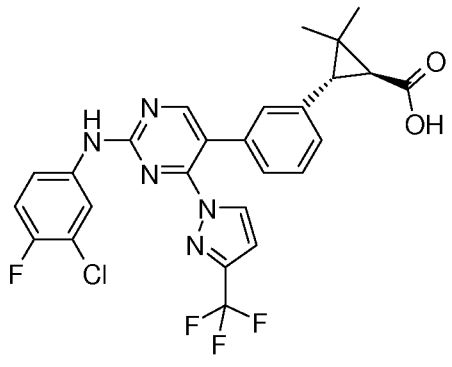
(1,3-*trans*)-tert-butyl 2,2-dimethyl-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropanecarboxylate **Intermediate 174** (342 mg, 0.92 mmol), 5-bromo-N-(3-chloro-4-fluorophenyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine (200 mg, 0.46

mmol) (**Intermediate 115**), Tris(dibenzylideneacetone)dipalladium(0) (41.9 mg, 0.05 mmol), 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (65.5 mg, 0.14 mmol), Na_2CO_3 (200 mg, 1.89 mmol), acetonitrile (3 mL) and water (0.750 mL) were combined and degassed with an argon stream for 10 min. The mixture was warmed at 80°C for 2.5 hrs, allowed to cool, diluted with acetonitrile, filtered and adsorbed on 15 ml silica gel. Purified by flash chromatography (80 g cartridge, 0-10% ethyl acetate in hexane). A crude sample of the tert-butyl ester of the title compound was thus obtained as a yellow-orange solid: (100 mg). This sample was converted to the title compound as follows: Sample was first combined with dichloromethane (1 mL) and trifluoroacetic acid (1 mL, 12.98 mmol). The clear solution was stirred at room temperature for 45 min then evaporated. The mixture was dissolved in dichloromethane and applied to 5 ml silica gel column. Eluted with 20% ethyl acetate in hexane, then with 50% ethyl acetate in hexane. Pure fractions evaporated and dissolved in 0.25 ml ethyl acetate then precipitated with 5 ml hexanes. Filtered to give a white solid (9 mg).

MS: ES+ 512 for $C_{26}H_{21}F_4N_5O_2$.

1H NMR (400 MHz, DMSO-D6) δ ppm 0.91 (s, 3 H), 1.32 (s, 3 H), 2.05 (d, 1 H), 2.56 (d, 1 H), 7.14 (d, 1 H), 7.24 - 7.28 (m, 1 H), 7.31 (d, 2 H), 7.37 (s, 1 H), 7.40 - 7.44 (m, 2 H), 7.80 - 7.87 (m, 2 H), 8.64 (d, 1 H), 8.72 (d, 1 H), 10.06 (s, 1 H), 12.20 (s, 1 H).

Example 572: (1,3-trans)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenyl)-2,2-dimethylcyclopropanecarboxylic acid



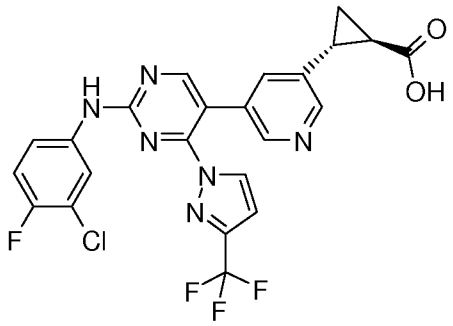
(1S,3S)-tert-butyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenyl)-2,2-dimethylcyclopropanecarboxylate **Intermediate 176** (35 mg, 0.06 mmol) was dissolved in dichloromethane (1 mL) then trifluoroacetic acid (1 ml, 12.98 mmol)

was added to give a clear yellow solution. The mixture was stirred at room temperature for 30 minutes. The solution was concentrated and the residue was triturated with 3 ml hexane to give the title compound as a light yellow solid (30 mg).

MS: ES+ 546 for $C_{26}H_{20}ClF_4N_5O_2$.

1H NMR (400 MHz, DMSO-D6) δ ppm 0.77 (s, 3 H), 1.26 (s, 3 H), 1.87 (d, 1 H), 2.40 (d, 1 H), 6.90 (s, 1 H), 6.93 (d, 1 H), 7.06 (d, 1 H), 7.17 (d,1 H), 7.29 (t, 1 H), 7.39 (t, 1 H), 7.66 - 7.73 (m, 1 H), 8.12 (dd, 1 H), 8.24 (s, 1 H), 8.77 (s, 1 H), 10.38 (s, 1 H).

Example 573: (1,2-trans)-2-(5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)pyridin-3-yl)cyclopropanecarboxylic acid

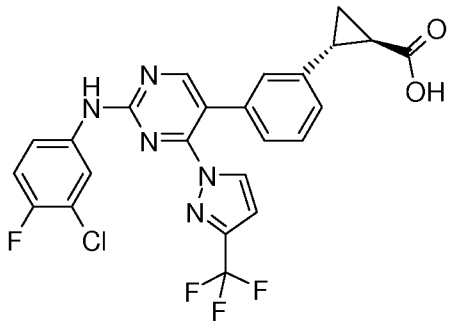


The title compound was prepared using the general method described above for **Example 572** using **Intermediate 180** as a starting material.

MS: ES+ 519 for C23H15ClF4N6O2.

1H NMR (300 MHz, DMSO-D6) δ ppm 0.78 - 0.90 (m, 1 H), 1.28 - 1.38 (m, 1 H), 1.40 - 1.51 (m, 1 H), 1.81 - 1.93 (m, 1 H), 7.05 (d, 1 H), 7.42 (t,1 H), 7.48 (m, 1 H), 7.67 - 7.76 (m, 1 H), 8.08 (dd, 1 H), 8.31 (s, 1 H), 8.49 (s, 1 H), 8.54 (s, 1 H), 8.82 (s, 1 H), 10.47 (s, 1 H).

Example 574: (1,2-trans)-2-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenyl)cyclopropanecarboxylic acid

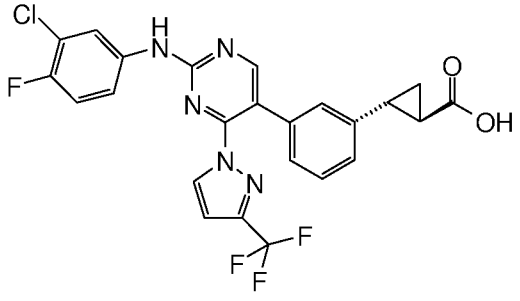


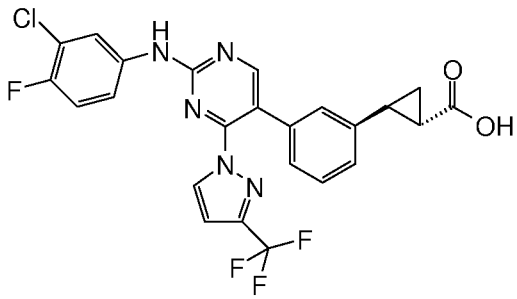
The title compound was prepared using the general method described above for **Example 572** using **Intermediate 183** as a starting material.

MS: ES+ 518 for C24H16ClF4N5O2.

1H NMR (400 MHz, DMSO-D6) δ ppm 1.17 - 1.27 (m, 1 H), 1.33 - 1.41 (m, 1 H), 1.68 - 1.76 (m, 1 H), 2.28 - 2.37 (m, 1 H), 6.86 (s, 1 H), 6.94 -7.00 (m, 2 H), 7.16 (d, 1 H), 7.24 (t, 1 H), 7.39 (t, 1 H), 7.66 - 7.73 (m, 1 H), 8.12 (dd, 1 H), 8.24 (s, 1 H), 8.79 (s, 1 H), 10.38 (s, 1 H), 12.25 (s, 1H).

Examples 575 and 576: (1R,2R)-2-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenyl)cyclopropanecarboxylic acid and (1S,2R)-2-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenyl)cyclopropanecarboxylic acid

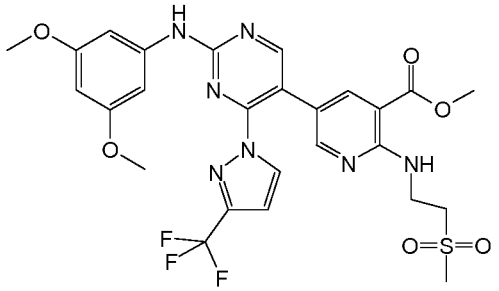




Racemic (1,2-trans)-tert-butyl 2-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenyl)cyclopropanecarboxylate **Intermediate 183** (170 mg)

was subjected to preparative chiral supercritical fluid chromatography using an instrument manufactured by Berger. Column: Chiralpak AD-H, dimensions: 250 x 21mm, 5µ; modifier: 25% isopropanol with 0.4% dimethylethylamine; flow rate: 60 ml/min; oven temperature: 40 ºC, outlet pressure: 100 bar. Samples of the separate ester enantiomers were thus obtained in >98% e.e. (60 mg each). These samples were separately deprotected under the conditions described for the racemate Example **574** to give the enantiopure title compounds. The absolute stereochemistry of the samples was unassigned, **Example 575** displays a (+) rotation and **Example 576** displays a (-) rotation. Mass spectral and 1H NMR data for both enantiomers are identical to that of the racemic sample.

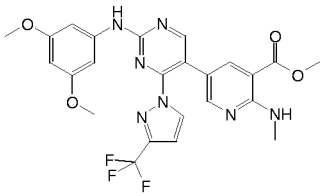
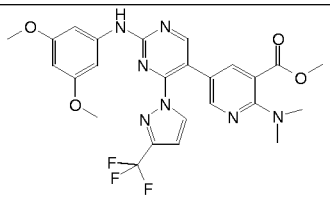
Example 577: methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(methylsulfonyl)ethylamino)nicotinate

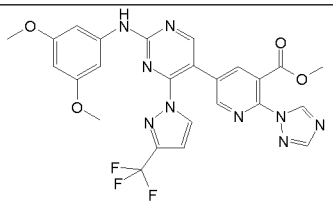
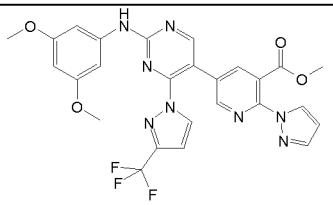
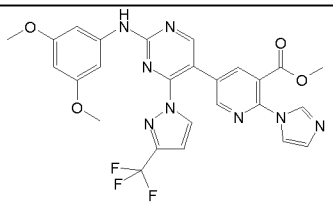


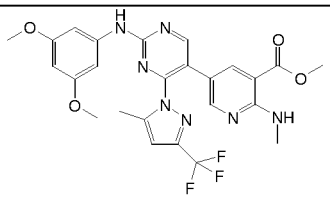
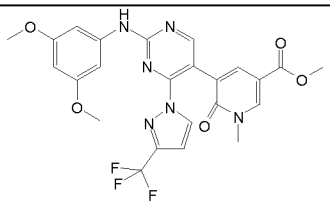
Methyl 5-bromo-2-(2-(methylsulfonyl)ethylamino)nicotinate **Intermediate 188** (200 mg, 0.59 mmol), PdCl2(dppf)-CH_2Cl_2 adduct (72.7 mg, 0.09 mmol), bis(pinacolato)diboron (181 mg, 0.71 mmol) and potassium acetate (175 mg, 1.78 mmol) were combined in dioxane (4 mL). Argon was bubbled through the mixture for 10 minutes and then it was warmed at 90 °C for 18 hours. The dark suspension was filtered through a celite pad and the solids were rinsed thoroughly with dichloromethane. The filtrate was concentrated to give the crude boronate ester intermediate: methyl 2-(2-(methylsulfonyl)ethylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (420 mg). This material was combined with 5-bromo-N-(3,5-dimethoxyphenyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine **Intermediate 215** (133 mg, 0.30 mmol), Tris(dibenzylideneacetone)dipalladium(0) (27.4 mg, 0.03 mmol) , Sodium carbonate (95 mg, 0.90 mmol) and 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (42.8 mg, 0.09 mmol) then suspended in acetonitrile (3 mL) and water (0.75 mL). The mixture was degassed with argon stream for 10 min then heated at 80 ºC for 1 hour. The mixture was diluted with

acetonitrile and adsorbed on 10 ml silica gel. Flash chromatography (0 to 50% acetonitrile in dichloromethane, 25g cartridge) gave the title compound as a yellow solid (133 mg).
MS: ES+ 662 for $C_{26}H_{26}F_3N_7O_6S$.
1H NMR (400 MHz, DMSO-d6) δ ppm 3.02 (s, 3 H), 3.41 (t, 2 H), 3.74 (s, 6 H), 3.77 (s, 3 H), 3.89 - 3.99 (m, 2 H), 6.20 (t, 1 H), 7.02 (d, 1 H),7.10 (d, 2 H), 7.80 (d, 1 H), 8.19 (t, 1 H), 8.22 (d, 1 H), 8.43 (d, 1 H), 8.77 (s, 1 H), 10.12 (s, 1 H)

The compounds in the table below were prepared using the general procedure described above for **Example 577** and the starting materials listed.

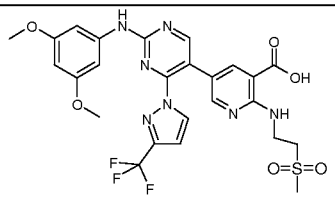
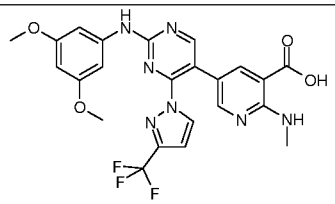
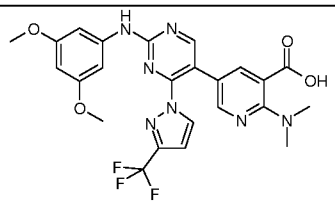
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 578	 methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(methylamino)nicotinate	MS: ES+ 530 for $C_{24}H_{22}F_3N_7O_4$ 1H NMR (400 MHz, DMSO-d6) δ ppm 2.97 (d, 3 H), 3.74 (s, 6 H), 3.76 (s, 3 H), 6.19 (t, 1 H), 7.01 (d, 1 H), 7.10 (d, 2 H), 7.74 (d, 1 H), 7.89 (q, 1H), 8.19 (d, 1 H), 8.40 (d, 1 H), 8.77 (s, 1 H), 10.11 (s, 1 H)	**Intermediate 184** methyl 5-bromo-2-(methylamino)nicotinate And **Intermediate 215** 5-bromo-N-(3,5-dimethoxyphenyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine
Example 579	 methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(dimethylamino)nicotinate	MS: ES+ 544 for $C_{25}H_{24}F_3N_7O_4$ H NMR (400 MHz, DMSO-d6) δppm 2.95 (s, 6 H), 3.74 (s, 6 H), 3.76 (s, 3 H), 6.19 (s, 1 H), 7.01 (d, 1 H), 7.10 (d, 2 H), 7.54 (d, 1 H), 8.09 (d, 1H), 8.41 (d, 1 H), 8.77 (s, 1 H), 10.11 (s, 1 H)	**Intermediate 185** methyl 5-bromo-2-(dimethylamino)nicotinate And **Intermediate 215** 5-bromo-N-(3,5-dimethoxyphenyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine

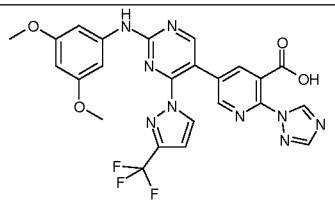
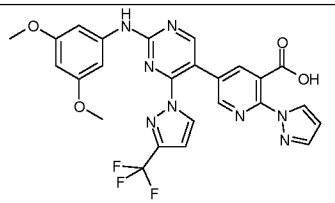
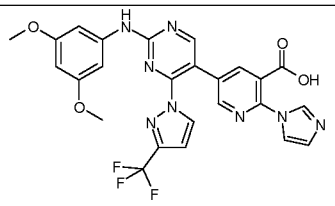
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 580	 methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(1H-1,2,4-triazol-1-yl)nicotinate	MS: ES+ 568 for $C_{25}H_{20}F_3N_9O_4$ 1H NMR (400 MHz, DMSO-d6) δ ppm 3.73 (s, 3 H), 3.76 (s, 6 H), 6.24 (t, 1 H), 7.08 (d, 1 H), 7.10 (d, 2 H), 8.10 (d, 1 H), 8.29 (s, 1 H), 8.57 (d, 1H), 8.58 (d, 1 H), 8.85 (s, 1 H), 9.32 (s, 1 H), 10.27 (s, 1 H)	**Intermediate 186** methyl 5-bromo-2-(1H-1,2,4-triazol-1-yl)nicotinate And **Intermediate 215** 5-bromo-N-(3,5-dimethoxyphenyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine
Example 581	 methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(1H-pyrazol-1-yl)nicotinate	MS: ES+ 567 for $C_{26}H_{21}F_3N_8O_4$ 1H NMR (400 MHz, DMSO-d6) δ ppm 3.71 (s, 3 H), 3.75 (s, 6 H), 6.17 - 6.26 (m, 1 H), 6.59 (s, 1 H), 7.06 (d, 1 H), 7.10 (d, 2 H), 7.80 (s, 1 H),7.92 (d, 1 H), 8.45 (d, 1 H), 8.53 (d, 2 H), 8.83 (s, 1 H), 10.23 (s, 1 H)	**Intermediate 187** methyl 5-bromo-2-(1H-pyrazol-1-yl)nicotinate And **Intermediate 215** 5-bromo-N-(3,5-dimethoxyphenyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine
Example 582	 methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(1H-imidazol-1-yl)nicotinate	MS: ES+ 567 for $C_{26}H_{21}F_3N_8O_4$ 1H NMR (400 MHz, DMSO-d6) δ ppm 3.75 (s, 9 H), 6.23 (t, 1 H), 7.03 - 7.14 (m, 4 H), 7.50 (s, 1 H), 8.04 (s, 1 H), 8.18 (d, 1 H), 8.56 (d, 1 H),8.59 (d, 1 H), 8.84 (s, 1 H), 10.25 (s, 1 H)	**Intermediate 189** methyl 5-bromo-2-(1H-imidazol-1-yl)nicotinate And **Intermediate 215** 5-bromo-N-(3,5-dimethoxyphenyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine

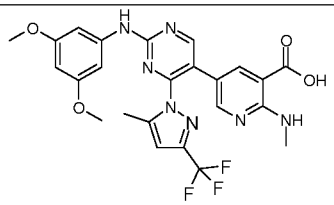
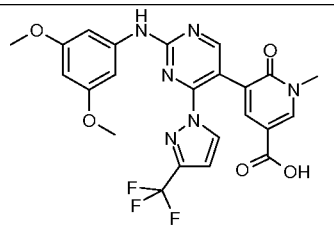
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 583	 methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(methylamino)nicotinate	MS: ES+ 544 for $C_{25}H_{24}F_3N_7O_4$ 1H NMR (400 MHz, DMSO-d6) δ ppm 2.15 (s, 3 H), 2.95 (d, 3 H), 3.72 (s, 6 H), 3.74 (s, 3 H), 6.19 (t, 1 H), 6.73 (s, 1 H), 7.05 (d, 2 H), 7.46 (d, 1H), 7.83 - 7.95 (m, 1 H), 8.22 (d, 1 H), 8.93 (s, 1 H), 10.15 (s, 1 H)	**Intermediate 184** methyl 5-bromo-2-(methylamino)nicotinate And **Intermediate 216** 5-bromo-N-(3,5-dimethoxyphenyl)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine
Example 584	 methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate	MS: ES+ 531 for C24H21F3N6O5 1H NMR (400 MHz, DMSO-d6) δ ppm 3.40 (s, 3 H), 3.75 (s, 6 H), 3.82 (s, 3 H), 6.21 (t, 1 H), 7.00 (d, 1 H), 7.08 (d, 2 H), 7.90 (d, 1 H), 8.59 (d, 1H), 8.61 (d, 1 H), 8.64 (s, 1 H), 10.09 (s, 1 H)	**Intermediate 190** methyl 5-bromo-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate And **Intermediate 215** 5-bromo-N-(3,5-dimethoxyphenyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine

The compounds in the below table were prepared using the general method described above for Example **214** using 1N sodium hydroxide (2 equivalents), dioxane : THF (1:1) as solvent and the starting material indicated.

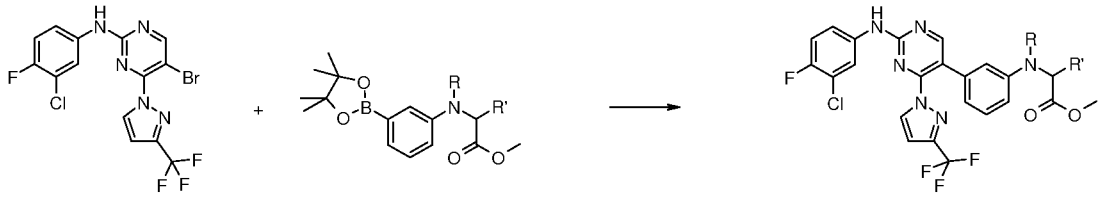
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Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 585	 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(methylsulfonyl)ethylamino)nicotinic acid	MS: ES+ 608 for $C_{25}H_{24}F_3N_7O_6S$ 1H NMR (400 MHz, DMSO-d6) δ ppm 3.01 (s, 3 H), 3.41 (t, 2 H), 3.73 (s, 6 H), 3.92 (dd, 2 H), 6.19 (t, 1 H), 7.01 (d, 1 H), 7.10 (d, 2 H), 7.78 (d,1 H), 8.19 (d, 1 H), 8.29 - 8.39 (m, 1 H), 8.40 - 8.46 (m, 1 H), 8.76 (s, 1 H), 10.11 (s, 1 H), 13.09 (bs, 1H).	**Example 577** methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(methylsulfonyl)ethylamino)nicotinate
Example 586	 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(methylamino)nicotinic acid	MS: ES+ 516 for $C_{23}H_{20}F_3N_7O_4$ H NMR (400 MHz, DMSO-d6) δ ppm 2.99 (s, 3 H), 3.73 (s, 6 H), 6.19 (t, 1 H), 7.01 (d, 1 H), 7.10 (d, 2 H), 7.79 (br. s., 1 H), 8.17 (d, 1 H), 8.41 (s, 1 H), 8.75 (s, 1 H), 10.11 (s, 1 H), 13.07 (br. s., 1 H)	**Example 578** methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(methylamino)nicotinate
Example 587	 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(dimethylamino)nicotinic acid	MS: ES+ 531 for $C_{24}H_{22}F_3N_7O_4$ 1H NMR (400 MHz, DMSO-d6) δ ppm 2.96 (s, 6 H), 3.74 (s, 6 H), 6.19 (t, 1 H), 6.95 - 7.05 (m, 1 H), 7.06 - 7.14 (m, 2 H), 7.54 (d, 1 H), 8.02 (d, 1H), 8.37 (s, 1 H), 8.74 - 8.79 (m, 1 H), 10.10 (s, 1 H), 12.84 (br. s., 1 H)	**Example 579** methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(dimethylamino)nicotinate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 588	 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(1H-1,2,4-triazol-1-yl)nicotinic acid	MS: ES+ 554 for $C_{24}H_{18}F_3N_9O_4$ 1H NMR (400 MHz, DMSO-d6) δ ppm 2.96 (s, 6 H), 3.74 (s, 6 H), 6.19 (t, 1 H), 6.95 - 7.05 (m, 1 H), 7.06 - 7.14 (m, 2 H), 7.54 (d, 1 H), 8.02 (d, 1H), 8.37 (s, 1 H), 8.74 - 8.79 (m, 1 H), 10.10 (s, 1 H), 12.84 (br. s., 1 H)	**Example 580** methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(1H-1,2,4-triazol-1-yl)nicotinate
Example 589	 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(1H-pyrazol-1-yl)nicotinic acid	MS: ES+ 553 for C25H19F3N8O4 1H NMR (400 MHz, DMSO-d6) δ ppm 3.75 (s, 6 H), 6.23 (t, 1 H), 6.57 (t, 1 H), 7.05 (d, 1 H), 7.10 (d, 2 H), 7.75 - 7.80 (m, 1 H), 7.89 (d, 1 H),8.40 (d, 1 H), 8.47 (d, 1 H), 8.50 - 8.56 (m, 1 H), 8.84 (s, 1 H), 10.23 (s, 1 H), 13.12 (s, 1 H)	**Example 581** methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(1H-pyrazol-1-yl)nicotinate
Example 590	 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(1H-imidazol-1-yl)nicotinic acid	MS: ES+ 553 for C25H19F3N8O4 1H NMR (400 MHz, DMSO-d6) δ ppm 3.76 (s, 6 H), 6.24 (t, 1 H), 7.07 (d, 1 H), 7.10 (d, 2 H), 7.38 (s, 1 H), 7.73 (s, 1 H), 8.23 (d, 1 H), 8.56 (d, 1H), 8.62 (d, 2 H), 8.85 (s, 1 H), 10.26 (s, 1 H), 13.65 (br. s., 1 H)	**Example 582** methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(1H-imidazol-1-yl)nicotinate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 591	 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(methylamino)nicotinic acid	MS: ES+ 530 for $C_{24}H_{22}F_3N_7O_4$ 1H NMR (400 MHz, DMSO-d6) δ ppm 2.21 (s, 3 H), 2.95 (s, 3 H), 3.72 (s, 6 H), 6.19 (s, 1 H), 6.72 (s, 1 H), 7.05 (d, 2 H), 7.55 (d, 1 H), 8.06 - 8.18 (m, 2 H), 8.90 (s, 1 H), 10.13 (s, 1 H), 13.05 (br. s., 1 H)	**Example 583** methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(methylamino)nicotinate
Example 592	 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid	MS: ES+ 517 for $C_{23}H_{19}F_3N_6O_5$ 1H NMR (400 MHz, DMSO-d6) δ ppm 3.39 (s, 3 H), 3.75 (s, 6 H), 6.21 (s, 1 H), 7.00 (d, 1 H), 7.08 (d, 2 H), 7.87 (d, 1 H), 8.53 (d, 1 H), 8.56 - 8.60 (m, 1 H), 8.64 (s, 1 H), 10.08 (s, 1 H), 12.86 (br. s., 1 H)	**Example 584** methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate

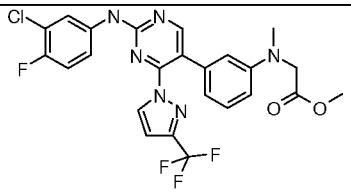
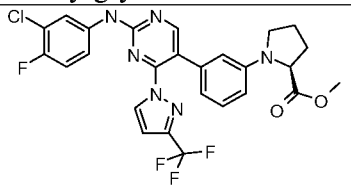
General method for biaryl synthesis



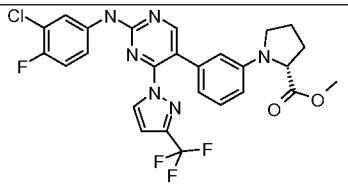
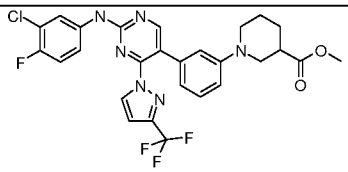
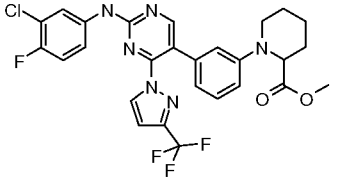
A suspension of 5-bromo-N-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1H-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 115**, 1 eq), boronate derivative (1.1 eq), [1,1′-bis (diphenylphosphino)ferrocene]dichloropalladium(II) (20 mol%) and sodium carbonate (1 eq) in acetonitrile/water (4 : 1) was degassed and heated to 90 °C for 15-20 min under inert atmosphere. The solvent was removed *in vacuo* and the crude mixture taken in $CHCl_3$ was washed with water,

brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using chloroform: methanol (9:1) as eluent to give the product.

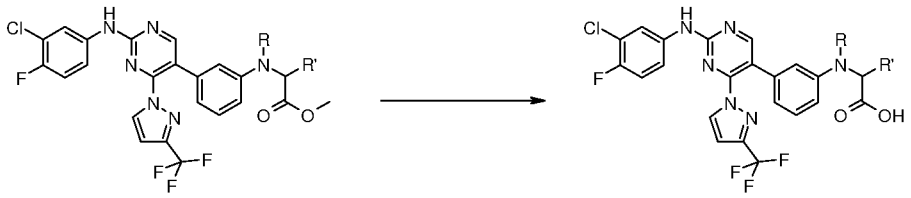
The compounds in the below table were prepared using this general procedure and the starting material specified.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 593	 methyl *N*-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)-*N*-methylglycinate	The compound was taken to the next step on the basis of LCMS. MS(ES): 535 (M+1) for $C_{24}H_{19}ClF_4N_6O_2$. (91 % pure by LCMS)	**Intermediate 201** methyl *N*-methyl-*N*-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]glycinate
Example 594	 methyl 1-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)-L-prolinate	MS(ES): 561 (M+1) for $C_{26}H_{21}ClF_4N_6O_2$. 400 MHz, DMSO-d_6: δ 2.89 (s, 3H), 3.60 (s, 3H), 4.16 (s, 2H), 6.45 (t, *J* = 6.40 Hz, 2H), 6.63 (dd, *J* = 1.60, 8.20 Hz, 1H), 6.95 (d, *J* = 10.40 Hz, 1H), 7.15 (t, *J* = 8.00 Hz, 1H), 7.40 (t, *J* = 9.20 Hz, 1H), 7.67-7.71 (m, 1H), 8.05 (s, 1H), 8.18 (dd, *J* = 2.40, 6.80 Hz, 1H), 8.79 (s, 1H), 10.41 (s, 1H).	**Intermediate 202** methyl 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-L-prolinate

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Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 595	 methyl 1-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)-D-prolinate	MS(ES): 561 (M+1) for $C_{26}H_{21}ClF_4N_6O_2$. The compound was taken to the next step on the basis of LCMS.	**Intermediate 203** methyl 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-D-prolinate
Example 596	 methyl 1-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)piperidine-3-carboxylate	MS(ES): 575 (M+1) for $C_{27}H_{23}ClF_4N_6O_2$. 300 MHz, DMSO-d_6: δ 1.47-1.65 (m, 4H), 1.85-1.90 (m, 2H), 2.72 (t, J = 7.53 Hz, 1H), 2.86-2.91 (m, 1H), 3.53-3.55 (m, 1H), 3.61 (s, 3H), 6.58 (s, 1H), 6.33 (d, J = 7.80 Hz, 1H), 6.92-6.94 (m, 2H), 7.19 (t, J = 6.00 Hz, 1H), 7.40 (t, J = 6.84 Hz, 2H), 8.15 (s, 2H), 8.78 (s, 1H), 10.39 (s, 1H).	**Intermediate 204** methyl 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-3-carboxylate
Example 597	 methyl 1-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)piperidine-2-carboxylate	Taken to the next step based on LCMS. MS(ES): 575 (M+1) for $C_{27}H_{23}ClF_4N_6O_2$. (96 % pure by LCMS)	**Intermediate 205** methyl 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-2-carboxylate

General method for the hydrolysis of amino ester derivatives



Method I:

To the amino ester derivative (1 eq) taken in a mixture of tetrahydrofuran and water (3:1), was added Barium hydroxide monohydrate (2 eq) and allowed to stir at room temperature for 12 h. After completion of the reaction, the mixture was then carefully acidified with 1 N HCl and the precipitate formed was filtered, washed with water and dried to yield the product.

Method II:

To the amino ester derivative (1 eq) taken in a mixture of tetrahydrofuran and water (3:1), was added Sodium hydroxide (2 eq) and allowed to stir at room temperature for 3 h. After completion of the reaction, the mixture was then carefully acidified with 1 N HCl and the precipitate formed was filtered, washed with water and dried to yield the product.

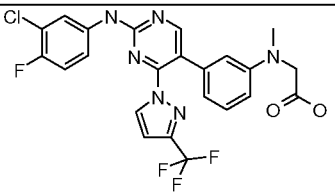
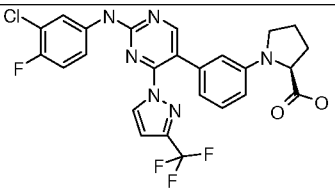
Method III:

To the amino ester derivative (1 eq) taken in a mixture of acetonitrile and water (3:1), was added 1 N aq. Sodium hydroxide (2.5 eq) and the mixture was heated at 85 °C for 1 h. After completion of the reaction, the mixture was then carefully acidified with 1.5 N HCl and the precipitate formed was filtered, washed with water and dried. It was further dissolved in minimum amount of ethyl acetate, then hexane was added dropwise with constant stirring. The precipitate formed was filtered, washed with water and dried to yield to yield the product.

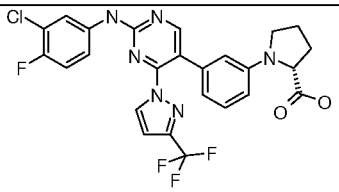
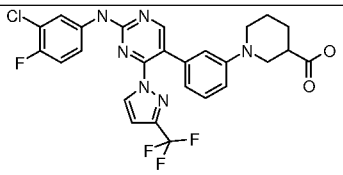
Method IV:

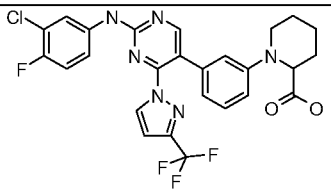
To the amino ester derivative (1 eq) taken in a mixture of dioxane and water (3:1), was added Sodium hydroxide (2 eq) and the reaction mixture allowed to stir at room temperature for 3 h. After completion of the reaction, the mixture was then carefully acidified with 1 N HCl, extracted with ethyl acetate. The organic layer was concentrated and the solid obtained was dissolved in minimum amount of CH_2Cl_2. Hexane was added dropwise with constant stirring and the precipitate formed was filtered, washed with water and dried to yield the product.

The compounds in the below table were prepared using this general procedure and the starting material specified.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 598[c]	 *N*-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)-*N*-methylglycine	MS(ES): 521 (M+1) for $C_{23}H_{17}ClF_4N_6O_2$. 400 MHz, DMSO-d_6: δ 2.88 (s, 3H), 4.03 (s, 2H), 6.42 (m, 2H), 6.61 (d, *J* = 8.40 Hz, 1H), 6.93 (d, *J* = 2.80 Hz, 1H), 7.13 (t, *J* = 7.60 Hz, 1H), 7.40 (t, *J* = 9.20 Hz, 1H), 7.67-7.70 (m, 1H), 8.05 (s, 1H), 8.17-8.20 (m, 1H), 8.78 (s, 1H), 10.42 (s, 1H), 12.46 (br s, 1H).	**Example 593** methyl *N*-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)-*N*-methylglycinate
Example 599[d]	 1-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)-L-proline	MS(ES): 547 (M+1) for $C_{25}H_{19}ClF_4N_6O_2$. 400 MHz, DMSO-d_6: δ 1.98-2.06 (m, 3H), 2.19-2.24 (m, 1H), 3.16-3.22 (m, 1H), 3.33 (m, 1H, merges with water peak), 4.09 (d, *J* = 9.12 Hz, 1H), 6.31 (s, 1H), 6.35 (d, *J* = 7.40 Hz, 1H), 6.42 (d, *J* = 8.24 Hz, 1H), 6.93 (d, *J* = 2.40 Hz, 1H), 7.12 (t, *J* = 7.76 Hz, 1H), 7.39 (t, *J* = 9.04 Hz, 1H), 7.66-7.70 (m, 1H), 8.06 (s, 1H), 8.17 (dd, *J* = 2.48, 6.72 Hz, 1H), 8.77 (s, 1H), 10.41 (s, 1H), 12.57 (br s, 1H).	**Example 594** methyl 1-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)-L-prolinate

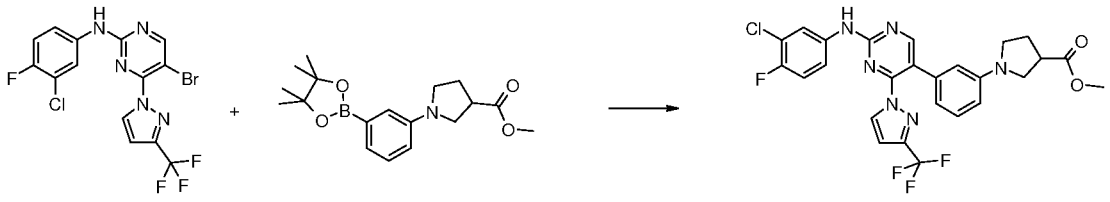
5

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 600[e)]	 1-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)-D-proline	MS(ES): 547 (M+1) for $C_{25}H_{19}ClF_4N_6O_2$. 400 MHz, DMSO-d_6: δ 1.98-2.06 (m, 3H), 2.21 (m, 1H), 3.20 (m, 1H), 3.34 (m, 1H, merges with water peak), 4.09 (d, J = 8.80 Hz, 1H), 6.31 (s, 1H), 6.36 (d, J = 7.60 Hz, 1H), 6.43 (d, J = 8.00 Hz, 1H), 6.94 (d, J = 2.00 Hz, 1H), 7.12 (t, J = 8.00 Hz, 1H), 7.40 (t, J = 8.80 Hz, 1H), 7.68-7.70 (m, 1H), 8.06 (s, 1H), 8.17-8.18 (m, 1H), 8.77 (s, 1H), 10.41 (s, 1H), 12.56 (br s, 1H).	**Example 595** methyl 1-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)-D-prolinate
Example 601[f)]	 1-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)piperidine-3-carboxylic acid	MS(ES): 561 (M+1) for $C_{26}H_{21}ClF_4N_6O_2$. 400 MHz, DMSO-d_6: δ 1.46-1.55 (m, 2H), 1.64-1.66 (m, 1H), 1.86-1.92 (m, 1H), 2.44-2.50 (m, 1H), 2.67 (m, 1H), 2.85 (dd, J = 9.76, 12.30 Hz, 1H), 3.34 (m, 1H, merges with water peak), 3.50-3.57 (m, 1H), 6.58-6.60 (m, 2H), 6.89-6.93 (m, 2H), 7.19 (t, J = 8.00 Hz, 1H), 7.39 (t, J = 9.12 Hz, 1H), 7.66-7.70 (m, 1H), 8.14-8.16 (m, 2H), 8.79 (s, 1H), 10.39 (s, 1H), 12.30 (br s, 1H).	**Example 596** methyl 1-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)piperidine-3-carboxylate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 602[f]	 1-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)piperidine-2-carboxylic acid	MS(ES): 561 (M+1) for $C_{26}H_{21}ClF_4N_6O_2$. 400 MHz, DMSO-d_6: δ 1.24-1.28 (m, 1H), 1.32-1.52 (m, 1H), 1.61-1.73 (m, 3H), 2.08 (d, *J* = 13.16 Hz, 1H), 3.06 (t, *J* = 2.88 Hz, 1H), 3.38 (m, 1H, merges with water peak), 4.49 (d, *J* = 2.88 Hz, 1H), 6.50 (d, *J* = 7.48 Hz, 1H), 6.59 (s, 1H), 6.83 (dd, *J* = 2.08, 8.46 Hz, 1H), 6.91 (d, *J* = 2.60 Hz, 1H), 7.14 (t, *J* = 8.04 Hz, 1H), 7.39 (t, *J* = 9.08 Hz, 1H), 7.66-7.70 (m, 1H), 8.04 (s, 1H), 8.16 (dd, *J* = 2.63, 6.67 Hz, 1H), 8.77 (s, 1H), 10.40 (s, 1H), 12.29 (br s, 1H).	**Example 597** methyl 1-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)piperidine-2-carboxylate

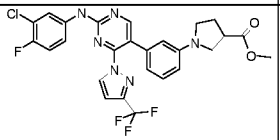
c) Method I; d) Method II; e) Method III; f) Method IV

Example 603: methyl 1-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)pyrrolidine-3-carboxylate



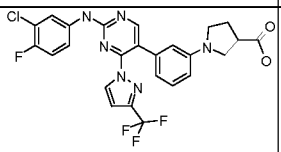
A suspension of 5-bromo-N-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1H-pyrazol-1-yl]pyrimidin-2-amine(**Intermediate 115**, 0.34 mmol, 0.15 g), the mixture of methyl 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidine-3-carboxylate and {3-[3-(methoxycarbonyl)pyrrolidin-1-yl]phenyl}boronic acid (**Intermediate 208**, 0.34 mmol based on the boronic ester, 113 mg), [1,1′-bis (diphenylphosphino)ferrocene]dichloropalladium(II) (0.068 mmol, 50 mg) and sodium carbonate (0.44 mmol, 47 mg) in acetonitrile/water (20 mL : 5 mL) was degassed and heated to 90 °C for 15-20 min under inert atmosphere. The solvent was

removed under vacuum and the crude mixture was taken in $CHCl_3$ (50 mL), washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using 12 % ethyl acetate/hexanes as eluent to yield 65 mg of the title compound.

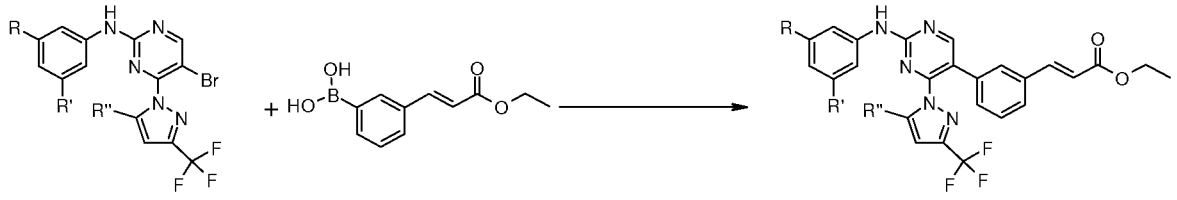
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 603	 methyl 1-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)pyrrolidine-3-carboxylate	MS(ES): 561 (M+1) for $C_{26}H_{21}ClF_4N_6O_2$. 300 MHz, DMSO-d_6: δ 1.13-1.24 (m, 2H), 2.12-2.19 (m, 2H), 3.17-3.28 (m, 2H), 3.40 (s, 1H), 3.63 (s, 3H), 6.30 (s, 1H), 6.36 (d, *J* = 7.53 Hz, 1H), 6.51 (d, *J* = 8.43 Hz, 1H), 6.92 (d, *J* = 2.52 Hz, 1H), 7.12 (t, *J* = 15.81 Hz, 1H), 7.38 (t, *J* = 18.18 Hz, 1H), 7.66-7.71 (m, 1H), 8.07 (s, 1H), 8.16 (dd, *J* = 2.61, 6.68 Hz, 1H), 8.80 (s, 1H), 10.39 (s, 1H).	**Intermediate 208** methyl 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidine-3-carboxylate and {3-[3-(methoxycarbonyl)pyrrolidin-1-yl]phenyl}boronic acid

Example 604: 1-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)pyrrolidine-3-carboxylic acid

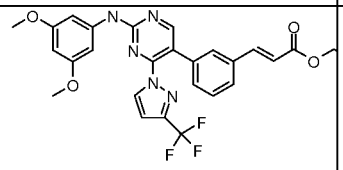
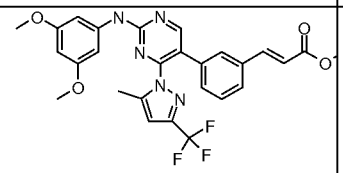
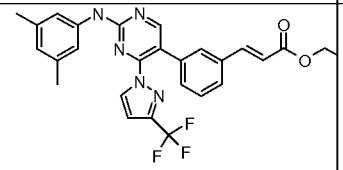
To a suspension of **Example 603** (0.15 mmol, 85 mg) taken in acetonitrile (6 mL) and water (3 mL), was added NaOH (0.42 mmol, 18 mg) and the mixture heated to 85 °C for 1 h. The reaction mixture was concentrated *in vacuo*, acidified with 1.5 N HCl and extracted with ethyl acetate (20 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude mass was purified by silica gel column chromatography (60-120 mesh) using chloroform and methanol (1%) as eluent to give the title compound (31 mg).

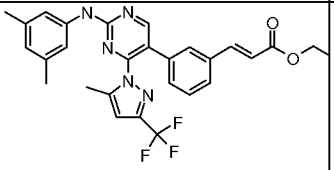
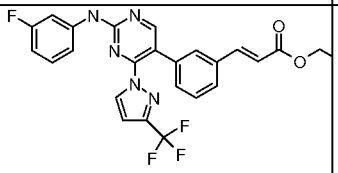
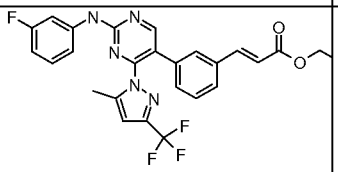
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 604	 1-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)pyrrolidine-3-carboxylic acid	MS(ES): 547 (M+1) for $C_{25}H_{19}ClF_4N_6O_2$. 400 MHz, DMSO-d_6: δ 2.11-2.18 (m, 2H), 3.12-3.24 (m, 4H), 3.38 (s, 1H, Merges with water peak), 6.32-6.36 (m, 2H), 6.51 (d, *J* = 8.00 Hz, 1H), 6.92 (d, *J* = 2.40 Hz, 1H), 7.12 (t, *J* = 7.80 Hz, 1H), 7.39 (t, *J* = 9.08 Hz, 1H), 7.66-7.70 (m, 1H), 8.07 (s, 1H), 8.18 (dd, *J* = 2.56, 6.70 Hz, 1H), 8.81 (s, 1H), 10.40 (s, 1H), 12.40 (br s, 1H).	**Example 603** methyl 1-(3-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)pyrrolidine-3-carboxylate

General procedure for ethyl (2*E*)-3-(3-{2-[arylamino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate and ethyl (2*E*)-3-(3-{2-[arylamino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate



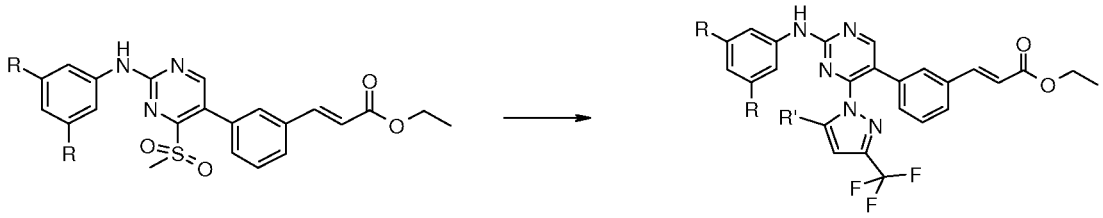
A suspension of 5-bromo-*N*-(aryl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine or 5-bromo-*N*-(aryl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (1 eq), {3-[(1*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]phenyl}boronic acid (1.1 – 1.2 eq), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (20 mol%) and sodium carbonate (1 eq) in acetonitrile/water (4 : 1) was degassed and heated to 90 °C for 15-30 min under inert atmosphere. The solvent was removed *in vacuo* and the crude mixture taken in $CHCl_3$ was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using chloroform: methanol (9:1) as eluent to give the product.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 605	 ethyl (2*E*)-3-(3-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 540 (M+1) for $C_{27}H_{24}F_3N_5O_4$. 400 MHz, DMSO-d_6: δ 1.25 (t, *J* = 7.12 Hz, 3H), 3.73 (s, 6H), 4.18 (q, *J* = 7.12 Hz, 2H), 6.19-6.20 (m, 1H), 6.59 (d, *J* = 16.04 Hz, 1H), 6.98 (d, *J* = 6.04 Hz, 1H), 7.12-7.15 (m, 3H), 7.37 (t, *J* = 7.68 Hz, 1H), 7.58 (s, 1H), 7.60 (d, *J* = 16.08 Hz, 1H), 7.66 (d, *J* = 7.76 Hz, 1H), 8.31 (br s, 1H), 8.80 (s, 1H), 10.18 (s, 1H).	**Intermediate 215** 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 606	 ethyl (2*E*)-3-(3-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 554 (M+1) for $C_{28}H_{26}F_3N_5O_4$. 400 MHz, DMSO-d_6: δ 1.26 (t, *J* = 7.20 Hz, 3H), 2.17 (s, 3H), 3.72 (s, 6H), 4.19 (q, *J* = 7.20 Hz, 2H), 6.20-6.21 (m, 1H), 6.55 (d, *J* = 16.00 Hz, 1H), 6.71 (s, 1H), 7.03-7.07 (m, 3H), 7.36 (t, *J* = 7.60 Hz, 1H), 7.41 (s, 1H), 7.57 (d, *J* = 16.00 Hz, 1H), 7.64 (d, *J* = 8.00 Hz, 1H), 8.96 (s, 1H), 10.23 (s, 1H).	**Intermediate 216** 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 607	 ethyl (2*E*)-3-(3-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 508 (M+1) for $C_{27}H_{24}F_3N_5O_2$. 300 MHz, DMSO-d_6: δ 1.24 (t, *J* = 7.08 Hz, 3H), 2.26 (s, 6H), 4.17 (q, *J* = 7.14 Hz, 2H), 6.59 (d, *J* = 16.02 Hz, 1H), 6.67 (s, 1H), 6.98 (d, *J* = 2.46 Hz, 1H), 7.12 (d, *J* = 7.32 Hz, 1H), 7.36 (t, *J* = 7.68 Hz, 1H), 7.43 (s, 2H), 7.60 (d, *J* = 16.65 Hz, 1H), 7.62-7.66 (m, 2H), 8.33 (br s, 1H), 8.77 (s, 1H), 10.08 (s, 1H).	**Intermediate 217** 5-bromo-*N*-(3,5-dimethylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 608	 ethyl (2*E*)-3-(3-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 522 (M+1) for $C_{28}H_{26}F_3N_5O_2$. 300 MHz, DMSO-d_6: δ 1.24 (t, *J* = 7.11 Hz, 3H), 2.22 (s, 3H), 2.24 (s, 6H), 4.17 (q, *J* = 7.11 Hz, 2H), 6.54 (d, *J* = 16.08 Hz, 1H), 6.68-6.70 (m, 2H), 6.99-7.01 (m, 1H), 7.34-7.39 (m, 4H), 7.55 (d, *J* = 16.08 Hz, 1H), 7.59-7.63 (m, 1H), 8.92 (s, 1H), 10.11 (br s, 1H).	**Intermediate 218** 5-bromo-*N*-(3,5-dimethylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 609	 ethyl (2*E*)-3-(3-{2-[(3-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 498 (M+1) for $C_{25}H_{19}F_4N_5O_2$. 400 MHz, $CDCl_3$: δ 1.34 (t, *J* = 7.12 Hz, 3H), 4.27 (q, *J* = 7.16 Hz, 2H), 6.41 (d, *J* = 16.00 Hz, 1H), 6.65 (d, *J* = 2.64 Hz, 1H), 6.80-6.85 (m, 1H), 7.18 (d, *J* = 7.80 Hz, 1H), 7.25 (dd, *J* = 1.12, 8.14 Hz, 1H), 7.33-7.35 (m, 2H), 7.40 (dd, *J* = 9.28, 16.22 Hz, 1H), 7.45 (br s, 1H), 7.54 (d, *J* = 7.80 Hz, 1H), 7.67 (d, *J* = 16.08 Hz, 1H), 7.71 (dt, *J* = 2.20, 6.74 Hz, 1H), 8.17 (br s, 1H), 8.57 (s, 1H).	**Intermediate 219** 5-bromo-*N*-(3-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 610	 ethyl (2*E*)-3-(3-{2-[(3-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 512 (M+1) for $C_{26}H_{21}F_4N_5O_2$. 400 MHz, DMSO-d_6: δ 1.25 (t, *J* = 7.08 Hz, 3H), 2.20 (s, 3H), 4.18 (q, *J* = 7.12 Hz, 2H), 6.55 (d, *J* = 16.04 Hz, 1H), 6.71 (s, 1H), 6.82-6.87 (m, 1H), 7.05 (d, *J* = 7.92 Hz, 1H), 7.34-7.40 (m, 3H), 7.51 (dd, *J* = 1.08, 8.20 Hz, 1H), 7.56 (d, *J* = 16.04 Hz, 1H), 7.64 (d, *J* = 7.92 Hz, 1H), 7.78 (d, *J* = 12.08 Hz, 1H), 8.99 (s, 1H), 10.49 (s, 1H).	**Intermediate 220** 5-bromo-*N*-(3-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

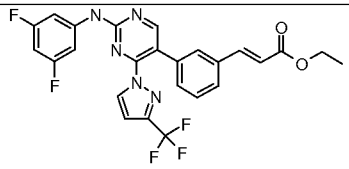
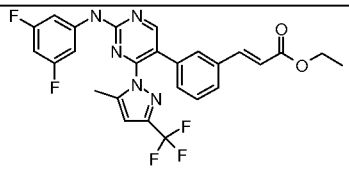
Example 611: ethyl (2*E*)-3-(3-{2-[(3,5-difluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate

Example 612: ethyl (2*E*)-3-(3-{2-[(3,5-difluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate



A suspension of either 3-(trifluoromethyl)-1*H*-pyrazole or 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole (1.2-1.5 eq), potassium *tert*-butoxide (1.5 eq) and ethyl (2*E*)-3-(3-{2-[(3,5-difluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}phenyl)prop-2-enoate (**Intermediate 223**, 1 eq) in DMSO (3 mL) was subjected to microwave irradiation at 130 °C for 1 h. After the reaction was cooled to RT, the mixture was diluted with EtOAc, washed successively with water and brine. The organic layer was dried over sodium sulphate, filtered, concentrated and further purified by silica gel column chromatography using ethyl acetate/hexanes to yield the product. The compounds in the below table were prepared using this procedure and the specified starting material.

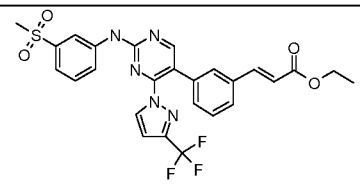
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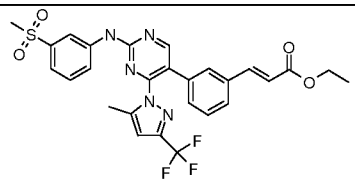
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 611	 ethyl (2*E*)-3-(3-{2-[(3,5-difluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 516 (M+1) for $C_{25}H_{18}F_5N_5O_2$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (t, *J* = 7.15 Hz, 3H), 4.18 (q, *J* = 7.03 Hz, 2H), 6.60 (d, *J* = 16.06 Hz, 1H), 6.85 (tt, *J* = 2.26, 9.29 Hz, 1H), 7.01 (d, *J* = 2.51 Hz, 1H), 7.15 (d, *J* = 7.78 Hz, 1H), 7.38 (t, *J* = 7.65 Hz, 1H), 7.54-7.64 (m, 4 H), 7.68 (d, *J* = 7.78 Hz, 1H), 8.36 (d, *J* = 1.51 Hz, 1H), 8.88 (s, 1H), 10.65 (s, 1H).	**Intermediate 223** ethyl (2*E*)-3-(3-{2-[(3,5-difluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}phenyl)prop-2-enoate
Example 612	 ethyl (2*E*)-3-(3-{2-[(3,5-difluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 530 (M+1) for $C_{26}H_{20}F_5N_5O_2$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (t, *J* = 7.15 Hz, 3H), 2.19 (s, 3H), 4.18 (q, *J* = 7.11 Hz, 2H), 6.55 (d, *J* = 16.06 Hz, 1H), 6.72 (s, 1H), 6.85 (tt, *J* = 2.29, 9.25 Hz, 1H), 7.05 (d, *J* = 8.03 Hz, 1H), 7.37 (t, *J* = 7.78 Hz, 1H), 7.41 (s, 1H), 7.50-7.60 (m, 3H), 7.65 (d, *J* = 7.78 Hz, 1H), 9.03 (s, 1H), 10.68 (s, 1H).	**Intermediate 223** ethyl (2*E*)-3-(3-{2-[(3,5-difluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}phenyl)prop-2-enoate

Example 613: ethyl (2*E*)-3-[3-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)phenyl]prop-2-enoate

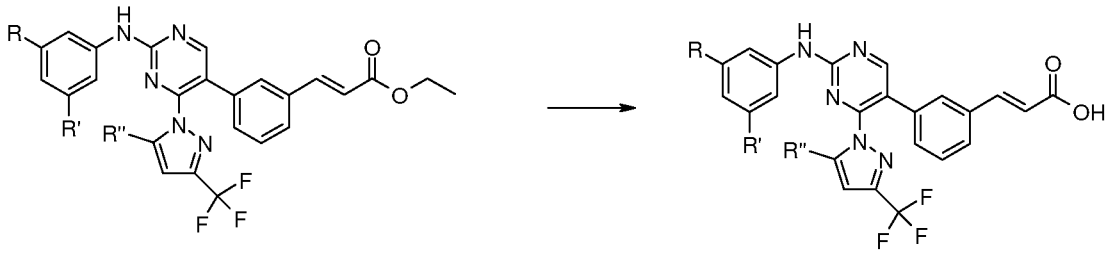
Example 614: ethyl (2*E*)-3-[3-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)phenyl]prop-2-enoate

NaH (60 % dispersion in mineral oil, 2 eq) was suspended in 1 mL of DMF and stirred for about 5 min at 0 °C. Then either 3-(trifluoromethyl)-1*H*-pyrazole or 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole (2 eq) in DMF (2 mL) was added dropwise at 0 °C for about 10 min and stirring continued for about 20 min under N_2. Then ethyl (2*E*)-3-{3-[4-(methylsulfonyl)-2-{[3-(methylsulfonyl)phenyl]amino}pyrimidin-5-yl]phenyl}prop-2-enoate (**Intermediate 224**, 1 eq) in DMF was added dropwise and the reaction was stirred overnight at room temperature. After completion of the reaction, water was added and the solid obtained was filtered off, dried and purified by silica gel column chromatography using ethyl acetate/hexanes as eluent to yield the product. The compounds in the below table were prepared using this procedure and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 613	 ethyl (2*E*)-3-[3-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)phenyl]prop-2-enoate	MS(ES): 558 (M+1) for $C_{26}H_{22}F_3N_5O_4S$. 400 MHz, DMSO-d_6: δ 1.25 (t, *J* = 6.96 Hz, 3H), 3.23 (s, 3H), 4.18 (q, *J* = 7.08 Hz, 2H), 6.61 (d, *J* = 16.08 Hz, 1H), 7.02 (d, *J* = 2.52 Hz, 1H), 7.17 (d, *J* = 7.84 Hz, 1H), 7.38 (t, *J* = 7.68 Hz, 1H), 7.56-7.69 (m, 5H), 7.98 (d, *J* = 8.36 Hz, 1H), 8.49 (br s, 1H), 8.61 (s, 1H), 8.85 (s, 1H), 10.62 (s, 1H).	**Intermediate 224** ethyl (2*E*)-3-{3-[4-(methylsulfonyl)-2-{[3-(methylsulfonyl)phenyl]amino}pyrimidin-5-yl]phenyl}prop-2-enoate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 614	 ethyl (2*E*)-3-[3-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)phenyl]prop-2-enoate	MS(ES): 572 (M+1) for $C_{27}H_{24}F_3N_5O_4S$. 400 MHz, DMSO-d_6: δ 1.25 (t, *J* = 7.04 Hz, 3H), 2.15 (s, 3H), 3.20 (s, 3H), 4.18 (q, *J* = 7.12 Hz, 2H), 6.57 (d, *J* = 16.04 Hz, 1H), 6.54 (s, 1H), 7.03 (d, *J* = 3.68 Hz, 1H), 7.36 (t, *J* = 7.72 Hz, 1H), 7.44 (s, 1H), 7.55-7.66 (m, 4H), 8.01 (d, *J* = 8.16 Hz, 1H), 8.47 (s, 1H), 9.01 (s, 1H), 10.67 (s, 1H).	**Intermediate 224** ethyl (2*E*)-3-{3-[4-(methylsulfonyl)-2-{[3-(methylsulfonyl)phenyl]amino}pyrimidin-5-yl]phenyl}prop-2-enoate

Hydrolysis of carboxylic esters to acids



Example 615: (2*E*)-3-(3-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid

To a suspension of **Example 605** (1 eq) taken in dioxane and water (1:1), was added Barium hydroxide monohydrate (2 eq) and the mixture was stirred at RT for 2 days. The reaction mixture was concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed was filtered off. The solid was taken in acetonitrile and stirred for 1 h. The solid was then filtered off, washed with dichloromethane and dried to give the title compound.

Example 616: (2*E*)-3-(3-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid

To a suspension of **Example 606** (1 eq) taken in dioxane and water (1:1), was added Barium hydroxide monohydrate (2 eq) and the mixture was warmed to 60 °C for 2 h. The

reaction mixture was concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed was filtered and dried to give the title compound.

Example 617: (2*E*)-3-(3-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid

To a suspension of **Example 607** (1 eq) taken in THF and water (2:1), was added Barium hydroxide monohydrate (3 eq) and the mixture was allowed to stir at RT for 2 days and refluxed at 60 °C for 2 days. The reaction mixture was concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed was filtered, washed with water and dried to give the title compound.

Example 618: (2*E*)-3-(3-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid

To a suspension of **Example 608** (1 eq) taken in THF and water (2:1), was added sodium hydroxide (2 eq) and the mixture was heated to 50 °C for 5 days. The reaction mixture was concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed was filtered, washed with water and dried to give the title compound.

Example 619: (2*E*)-3-(3-{2-[(3,5-difluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid

To a suspension of **Example 611** (1 eq) taken in THF and water (2:1), was added Barium hydroxide monohydrate (4 eq) and the mixture was allowed to stir overnight at RT. The reaction mixture was concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed was filtered off. The solid was taken in10 mL of dichloromethane and stirred for 1 h. The solid was then filtered off, washed with dichloromethane and dried to give the title compound.

Example 620: (2*E*)-3-(3-{2-[(3,5-difluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid

To a suspension of **Example 612** (1 eq) taken in dioxane and water (1:1), was added Barium hydroxide monohydrate (4 eq) and the mixture was heated overnight at 70 °C. The reaction mixture was concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed

was filtered off. The solid was taken in dichloromethane and stirred for 1 h. The solid was then filtered off, washed with dichloromethane and dried to give the title compound.

Example 621: (2*E*)-3-(3-{2-[(3-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid

To a suspension of **Example 609** (1 eq) taken in THF and water (1:1), was added lithium hydroxide monohydrate (4 eq) and the mixture was stirred overnight at RT. The reaction mixture was concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed was filtered off. The solid was taken in acetonitrile and stirred overnight. The solid was then filtered off, washed with acetonitrile and dried to give the title compound.

Example 622: (2*E*)-3-(3-{2-[(3-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid

To a suspension of **Example 610** (1 eq) taken in THF and water (1:1), was added lithium hydroxide monohydrate (4 eq) and the mixture was stirred at RT for 2 days. The reaction mixture was concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed was filtered off. The solid was taken in acetonitrile and stirred for 1 h. The solid was then filtered off, washed with acetonitrile and dried to give the title compound.

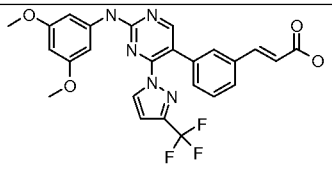
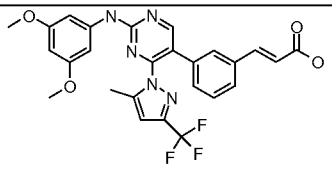
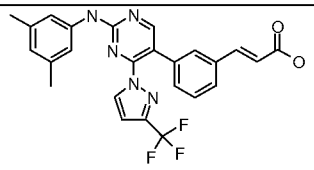
Example 623: (2*E*)-3-[3-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)phenyl]prop-2-enoic acid

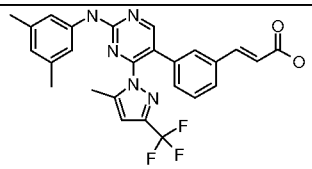
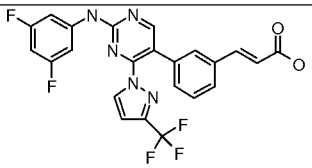
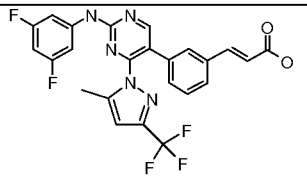
To a suspension of **Example 613** (1 eq) taken in dioxane and water (2:1), was added sodium hydroxide (2 eq) and the mixture was allowed to stir overnight at RT. The reaction mixture was concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed was filtered, washed with water and dried to give the title compound.

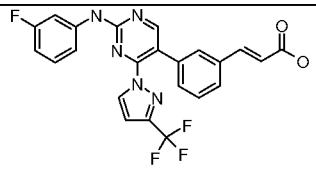
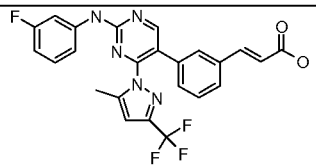
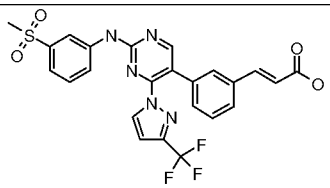
Example 624: (2*E*)-3-[3-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)phenyl]prop-2-enoic acid

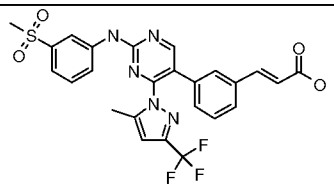
To a suspension of **Example 614** (1 eq) taken in dioxane and water (2:1), was added sodium hydroxide (2 eq) and the mixture was allowed to stir overnight at RT. The reaction mixture was

concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed was filtered, washed with water and dried to give the title compound.

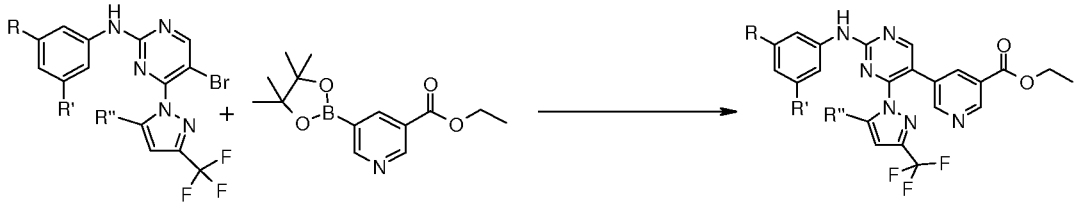
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 615	 (2*E*)-3-(3-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 512 (M+1) for $C_{25}H_{20}F_3N_5O_4$. 400 MHz, DMSO-d_6: δ 3.73 (s, 6H), 6.19 (t, *J* = 2.13 Hz, 1H), 6.48 (d, *J* = 16.06 Hz, 1H), 6.98 (d, *J* = 2.51 Hz, 1H), 7.10-7.17 (m, 3H), 7.37 (t, *J* = 7.78 Hz, 1H), 7.50-7.57 (m, 2H), 7.63 (d, *J* = 7.78 Hz, 1H), 8.31 (d, *J* = 1.76 Hz, 1H), 8.80 (s, 1H), 10.18 (s, 1H), 12.41 (br s, 1H).	**Example 605** ethyl (2*E*)-3-(3-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate
Example 616 PE-045-02	 (2*E*)-3-(3-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 526 (M+1) for $C_{26}H_{22}F_3N_5O_4$. 400 MHz, DMSO-d_6: δ 2.18 (s, 3H), 3.71 (s, 6 H), 6.20 (s, 1H), 6.43 (d, *J* = 16.06 Hz, 1H), 6.71 (s, 1H), 6.99-7.11 (m, 3H), 7.30-7.39 (m, 2H), 7.49 (d, *J* = 16.06 Hz, 1H), 7.60 (d, *J* = 7.78 Hz, 1H), 8.95 (s, 1H), 10.22 (s, 1H), 12.36-12.48 (m, 1H).	**Example 606** ethyl (2*E*)-3-(3-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate
Example 617	 (2*E*)-3-(3-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 480 (M+1) for $C_{25}H_{20}F_3N_5O_2$. 400 MHz, DMSO-d_6: δ 2.27 (s, 6H), 6.47 (d, *J* =15.87 Hz, 1H), 6.68 (s, 1H), 6.99 (br s, 1H), 7.12 (d, *J* =7.32 Hz, 1H), 7.36 (t, *J* =7.63 Hz, 1H), 7.41-7.55 (m, 4H), 7.61 (d, *J* =7.93 Hz, 1H), 8.33 (br s, 1H), 8.78 (s, 1H), 10.09 (s, 1H), 12.5 (br s, 1H).	**Example 607** ethyl (2*E*)-3-(3-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 618	 (2*E*)-3-(3-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 494 (M+1) for $C_{26}H_{22}F_3N_5O_2$. 400 MHz, DMSO-d_6: δ 2.24 (s, 3H), 2.25 (s, 6H), 6.45 (d, *J* = 15.96 Hz, 1H), 6.68 (s, 1H), 6.71 (s, 1H), 7.01 (d, *J* = 7.80 Hz, 1H), 7.32-7.35 (m, 2H), 7.39 (s, 2H), 7.42 (d, *J* = 16.00 Hz, 1H), 7.57 (d, *J* = 7.84 Hz, 1H), 8.92 (s, 1H), 10.11 (s, 1H).	**Example 608** ethyl (2*E*)-3-(3-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate
Example 619	 (2*E*)-3-(3-{2-[(3,5-difluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 488 (M+1) for $C_{23}H_{14}F_5N_5O_2$. 400 MHz, DMSO-d_6: δ 6.48 (d, *J* = 16.00 Hz, 1H), 6.85 (t, *J* = 9.20 Hz, 1H), 7.01 (d, *J* = 2.32 Hz, 1H), 7.15 (d, *J* = 7.76 Hz, 1H), 7.32 (t, *J* = 7.68 Hz, 1H), 7.52-7.66 (m, 5H), 8.35 (br s, 1H), 8.88 (s, 1H), 10.64 (s, 1H), 12.50 (br s, 1H).	**Example 611** ethyl (2*E*)-3-(3-{2-[(3,5-difluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate
Example 620	 (2*E*)-3-(3-{2-[(3,5-difluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 502 (M+1) for $C_{24}H_{16}F_5N_5O_2$. 400 MHz, DMSO-d_6: δ 2.21 (s, 3H), 6.45 (d, *J* = 16.04 Hz, 1H), 6.73 (s, 1H), 6.83-6.88 (m, 1H), 7.06 (d, *J* = 7.80 Hz, 1H), 7.35-7.39 (m, 2H), 7.48-7.56 (m, 3H), 7.62 (d, *J* = 7.84 Hz, 1H), 9.03 (s, 1H), 10.69 (s, 1H), 12.53 (br s, 1H).	**Example 612** ethyl (2*E*)-3-(3-{2-[(3,5-difluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate

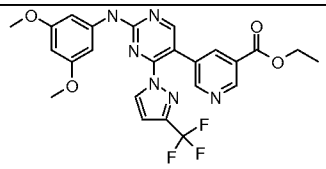
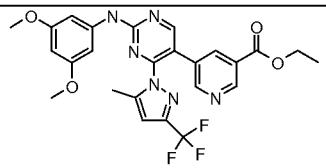
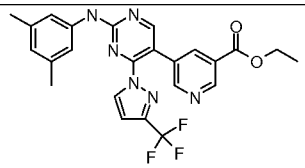
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 621	 (2*E*)-3-(3-{2-[(3-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 470 (M+1) for $C_{23}H_{15}F_4N_5O_2$. 400 MHz, DMSO-d_6: δ 6.47 (d, J = 16.04 Hz, 1H), 6.84 (td, J = 2.16, 11.84 Hz, 1H), 7.00 (d, J = 2.48 Hz, 1H), 7.14 (d, J = 7.68 Hz, 1H), 7.34-7.39 (m, 2H), 7.52-7.56 (m, 3H), 7.63 (d, J = 7.84 Hz, 1H), 7.81 (d, J = 12.16 Hz, 1H), 8.38 (br s, 1H), 8.83 (s, 1H), 10.45 (s, 1H), 12.41 (br s, 1H).	**Example 609** ethyl (2*E*)-3-(3-{2-[(3-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate
Example 622	 (2*E*)-3-(3-{2-[(3-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 484 (M+1) for $C_{24}H_{17}F_4N_5O_2$. 400 MHz, DMSO-d_6: δ 2.22 (s, 3H), 6.44 (d, J = 15.60 Hz, 1H), 6.73 (s, 1H), 6.85 (t, J = 8.00 Hz, 1H), 7.05 (d, J = 7.60 Hz, 1H), 7.34-7.40 (m, 3H), 7.48-7.52 (m, 2H), 7.61 (d, J = 8.00 Hz, 1H), 7.78 (d, J = 12.00 Hz, 1H), 8.99 (s, 1H), 10.50 (s, 1H), 12.41 (br s, 1H).	**Example 610** ethyl (2*E*)-3-(3-{2-[(3-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate
Example 623	 (2*E*)-3-[3-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)phenyl]prop-2-enoic acid	MS(ES): 530 (M+1) for $C_{24}H_{18}F_3N_5O_4S$. 400 MHz, DMSO-d_6: δ 3.23 (s, 3H), 6.49 (d, J = 16.00 Hz, 1H), 7.02 (d, J = 2.52 Hz, 1H), 7.17 (d, J = 7.72 Hz, 1H), 7.38 (t, J = 7.72 Hz, 1H), 7.53-7.65 (m, 5H), 7.98 (d, J = 8.00 Hz, 1H), 8.49 (br s, 1H), 8.61 (br s, 1H), 8.85 (s, 1H), 10.64 (s, 1H), 12.41 (br s, 1H).	**Example 613** ethyl (2*E*)-3-[3-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)phenyl]prop-2-enoate

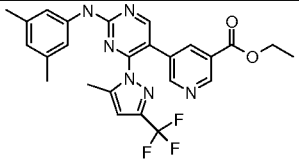
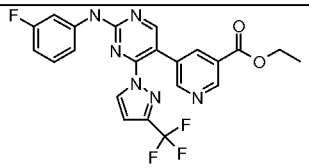
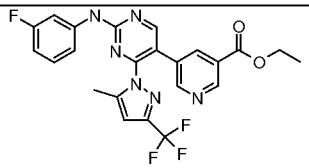
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 624	 (2*E*)-3-[3-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)phenyl]prop-2-enoic acid	MS(ES): 544 (M+1) for $C_{25}H_{20}F_3N_5O_4S$. 400 MHz, DMSO-d_6: δ 2.29 (s, 3H), 3.20 (s, 3H), 6.45 (d, *J* = 16.00 Hz, 1H), 6.74 (s, 1H), 7.04 (d, *J* = 7.60 Hz, 1H), 7.36 (t, *J* = 7.72 Hz, 1H), 7.38 (br s, 1H), 7.50 (d, *J* = 15.96 Hz, 1H), 7.56-7.65 (m, 3H), 8.01 (d, *J* = 7.96 Hz, 1H), 8.47 (br s, 1H), 9.01 (s, 1H), 10.66 (s, 1H), 12.44 (br s, 1H).	**Example 614** ethyl (2*E*)-3-[3-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)phenyl]prop-2-enoate

General procedure for the synthesis of ethyl 5-{2-[arylamino]-4-[1H-azol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate



A suspension of either 5-bromo-*N*-(aryl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine or 5-bromo-*N*-(aryl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (1 eq), ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (1.1–1.2 eq), [1,1′-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (10-20 mol%) and sodium carbonate (1-2 eq) in acetonitrile/water (4:1) was degassed and heated to 90 °C for 15-30 min under inert atmosphere. The solvent was removed *in vacuo* and the crude mixture taken in $CHCl_3$ was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using 30 % ethyl acetate / hexanes as eluent to give the product. The compounds in the below table were prepared using this method and the specified starting material.

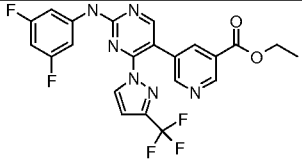
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 625	 Ethyl 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 515 (M+1) for $C_{24}H_{21}F_3N_6O_4$. 400 MHz, DMSO-d_6: δ 1.30 (t, J = 7.08 Hz, 3H), 3.75 (s, 6H), 4.33 (q, J = 7.12 Hz, 2H), 6.22 (t, J = 2.20 Hz, 1H), 7.05 (d, J = 2.64 Hz, 1H), 7.09 (s, 1H), 7.10 (s, 1H), 8.03 (t, J = 2.12 Hz, 1H), 8.53 (d, J = 1.72 Hz, 1H), 8.69 (d, J = 2.24 Hz, 1H), 8.82 (s, 1H), 9.02 (s, 1H), 10.24 (s, 1H).	**Intermediate 215** 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 626	 Ethyl 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 529 (M+1) for $C_{25}H_{23}F_3N_6O_4$. 400 MHz, DMSO-d_6: δ 1.30 (t, J = 7.20 Hz, 3H), 2.40 (s, 3H), 3.73 (s, 6H), 4.31 (q, J = 7.20 Hz, 2H), 6.23 (t, J = 2.00 Hz, 1H), 6.78 (s, 1H), 7.05 (m, 2H), 7.80 (t, J = 2.00 Hz, 1H), 8.61 (d, J = 2.40 Hz, 1H), 8.98 (d, J = 1.60 Hz, 1H), 8.99 (s, 1H), 10.27 (s, 1H).	**Intermediate 216** 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 627	 Ethyl 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 483 (M+1) for $C_{24}H_{21}F_3N_6O_2$. 400 MHz, DMSO-d_6: δ 1.31 (t, J = 7.20 Hz, 3H), 2.28 (s, 6H), 4.33 (q, J = 6.80 Hz, 2H), 6.71 (s, 1H), 7.05 (d, J = 2.80 Hz, 1H), 7.42 (s, 2H), 8.03 (t, J = 2.00 Hz, 1H), 8.54 (s, 1H), 8.69 (d, J = 2.40 Hz, 1H), 8.80 (s, 1H), 9.02 (d, J = 2.00 Hz, 1H), 10.15 (br s, 1H).	**Intermediate 217** 5-bromo-*N*-(3,5-dimethylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

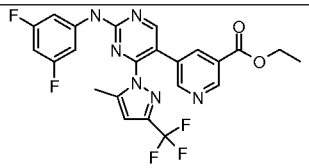
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 628	 ethyl 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 497 (M+1) for $C_{25}H_{23}F_3N_6O_2$. 400 MHz, DMSO-d_6: δ 1.30 (t, J = 7.20 Hz, 3H), 2.28 (s, 6H), 2.44 (s, 3H), 4.31 (q, J = 6.80 Hz, 2H), 6.71 (s, 1H), 6.77 (s, 1H), 7.37 (s, 2H), 7.79 (t, J = 2.00 Hz, 1H), 8.60 (d, J = 2.00 Hz, 1H), 8.96 (s, 1H), 8.97 (d, J = 2.00 Hz, 1H), 10.17 (br s, 1H).	**Intermediate 218** 5-bromo-*N*-(3,5-dimethylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 629	 ethyl 5-{2-[(3-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 473 (M+1) for $C_{22}H_{16}F_4N_6O_2$. 400 MHz, DMSO-d_6: δ 1.30 (t, J = 7.08 Hz, 3H), 4.33 (q, J = 7.08 Hz, 2H), 6.86 (td, J = 2.36, 8.38 Hz, 1H), 7.05 (d, J = 2.60 Hz, 1H), 7.38 (dd, J = 8.08, 15.24 Hz, 1H), 7.56 (d, J = 8.24 Hz, 1H), 7.77 (d, J = 12.04 Hz, 1H), 8.03 (t, J = 2.08 Hz, 1H), 8.57 (br s, 1H), 8.69 (d, J = 2.12 Hz, 1H), 8.84 (s, 1H), 9.02 (d, J = 1.92 Hz, 1H), 10.49 (s, 1H).	**Intermediate 219** 5-bromo-*N*-(3-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 630	 ethyl 5-{2-[(3-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 487 (M+1) for $C_{23}H_{18}F_4N_6O_2$. 400 MHz, DMSO-d_6: δ 1.30 (t, J = 7.20 Hz, 3H), 2.42 (s, 3H), 4.32 (q, J = 7.20 Hz, 2H), 6.79 (s, 1H), 6.87 (td, J = 2.00, 8.20 Hz, 1H), 7.39 (dd, J = 8.40, 15.20 Hz, 1H), 7.52 (d, J = 8.40 Hz, 1H), 7.76-7.79 (m, 1H), 7.81 (t, J = 2.00 Hz, 1H), 8.62 (d, J = 2.00 Hz, 1H), 8.99 (d, J = 2.00 Hz, 1H), 9.03 (s, 1H), 10.54 (s, 1H),.	**Intermediate 220** 5-bromo-*N*-(3-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

Example 631: ethyl 5-{2-[(3,5-difluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

Example 632: ethyl 5-{2-[(3,5-difluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

A suspension of either 3-(trifluoromethyl)-1*H*-pyrazole or 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole (1.2-1.5 eq), potassium *tert*-butoxide (1 eq) and ethyl 5-{2-[(3,5-difluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}pyridine-3-carboxylate **Intermediate 225** (1 eq) in DMSO was subjected to microwave irradiation at 130 °C for 1 h. After the reaction was cooled to RT, the mixture was diluted with EtOAc, washed successively with water and brine. The organic layer was dried over sodium sulphate, filtered, concentrated and further purified by silica gel column chromatography using ethyl acetate/hexanes to yield the product. The compounds in the below table were prepared using this method and the specified starting material.

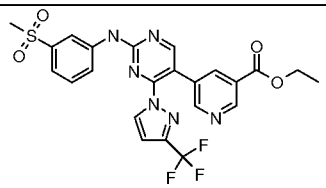
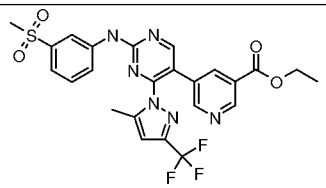
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 631	 ethyl 5-{2-[(3,5-difluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 491 (M+1) for $C_{22}H_{15}F_5N_6O_2$. 400 MHz, DMSO-d_6: δ 1.31 (t, J = 7.20 Hz, 3H), 4.34 (q, J = 7.20 Hz, 2H), 6.88 (m, 1H), 7.07 (d, J = 2.80 Hz, 1H), 7.58 (dd, J = 2.00, 10.00 Hz, 2H), 8.05 (t, J = 2.00 Hz, 1H), 8.57 (d, J = 1.20 Hz, 1H), 8.70 (d, J = 2.40 Hz, 1H), 8.90 (s, 1H), 9.04 (d, J = 2.00 Hz, 1H), 10.70 (s, 1H).	**Intermediate 225** ethyl 5-{2-[(3,5-difluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}pyridine-3-carboxylate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 632	 ethyl 5-{2-[(3,5-difluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 505 (M+1) for $C_{23}H_{17}F_5N_6O_2$. 400 MHz, DMSO-d_6: δ 1.31 (t, *J* = 7.08 Hz, 3H), 2.41 (s, 3H), 4.31 (q, *J* = 7.08 Hz, 2H), 6.79 (s, 1H), 6.87 (t, *J* = 9.28 Hz, 1H), 7.54 (dd, *J* = 2.00, 9.96 Hz, 2H), 7.82 (t, *J* = 2.16 Hz, 1H), 8.62 (d, *J* = 2.28 Hz, 1H), 8.99 (d, *J* = 2.00 Hz, 1H), 9.06 (s, 1H), 10.70 (s, 1H).	**Intermediate 225** ethyl 5-{2-[(3,5-difluorophenyl)amino]-4-(methylsulfonyl)pyrimidin-5-yl}pyridine-3-carboxylate

Example 633: ethyl 5-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylate

Example 634: ethyl 5-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylate

NaH (60 % dispersion in mineral oil, 2 eq) was dissolved in 1 mL of DMF and stirred for about 5 min at 0 °C. Then either 3-(trifluoromethyl)-1*H*-pyrazole or 5-methyl-3-(trifluoromethyl)-1*H*-pyrazole (2 eq) in DMF (2 mL) was added dropwise at 0 °C for about 10 min and stirring continued for about 20 min under N_2. Then ethyl 5-[4-(methylsulfonyl)-2-{[3-(methylsulfonyl)phenyl]amino}pyrimidin-5-yl]pyridine-3-carboxylate (**Intermediate 226**, 1 eq) in DMF was added dropwise and the reaction was stirred overnight at room temperature. Water was added and the solid obtained was filtered off, dried and purified by silica gel column chromatography using ethyl acetate/hexanes as eluent to yield the product. The compounds in the below table were prepared using this method and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 633	 ethyl 5-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylate	MS(ES): 533 (M+1) for $C_{23}H_{19}F_3N_6O_4S$. 400 MHz, DMSO-d_6: δ 1.30 (t, J = 7.08 Hz, 3H), 3.24 (s, 3H), 4.34 (q, J = 7.08 Hz, 2H), 7.07 (d, J = 2.64 Hz, 1H), 7.58-7.61 (m, 1H), 7.65 (t, J = 7.88 Hz, 1H), 7.97 (d, J = 7.92 Hz, 1H), 8.10 (t, J = 2.08 Hz, 1H), 8.63 (br s, 1H), 8.67 (br s, 1H), 8.72 (d, J = 2.16 Hz, 1H), 8.86 (s, 1H), 9.04 (d, J = 1.92 Hz, 1H), 10.70 (br s, 1H).	**Intermediate 226** ethyl 5-[4-(methylsulfonyl)-2-{[3-(methylsulfonyl)phenyl]amino}pyrimidin-5-yl]pyridine-3-carboxylate
Example 634	 ethyl 5-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylate	MS(ES): 547 (M+1) for $C_{24}H_{21}F_3N_6O_4S$. 400 MHz, DMSO-d_6: δ 1.32 (t, J = 7.08 Hz, 3H), 2.48 (s, 3H), 3.21 (s, 3H), 4.31 (q, J = 7.12 Hz, 2H), 6.80 (s, 1H), 7.58-7.60 (m, 1H), 7.64 (t, J = 7.88 Hz, 1H), 7.82 (t, J = 2.12 Hz, 1H), 8.02 (d, J = 7.96 Hz, 1H), 8.47 (t, J = 1.76 Hz, 1H), 8.62 (d, J = 2.24 Hz, 1H), 8.99 (d, J = 1.96 Hz, 1H), 9.04 (s, 1H), 10.70 (br s, 1H).	**Intermediate 226** ethyl 5-[4-(methylsulfonyl)-2-{[3-(methylsulfonyl)phenyl]amino}pyrimidin-5-yl]pyridine-3-carboxylate

Example 635: 5-{2-[(3,5-Dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

To a suspension of **Example 625** (1 eq) taken in dioxane and water (1:1) was added barium hydroxide monohydrate (2 eq) and the mixture was stirred at RT for 2 days. The reaction mixture was concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed was filtered, washed with water and dried to give the title compound.

Example 636: 5-{2-[(3,5-Dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

To a suspension of **Example 626** (1 eq) taken in dioxane and water (1:1), was added Barium hydroxide monohydrate (2 eq) and the mixture was stirred at RT for 24 h. The reaction mixture was concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed was filtered and dried to give the title compound.

Example 637: 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

To a suspension of **Example 627** (1 eq) taken in THF and water (1:1), was added sodium hydroxide (2 eq) and the mixture was stirred at RT for 2 days. The reaction mixture was concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed was filtered, washed with water and dried to give the title compound.

Example 638: 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

To a suspension of **Example 628** (1 eq) taken in THF and water (1:1), was added sodium hydroxide (2 eq) and the mixture was heated to 50 °C for 5 days. The reaction mixture was concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed was filtered, washed with water and dried to give the title compound.

Example 639: 5-{2-[(3,5-difluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

To a suspension of **Example 631** (1 eq) taken in THF and water (3:1), was added Barium hydroxide monohydrate (2 eq) and the mixture was stirred at RT for 1 h. The reaction mixture was concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed was filtered, washed with water and dried to give the title compound.

Example 640: 5-{2-[(3,5-difluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

To a suspension of **Example 632** (1 eq) taken in THF and water (2:1), was added sodium hydroxide (2 eq) and the mixture was allowed to stir at RT for 2 h. The reaction mixture was concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed was filtered, washed with water and dried to give the title compound.

Example 641: 5-{2-[(3-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

To a suspension of **Example 629** (1 eq) taken in THF and water (1:1), was added lithium hydroxide monohydrate (4 eq) and the mixture was stirred for 30' at RT. The reaction mixture was concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed was stirred with acetonitrile. It was then filtered, washed with acetonitrile and dried to give the title compound.

Example 642: 5-{2-[(3-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

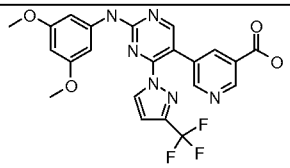
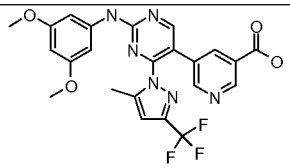
To a suspension of **Example 630** (1 eq) taken in acetonitrile and water (1:1), was added sodium hydroxide (4 eq) and the mixture was stirred at RT for 1 h. The reaction mixture was concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed was filtered, washed and dried to give the title compound.

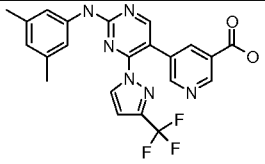
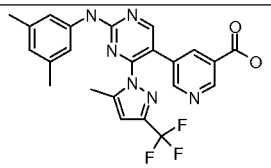
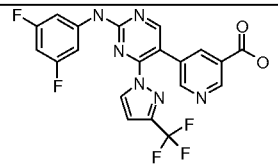
Example 643: 5-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylic acid

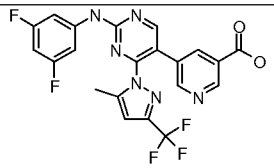
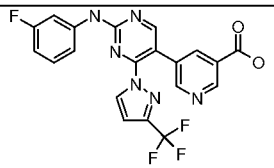
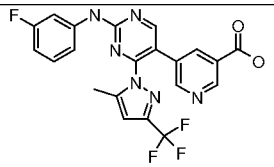
To a suspension of **Example 633** (1 eq) taken in dioxane and water (2:1), was added Barium hydroxide monohydrate (2 eq) and the mixture was allowed to stir overnight at RT. The reaction mixture was concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed was filtered, washed with water and dried to give the title compound.

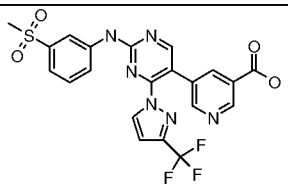
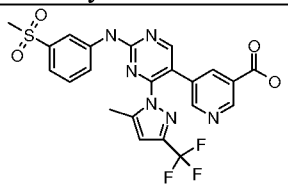
Example 644: 5-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylic acid

To a suspension of **Example 634** (1 eq) taken in dioxane and water (2:1), was added Barium hydroxide monohydrate (2 eq) and the mixture was allowed to stir overnight at RT. The reaction mixture was concentrated *in vacuo*, acidified with 1 N HCl and the precipitate formed was filtered, washed with water and dried to give the title compound.

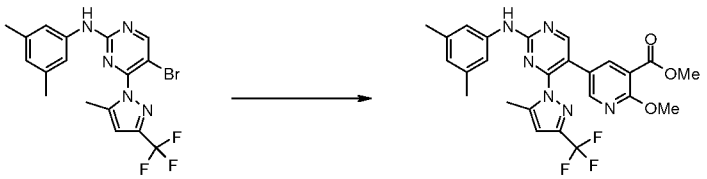
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 635	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 487 (M+1) for $C_{22}H_{17}F_3N_6O_4$. 400 MHz, DMSO-d_6: δ 3.74 (s, 6H), 6.20 (s, 1H), 7.00 (d, J = 2.04 Hz, 1H), 7.10 (d, J = 1.72 Hz, 2H), 7.98 (s, 1H), 8.39 (br s, 1H), 8.43 (br s, 1H), 8.77 (s, 1H), 8.95 (s, 1H), 10.20 (s, 1H).	**Example 625** ethyl 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 636	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 501 (M+1) for $C_{23}H_{19}F_3N_6O_4$. 400 MHz, DMSO-d_6: δ 2.40 (s, 3 H), 3.72 (s, 6H), 6.22 (s, 1H), 6.76 (s, 1H), 7.04 (d, J = 1.76 Hz, 2H), 7.82 (d, J = 2.01 Hz, 1H), 8.54 (d, J = 1.76 Hz, 1H), 8.95 (d, J = 1.25 Hz, 1H), 8.96 (s, 1H), 10.24 (s, 1H), 13.43 (br s, 1H).	**Example 626** ethyl 5-{2-[(3,5-dimethoxyphenyl)amino-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 637	 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 455 (M+1) for $C_{22}H_{17}F_3N_6O_2$. 400 MHz, DMSO-d_6: δ 2.27 (s, 6H), 6.69 (s, 1H), 7.03 (d, J = 2.64 Hz, 1H), 7.41 (s, 2H), 8.01 (t, J = 2.04 Hz, 1H), 8.52 (d, J = 1.68 Hz, 1H), 8.64 (d, J = 2.20 Hz, 1H), 8.77 (s, 1H), 8.99 (d, J = 1.92 Hz, 1H), 10.12 (s, 1H).	**Example 627** ethyl 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 638	 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 469 (M+1) for $C_{23}H_{19}F_3N_6O_2$. 400 MHz, DMSO-d_6: δ 2.26 (s, 6H), 2.45 (s, 3H), 6.70 (s, 1H), 6.76 (s, 1H), 7.36 (s, 2H), 7.81 (s, 1H), 8.53 (s, 1H), 8.93-8.94 (m, 2H), 10.10 (s, 1H), 13.50 (s, 1H).	**Example 628** ethyl 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 639	 5-{2-[(3,5-difluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 463 (M+1) for $C_{20}H_{11}F_5N_6O_2$. 400 MHz, DMSO-d_6: δ 6.86 (tt, J = 2.10, 9.19 Hz, 1H), 7.04 (d, J = 2.44 Hz, 2H), 7.58 (d, J = 8.24 Hz, 1H), 7.99 (s, 1H), 8.48 (br s, 1H), 8.49 (br s, 1H), 8.86 (s, 1H), 8.96 (s, 1H), 10.67 (s, 1H).	**Example 631** 5-{2-[(3,5-difluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 640	 5-{2-[(3,5-difluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 477 (M+1) for $C_{21}H_{13}F_5N_6O_2$. 400 MHz, DMSO-d_6: δ 2.42 (s, 3H), 6.78 (s, 1H), 6.88 (t, J = 9.12 Hz, 1H), 7.54 (d, J = 8.68 Hz, 2H), 7.84 (s, 1H), 8.56 (br s, 1H), 8.98 (br s, 1H), 9.05 (s, 1H), 10.69 (s, 1H), 13.20 (br s, 1H).	**Example 632** ethyl 5-{2-[(3,5-difluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 641	 5-{2-[(3-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 445 (M+1) for $C_{20}H_{12}F_4N_6O_2$. 400 MHz, DMSO-d_6: δ 6.86 (td, J = 2.51, 8.41 Hz, 1H), 7.05 (d, J = 2.76 Hz, 1H), 7.34-7.44 (m, 1H), 7.56 (dd, J = 1.38, 8.16 Hz, 1H), 7.77 (dt, J = 1.98, 12.11, Hz, 1H), 8.02 (t, J = 2.01 Hz, 1H), 8.57 (d, J =1.51 Hz, 1H), 8.65 (d, J = 2.01 Hz, 1H), 8.84 (s, 1H), 9.00 (d, J = 2.01 Hz, 1H), 10.49 (s, 1H), 13.43 (br s, 1H).	**Example 629** ethyl 5-{2-[(3-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 642	 5-{2-[(3-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 459 (M+1) for $C_{21}H_{14}F_4N_6O_2$. 400 MHz, DMSO-d_6: δ 2.42 (s, 3H), 6.77 (s, 1H), 6.86 (td, J = 2.13, 8.38 Hz, 1H), 7.34-7.42 (m, 1H), 7.52 (d, J = 8.22 Hz, 1H), 7.76 (d, J = 11.57 Hz, 1H), 7.83 (s, 1H), 8.52-8.57 (m, 1H), 8.96 (s, 1H), 9.01 (s, 1H), 10.52 (s, 1H), 13.42 (br s, 1H).	**Example 630** ethyl 5-{2-[(3-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

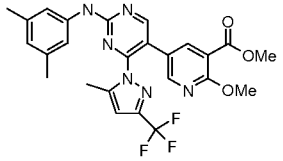
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 643	 5-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylic acid	MS(ES): 505 (M+1) for $C_{21}H_{15}F_3N_6O_4S$. 400 MHz, DMSO-d_6: δ 3.24 (s, 3H), 7.06 (d, J = 2.75 Hz, 1H), 7.53-7.76 (m, 2H), 7.98 (d, J = 7.93 Hz, 1H), 8.08 (s, 1H), 8.68 (s, 2H), 8.63 (s, 1H), 8.85 (s, 1H), 9.02 (s, 1H), 10.69 (s, 1H).	**Example 633** ethyl 5-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylate
Example 644	 5-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylic acid	MS(ES): 519 (M+1) for $C_{22}H_{17}F_3N_6O_4S$. 400 MHz, CD_3COOD: δ 2.63 (br s, 3H), 3.16 (s, 3H), 6.62 (s, 1H), 7.60-7.67 (m, 1H), 7.69-7.76 (m, 1H), 7.95 (d, J = 7.78 Hz, 1H), 8.26 (br s, 1H), 8.62 (br s, 2H), 8.87 (br s, 1H), 9.22 (br s, 1H).	**Example 634** ethyl 5-(2-{[3-(methylsulfonyl)phenyl]amino}-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylate

Example 645: methyl 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

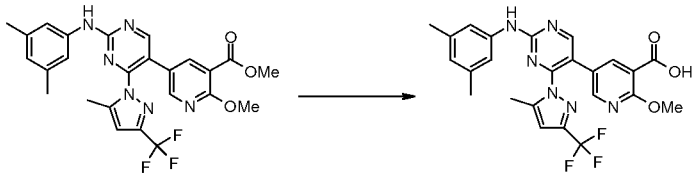


A suspension of 5-bromo-*N*-(3,5-dimethylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 218**, 0.59 mmol, 250 mg), methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate(0.58 mmol, 171 mg), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (0.099

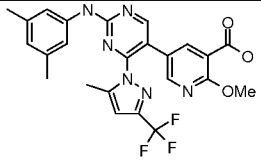
mmol, 81 mg) and sodium carbonate(0.58 mmol, 61 mg) were taken in a mixture of acetonitrile and water (20 mL : 5 mL) and heated to 90 °C for 10-20'. Acetonitrile was concentrated *in vacuo*. The residue was taken in ethyl acetate, washed with water and brine, dried over sodium sulphate, filtered and concentrated. The crude mass was purified by silica gel column chromatography (230-400 mesh) using 20 % ethyl acetate/hexanes to yield 150 mg of the product.

Compound	**Structure**	**Mass spectrum and ^{1}H NMR**	**SM**
Example 645	 methyl 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 513 (M+1) for $C_{25}H_{23}F_3N_6O_3$. 300 MHz, DMSO-d_6: δ 2.24 (s, 6H), 2.33 (s, 3H), 3.74 (s, 3H), 3.90 (s, 3H), 6.68 (s, 1H), 6.74 (s, 1H), 7.35 (s, 2H), 7.58 (d, *J* = 2.49 Hz, 1H), 8.21 (d, *J* = 2.49 Hz, 1H), 8.89 (s, 1H), 10.09 (s, 1H).	**Intermediate 218** 5-bromo-*N*-(3,5-dimethylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

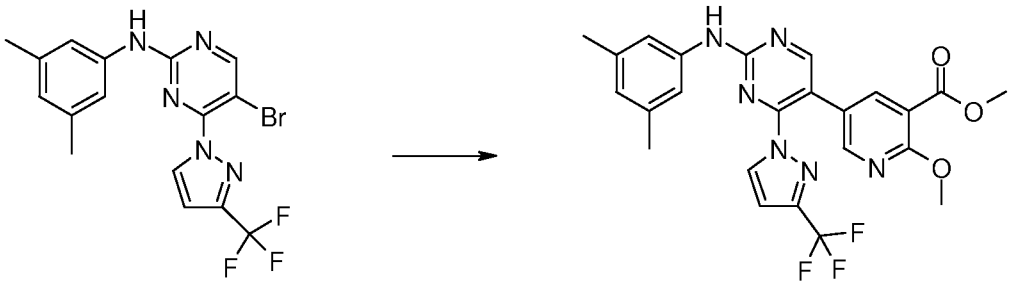
Example 646: 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid



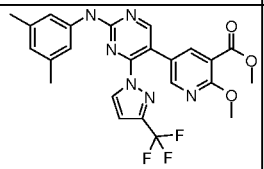
To a suspension of methyl 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate (**Example 645**, 0.29 mmol, 0.15 g) in THF and water (1:1), NaOH (0.58 mmol, 23 mg) was added and the mixture was stirred for 4 hours at rt. The THF was removed *in vacuo* and the reaction mixture diluted with water, acidified to pH = 2 using 1.5 N HCl and the solid that precipitated was filtered and dried to get 0.065 g of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 646	 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 499 (M+1) for $C_{24}H_{21}F_3N_6O_3$. 400 MHz, DMSO-d_6: δ 2.26 (s, 6H), 2.36 (s, 3H), 3.90 (s, 3H), 6.70 (s, 1H), 6.75 (s, 1H), 7.36 (s, 2H), 7.61 (d, J = 2.40 Hz, 1H), 8.15 (d, J = 2.24 Hz, 1H), 8.90 (s, 1H), 10.10 (s, 1H), 12.9 (br s, 1H).	**Example 645** methyl 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

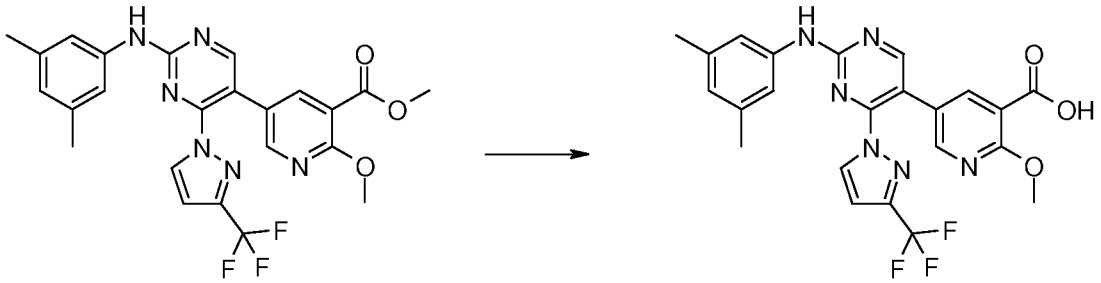
Example 647: methyl 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate



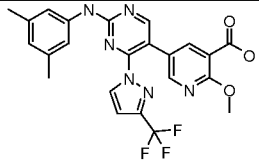
A solution of 5-bromo-*N*-(3,5-dimethylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 217**, 0.8 mmol, 330 mg), methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (0.8 mmol, 234 mg), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)complex with CH_2Cl_2 (0.16 mmol, 130 mg) and sodium carbonate (0.8 mmol, 85 mg) in acetonitrile (16 mL)/water (4 mL) was degassed and heated to 90 °C for 20' under nitrogen. The reaction mixture was concentrated *in vacuo*. The residue obtained was taken in ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using 15% ethyl acetate/hexanes to yield 150 mg of methyl 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 647	 methyl 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 499 (M+1) for $C_{24}H_{21}F_3N_6O_3$. 300 MHz, DMSO-d_6: δ 2.26 (s, 6H), 3.75 (s, 3H), 3.93 (s, 3H), 6.68 (s, 1H), 7.02 (d, J = 2.64 Hz, 1H), 7.40 (s, 2H), 7.84 (d, J = 2.46 Hz, 1H), 8.26 (d, J = 2.49 Hz, 1H), 8.48 (d, J = 1.68 Hz, 1H), 8.73 (s, 1H), 10.07 (s, 1H).	**Intermediate 217** 5-bromo-*N*-(3,5-dimethylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

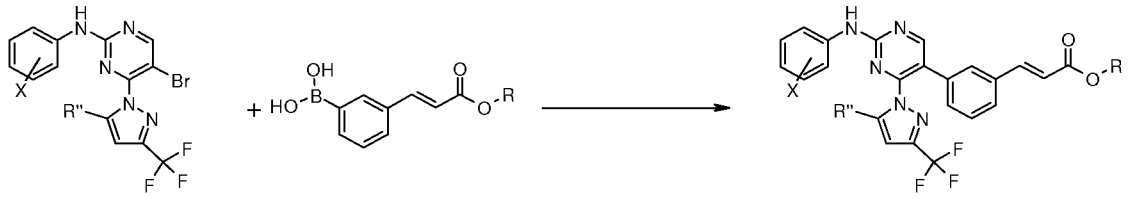
Example 648: 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid



A solution of methyl 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate (**Example 647**, 0.3 mmol, 150 mg) and sodium hydroxide (0.6 mmol, 24 mg) in THF (3 mL) and water (3 mL) was stirred at room temperature for 3 h. THF was removed *in vacuo* and the reaction mixture was neutralized using 1.5 N HCl. The solid that precipitated out was filtered, washed with water and dried to give the title compound (65 mg).

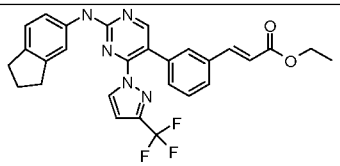
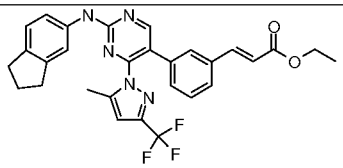
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 648	 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 485 (M+1) for $C_{23}H_{19}F_3N_6O_3$. 300 MHz, DMSO-d_6: δ 2.28 (s, 6H), 3.94 (s, 3H), 6.69 (s, 1H), 7.03 (d, J = 1.92 Hz, 1H), 7.42 (s, 2H), 7.82 (d, J = 1.83 Hz, 1H), 8.24 (d, J = 1.86 Hz, 1H), 8.48 (d, J = 1.29 Hz, 1H), 8.75 (s, 1H), 10.08 (s, 1H), 12.93 (br s, 1H).	**Example 647** methyl 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

General method for the synthesis of ethyl (2*E*)-3-(3-{2-[arylamino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate, ethyl (2*E*)-3-(3-{2-[arylamino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate and (2*E*)-3-[3-(2-{[3-methoxy-5-(methylsulfonyl)phenyl]amino}-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)phenyl]prop-2-enoic acid

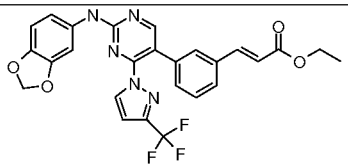
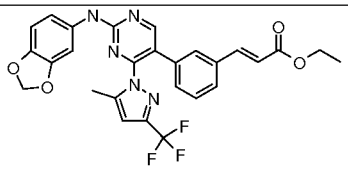


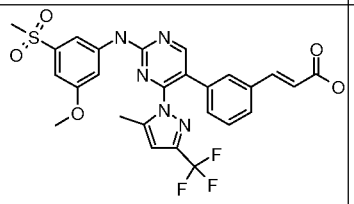
A suspension of 5-bromo-*N*-(aryl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine derivative or 5-bromo-*N*-(aryl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine derivative (1 eq), {3-[(1*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]phenyl}boronic acid or 3-(*trans*-2-carboxyvinyl)phenylboronic acid (1.1 – 1.2 eq), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (20 mol%) and sodium carbonate (1 eq) in acetonitrile/water (4 : 1) was degassed and heated to 90 °C for 15-30 min under inert atmosphere. The solvent was removed *in vacuo* and the crude mixture taken in $CHCl_3$ was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using chloroform: methanol (9:1) as eluent to give

the product. The compounds in the below table were prepared using the above method and the starting material specified.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 649[h)]	 ethyl (2*E*)-3-(3-{2-(2,3-dihydro-1*H*-inden-5-ylamino)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 520 (M+1) for $C_{28}H_{24}F_3N_5O_2$. 300 MHz, DMSO-d_6: δ 1.24 (t, *J* = 7.08 Hz, 3H), 1.98-2.03 (m, 2H), 2.78-2.87 (m, 4H), 4.17 (q, *J* = 7.08 Hz, 2H), 6.57 (d, *J* = 16.05 Hz, 1H), 6.97 (d, *J* = 2.25 Hz, 1H), 7.11 (d, *J* = 7.86 Hz, 1H), 7.17 (d, *J* = 8.20 Hz, 1H), 7.35 (t, *J* = 7.65 Hz, 1H), 7.48-7.56 (m, 3H), 7.62 (d, *J* = 3.63 Hz, 1H), 7.66 (s, 1H), 8.35 (s, 1H), 8.74 (s, 1H), 10.10 (s, 1H).	**Intermediate 242** 5-bromo-*N*-(2,3-dihydro-1*H*-inden-5-yl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 650[h)]	 ethyl (2*E*)-3-(3-{2-(2,3-dihydro-1*H*-inden-5-ylamino)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 534 (M+1) for $C_{29}H_{26}F_3N_5O_2$. 400 MHz, DMSO-d_6: δ 1.26 (t, *J* = 7.08 Hz, 3H), 2.01-2.04 (m, 2H), 2.21 (s, 3H), 2.80-2.87 (m, 4H), 4.19 (q, *J* = 7.08 Hz, 2H), 6.55 (d, *J* = 16.04 Hz, 1H), 6.71 (s, 1H), 7.04 (d, *J* = 7.36 Hz, 1H), 7.18 (d, *J* = 8.08 Hz, 1H), 7.33-7.37 (m, 2H), 7.47 (d, *J* = 8.24 Hz, 1H), 7.56 (d, *J* = 16.00 Hz, 1H), 7.62-7.66 (m, 2H), 8.91 (s, 1H), 10.15 (s, 1H).	**Intermediate 243** 5-bromo-*N*-(2,3-dihydro-1*H*-inden-5-yl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

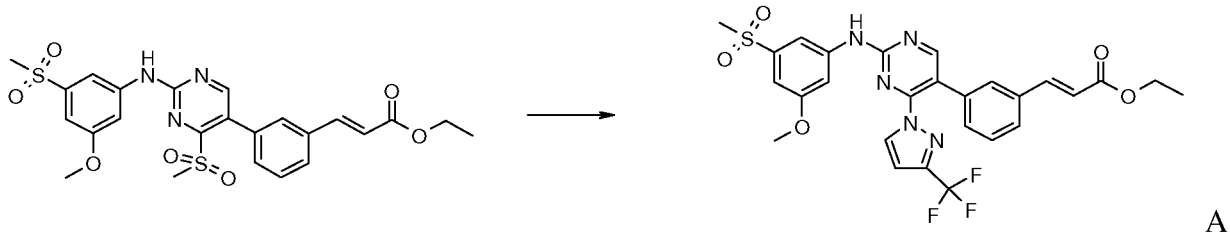
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Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 651[h)]	 ethyl (2*E*)-3-(3-{2-(1,3-benzodioxol-5-ylamino)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 524 (M+1) for $C_{26}H_{20}F_3N_5O_4$. 300 MHz, DMSO-d_6: δ 1.24 (t, J = 7.05 Hz, 3H), 4.17 (q, J = 7.02 Hz, 2H), 5.99 (s, 2H), 6.57 (d, J = 16.41 Hz, 1H), 6.89 (d, J = 8.34 Hz, 1H), 6.98 (s, 1H), 7.13 (t, J = 12.57 Hz, 2H), 7.35 (t, J = 8.40 Hz, 1H), 7.47 (s, 1H), 7.54 (d, J = 10.53 Hz, 1H), 7.63 (d, J = 11.88 Hz, 2H), 8.35 (s, 1H), 8.74 (s, 1H), 10.11 (s, 1H).	**Intermediate 244** *N*-(1,3-benzodioxol-5-yl)-5-bromo-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 652[h)]	 ethyl (2*E*)-3-(3-{2-(1,3-benzodioxol-5-ylamino)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate	MS(ES): 538 (M+1) for $C_{27}H_{22}F_3N_5O_4$. 300 MHz, DMSO-d_6: δ 1.24 (t, J = 7.08 Hz, 3H), 2.17 (s, 3H), 4.17 (q, J = 7.11 Hz, 2H), 5.98 (s, 2H), 6.53 (d, J = 16.05 Hz, 1H), 6.69 (s, 1H), 6.89 (d, J = 8.40 Hz, 1H), 7.01 (d, J = 7.44 Hz, 1H), 7.11 (d, J = 8.49 Hz, 1H), 7.31 (s, 1H), 7.34 (d, J = 4.35 Hz, 1H), 7.41 (s, 1H), 7.54 (d, J = 15.99 Hz, 1H), 7.62 (d, J = 7.47 Hz, 1H), 8.88 (s, 1H), 10.14 (s, 1H).	**Intermediate 245** benzodioxol-5-yl)-5-bromo-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

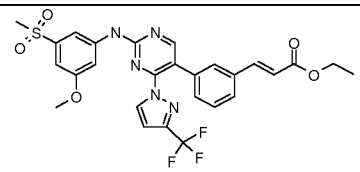
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 653[i]	 (2*E*)-3-[3-(2-{[3-methoxy-5-(methylsulfonyl)phenyl]amino}-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)phenyl]prop-2-enoic acid	MS(ES): 574 (M+1) for $C_{26}H_{22}F_3N_5O_5S$. 400 MHz, DMSO-d_6: δ 2.27 (s, 3H), 3.23 (s, 3H), 3.85 (s, 3H), 6.46 (d, J = 16.04 Hz, 1H), 6.75 (s, 1H), 7.05 (d, J = 7.76 Hz, 1H), 7.12 (s, 1H), 7.36-7.39 (m, 2H), 7.50 (d, J = 15.88 Hz, 1H), 7.62 (d, J = 7.72 Hz, 1H), 7.76 (s, 1H), 8.02 (s, 1H), 9.03 (s, 1H), 10.64 (s, 1H), 12.44 (br s, 1H).	**Intermediate 246** 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine and 3-(*trans*-2-carboxyvinyl)phenylboronic acid

[h] {3-[(1*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]phenyl}boronic acid was used [i] 3-(*trans*-2-carboxyvinyl)phenylboronic acid (1.1 eq) and Na_2CO_3 (2 eq) were used

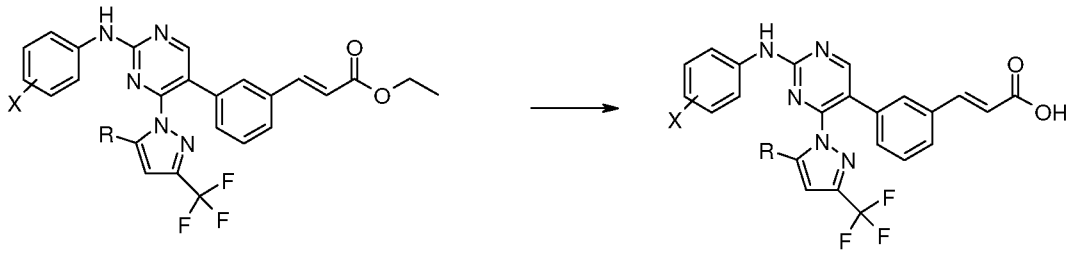
Example 654: ethyl (2*E*)-3-{3-[2-{[3-methoxy-5-(methylsulfonyl)phenyl]amino}-4-(methylsulfonyl)pyrimidin-5-yl]phenyl}prop-2-enoate



A suspension of 3-(trifluoromethyl)-1*H*-pyrazole (1.2-1.5 eq), potassium *tert*-butoxide (1.5 eq) and ethyl (2*E*)-3-{3-[2-{[3-methoxy-5-(methylsulfonyl)phenyl]amino}-4-(methylsulfonyl)pyrimidin-5-yl]phenyl}prop-2-enoate (**Intermediate 249**, 1 eq) in DMSO (3 mL) was subjected to microwave irradiation at 130 °C for 1 h. After the reaction was cooled to RT, the mixture was diluted with EtOAc, washed successively with water and brine. The organic layer was dried over sodium sulphate, filtered, concentrated and further purified by silica gel column chromatography using ethyl acetate/hexanes to yield the title compound.

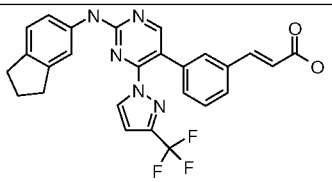
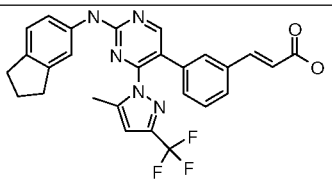
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 654	 ethyl (2*E*)-3-{3-[2-{[3-methoxy-5-(methylsulfonyl)phenyl]amino}-4-(methylsulfonyl)pyrimidin-5-yl]phenyl}prop-2-enoate	Taken to the next step based on LCMS without further purification. MS(ES): 588 (M+1) for $C_{27}H_{24}F_3N_5O_5S$. (43% pure by LCMS).	**Intermediate 249** ethyl (2*E*)-3-{3-[2-{[3-methoxy-5-(methylsulfonyl)phenyl]amino}-4-(methylsulfonyl)pyrimidin-5-yl]phenyl}prop-2-enoate

General procedure for the synthesis of (2*E*)-3-(3-{2-(arylamino)-4-[-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid

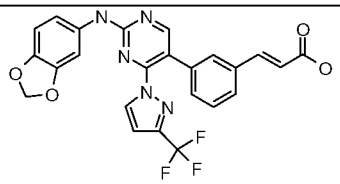
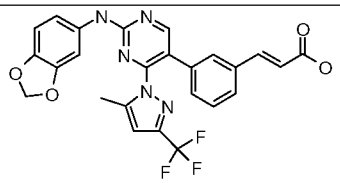


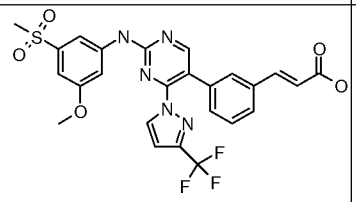
To 1 eq of the ethyl (2*E*)-3-(3-{2-[arylamino]-4-[1*H*-azol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate derivative taken in dioxane (5 mL), was added Barium hydroxide (2- 6 eqs) and was warmed to 60 ^{o}C for 1 to 2 h. The reaction mixture was carefully acidified with 1 N HCl and the solid that precipitated was filtered, washed with water and dried *in vacuo* to yield the desired carboxylic acid. The compounds in the below table were prepared using the above method and the starting material specified.

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Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 655[j]	 (2*E*)-3-(3-{2-(2,3-dihydro-1*H*-inden-5-ylamino)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 492 (M+1) for $C_{26}H_{20}F_3N_5O_2$ 400 MHz, DMSO-d_6: δ 1.99-2.06 (m, 2H), 2.81-2.88 (m, 4H), 6.47 (d, *J* = 15.96 Hz, 1H), 6.97 (d, *J* = 2.32 Hz, 1H), 7.13 (d, *J* = 7.72 Hz, 1H), 7.18 (d, *J* = 8.08 Hz, 1H), 7.36 (t, *J* = 7.72 Hz, 1H), 7.49-7.55 (m, 3H), 7.62 (d, *J* = 7.48 Hz, 1H), 7.68 (s, 1H), 8.36 (s, 1H), 8.75 (s, 1H), 10.08 (s, 1H), 12.40 (s, 1H).	**Example 649** ethyl (2*E*)-3-(3-{2-(2,3-dihydro-1*H*-inden-5-ylamino)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate
Example 656[k]	 (2*E*)-3-(3-{2-(2,3-dihydro-1*H*-inden-5-ylamino)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 506 (M+1) for $C_{27}H_{22}F_3N_5O_2$ 400 MHz, DMSO-d_6: δ 1.98-2.05 (m, 2H), 2.20 (s, 3H), 2.80-2.86 (m, 4H), 6.40 (d, *J* = 16.04 Hz, 1H), 6.69 (s, 1H), 6.99 (d, *J* = 7.92 Hz, 1H), 7.17 (d, *J* = 8.08 Hz, 1H), 7.25 (s, 1H), 7.31 (t, *J* = 7.72 Hz, 1H), 7.35 (s, 1H), 7.46 (d, *J* = 7.40 Hz, 1H), 7.53 (d, *J* = 7.84 Hz, 1H), 7.64 (s, 1H), 8.88 (s, 1H), 10.12 (s, 1H).	**Example 650** ethyl (2*E*)-3-(3-{2-(2,3-dihydro-1*H*-inden-5-ylamino)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate

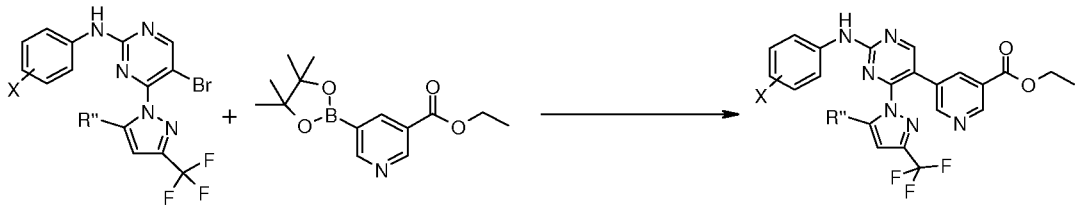
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Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 657[j]	 (2*E*)-3-(3-{2-(1,3-benzodioxol-5-ylamino)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 496 (M+1) for $C_{24}H_{16}F_3N_5O_4$ 400 MHz, DMSO-d_6: δ 6.01 (s, 2H), 6.47 (d, *J* = 16.04 Hz, 1H), 6.91 (d, *J* = 8.36 Hz, 1H), 6.99 (d, *J* = 2.28 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.17 (dd, *J* = 1.88, 8.32 Hz, 1H), 7.36 (t, *J* = 7.64 Hz, 1H), 7.48 (t, *J* = 2.08 Hz, 1H), 7.54 (d, *J* = 16.00 Hz, 1H), 7.63 (d, *J* = 7.56 Hz, 1H), 8.37 (s, 1H), 8.76 (s, 1H), 10.11 (s, 1H), 12.41 (br s, 1H).	**Example 651** ethyl (2*E*)-3-(3-{2-(1,3-benzodioxol-5-ylamino)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate
Example 658[k]	 (2*E*)-3-(3-{2-(1,3-benzodioxol-5-ylamino)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 510 (M+1) for $C_{25}H_{18}F_3N_5O_4$ 400 MHz, DMSO-d_6: δ 2.20 (s, 3H), 6.00 (s, 2H), 6.43 (d, *J* = 16.00 Hz, 1H), 6.70 (s, 1H), 6.90 (d, *J* = 8.40 Hz, 1H), 7.03 (d, *J* = 7.76 Hz, 1H), 7.12 (dd, *J* = 1.96, 8.46 Hz, 1H), 7.31 (br s, 1H), 7.35 (t, *J* = 7.76 Hz, 1H), 7.42 (br s, 1H), 7.49 (d, *J* = 15.96 Hz, 1H), 7.59 (d, *J* = 7.80 Hz, 1H), 8.89 (s, 1H), 10.13 (s, 1H), 12.41 (br s, 1H) .	**Example 652** ethyl (2*E*)-3-(3-{2-(1,3-benzodioxol-5-ylamino)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoate

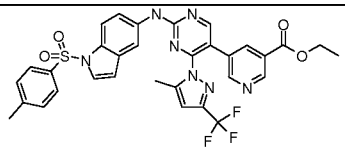
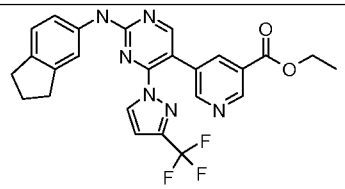
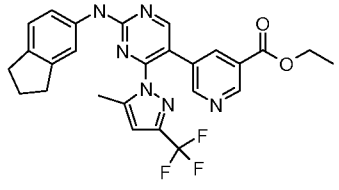
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 659[j]	 (2*E*)-3-[3-(2-{[3-methoxy-5-(methylsulfonyl)phenyl]amino}-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)phenyl]prop-2-enoic acid	MS(ES): 560 (M+1) for $C_{25}H_{20}F_3N_5O_5S$. 400 MHz, DMSO-d_6: δ 3.23 (s, 3H), 3.86 (s, 3H), 6.48 (d, J = 15.92 Hz, 1H), 7.01 (d, J = 2.52 Hz, 1H), 7.10 (s, 1H), 7.16 (d, J = 8.08 Hz, 1H), 7.37 (t, J = 7.64 Hz, 1H), 7.50-7.55 (m, 2H), 7.63 (d, J = 7.76 Hz, 1H), 7.75 (s, 1H), 8.12 (s, 1H), 8.41 (s, 1H), 8.85 (s, 1H), 10.60 (s, 1H), 12.30 (br s, 1H).	**Example 654** ethyl (2*E*)-3-{3-[2-{[3-methoxy-5-(methylsulfonyl)phenyl]amino}-4-(methylsulfonyl)pyrimidin-5-yl]phenyl}prop-2-enoate

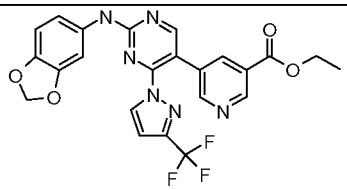
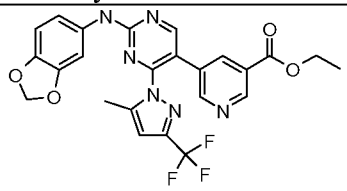
[j] $Ba(OH)_2$, dioxane-H_2O, RT, 12-24 h [k] $Ba(OH)_2$, dioxane-H_2O, 55 °C, 1-2 h

General procedure for the synthesis of ethyl 5-(2-{arylamino}-4-[1*H*-azol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylate



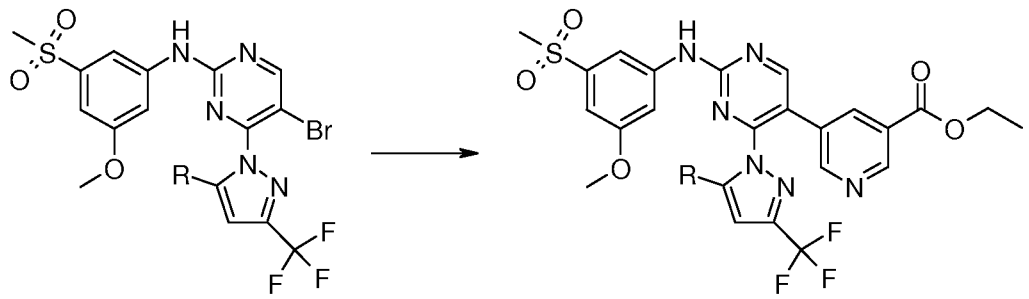
A suspension of 5-bromo-*N*-(aryl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine or 5-bromo-*N*-(aryl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (1 eq), ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (1.1–1.2 eq), [1,1′-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (10-20 mol%) and sodium carbonate (1-2 eq) in acetonitrile/water (4:1) was degassed and heated to 90 °C for 15-30 min under inert atmosphere. The solvent was removed *in vacuo* and the crude mixture taken in $CHCl_3$ was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using 30 % ethyl acetate / hexanes as eluent to give the product. The compounds in the below table were prepared using this method and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 660	 ethyl 5-{2-({1-[(4-methylphenyl)sulfonyl]-1*H*-indol-5-yl}amino)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 662 (M+1) for $C_{32}H_{26}F_3N_7O_4S$. 300 MHz, DMSO-d_6: δ 1.30 (t, *J* = 7.08 Hz, 3H), 2.30 (s, 3H), 2.38 (s, 3H), 4.30 (q, *J* = 7.11 Hz, 2H), 6.75 (s, 1H), 6.82 (d, *J* = 3.60 Hz, 1H), 7.37 (d, *J* = 8.28 Hz, 2H), 7.60 (dd, *J* = 1.98, 9.06 Hz, 1H), 7.75-7.76 (m, 2H), 7.84-7.91 (m, 3H), 7.99 (s, 1H), 8.58 (d, *J* = 2.13 Hz, 1H), 8.92 (s, 1H), 8.96 (d, *J* = 1.92 Hz, 1H), 10.33 (s, 1H).	**Intermediate 241** *N*-{5-bromo-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}-1-[(4-methylphenyl)sulfonyl]-1*H*-indol-5-amine
Example 661	 ethyl 5-{2-(2,3-dihydro-1*H*-inden-5-ylamino)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 495 (M+1) for $C_{25}H_{21}F_3N_6O_2$. 400 MHz, DMSO-d_6: δ 1.28-1.36 (m, 3H), 1.98-2.04 (m, 2H), 2.80-2.88 (m, 4H), 4.30-4.35 (m, 2H), 7.02 (d, *J* = 2.44 Hz, 1H), 7.19 (d, *J* = 8.12 Hz, 1H), 7.50 (d, *J* = 8.12 Hz, 1H), 7.64 (s,1H), 8.00 (s, 1H), 8.54 (s, 1H), 8.67 (d, *J* = 2.08 Hz, 1H), 8.76 (s, 1H), 9.00 (d, *J* = 1.84 Hz, 1H), 10.15 (s, 1H).	**Intermediate 242** 5-bromo-*N*-(2,3-dihydro-1*H*-inden-5-yl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 662	 ethyl 5-{2-(2,3-dihydro-1*H*-inden-5-ylamino)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 509 (M+1) for $C_{26}H_{23}F_3N_6O_2$. 400 MHz, DMSO-d_6: δ 1.31 (t, *J* = 7.2 Hz, 3H), 2.01-2.05 (m, 2H), 2.42 (s, 3H), 2.81-2.88 (m, 4H), 4.31 (q, *J* = 7.20 Hz, 2H), 6.77 (s, 1H), 7.20 (d, *J* = 8.00 Hz, 1H), 7.46 (d, *J* = 7.60 Hz, 1H), 7.63 (s, 1H), 7.78 (s, 1H), 8.60 (s, 1H), 8.94 (s, 1H), 8.97 (s, 1H), 10.20 (s, 1H) .	**Intermediate 243** 5-bromo-*N*-(2,3-dihydro-1*H*-inden-5-yl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

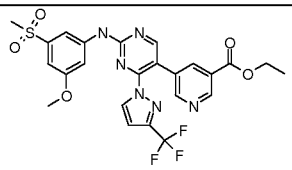
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 663	 ethyl 5-{2-(1,3-benzodioxol-5-ylamino)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	Taken to the next step based on LCMS MS(ES): 499 (M+1) $C_{23}H_{17}F_3N_6O_4$.	**Intermediate 244** *N*-(1,3-benzodioxol-5-yl)-5-bromo-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 664	 ethyl 5-{2-(1,3-benzodioxol-5-ylamino)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 513 (M+1) for $C_{24}H_{19}F_3N_6O_4$. 400 MHz, DMSO-d_6: δ 1.28 (t, J = 9.48 Hz, 3H), 2.37 (s, 3H), 4.30 (d, J = 9.92 Hz, 2H), 5.99 (s, 1H), 6.75 (s, 1H), 6.90 (d, J = 10.84 Hz, 1H), 7.09 (s, 1H), 7.47 (t, J = 46.68 Hz, 3H), 7.75 (s, 1H), 8.57 (s, 1H), 8.94 (d, J = 14.80 Hz, 1H), 10.19 (s, 1H) .	**Intermediate 244** *N*-(1,3-benzodioxol-5-yl)-5-bromo-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

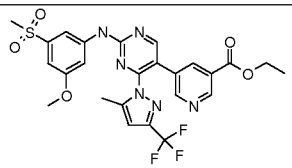
Example 665: ethyl 5-(2-{[3-methoxy-5-(methylsulfonyl)phenyl]amino}-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylate

Example 666: ethyl 5-(2-{[3-methoxy-5-(methylsulfonyl)phenyl]amino}-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylate

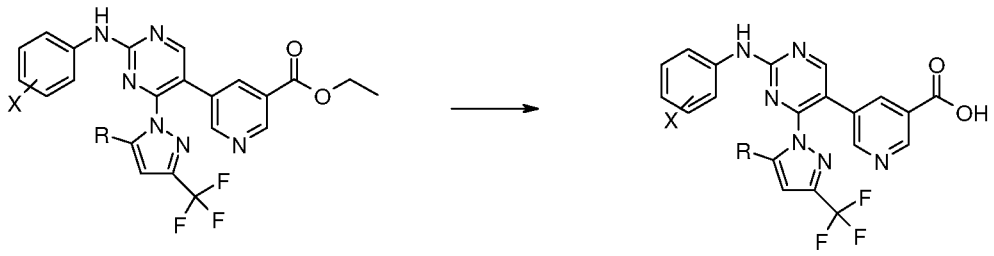


A suspension of 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 250**) or 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 251**) (1 eq), ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (1.1–1.2 eq), [1,1′-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (10-20 mol%) and sodium carbonate (1-2 eq) in acetonitrile/water (4:1) was degassed and heated to 90 °C for 15-30 min under inert atmosphere. The solvent was removed *in vacuo* and the crude mixture taken in $CHCl_3$ was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using 50 % ethyl acetate / hexanes as eluent to give the product. The compounds in the below table were prepared following this procedure and using the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 665	 ethyl 5-(2-{[3-methoxy-5-(methylsulfonyl)phenyl]amino}-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylate	MS(ES): 563 (M+1) for $C_{24}H_{21}F_3N_6O_5S$. 400 MHz, DMSO-d_6: δ 1.31 (t, J = 7.08 Hz, 3H), 3.24 (s, 3H), 3.87 (s, 3H), 4.33 (q, J = 7.08 Hz, 2H), 7.08 (d, J = 2.56 Hz, 1H), 7.14 (s, 1H), 7.67 (s, 1H), 8.09 (t, J = 1.96 Hz, 1H), 8.19 (s, 1H), 8.62 (s, 1H), 8.72 (d, J = 2.16 Hz, 1H), 8.87 (s, 1H), 9.04 (d, J = 1.92 Hz, 1H), 10.66 (s, 1H).	**Intermediate 250** 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

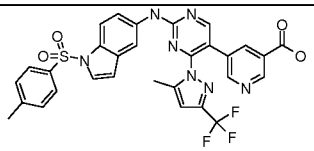
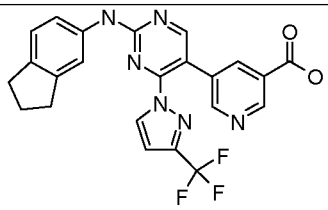
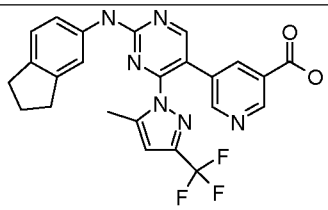
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 666	 ethyl 5-(2-{[3-methoxy-5-(methylsulfonyl)phenyl]amino}-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylate	Taken to the next step based on LCMS without further purification. MS(ES): 577 (M+1) for $C_{25}H_{23}F_3N_6O_5S$. (88% pure by LCMS).	**Intermediate 251** 5-bromo-*N*-[3-methoxy-5-(methylsulfonyl)phenyl]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

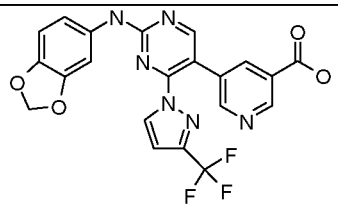
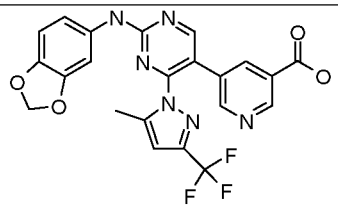
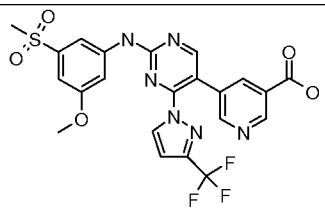
General procedure for the synthesis of 5-{2-(arylamino)-4-[1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

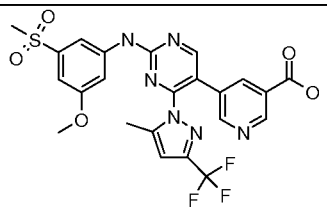


To 1 eq of the ethyl 5-(2-{arylamino}-4-[1*H*-azol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylate derivative taken in dioxane (5 mL), was added 1 N aq. sodium hydroxide/Barium hydroxide (2- 6 eqs) and was heated to 60 °C for 1 h. The reaction mixture was carefully acidified with 1 N HCl and the solid that precipitated was filtered, washed with water and dried *in vacuo* to yield the desired carboxylic acid. The compounds in the below table were prepared following this procedure and using the specified starting material.

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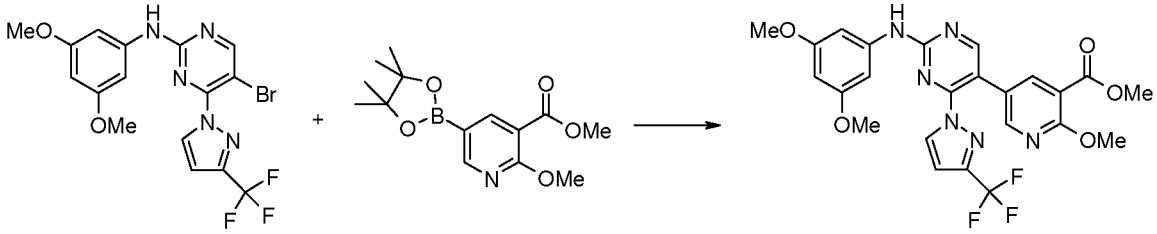
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 667[l)]	 5-{2-({1-[(4-methylphenyl)sulfonyl]-1*H*-indol-5-yl}amino)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 634 (M+1) for $C_{30}H_{22}F_3N_7O_4S$. 400 MHz, DMSO-d_6: δ 2.31 (s, 3H), 2.34 (s, 3H), 6.72 (s, 1H), 6.83 (d, *J* = 3.56 Hz, 1H), 7.38 (d, *J* = 8.24 Hz, 2H), 7.61 (dd, *J* = 1.76, 5.46 Hz, 1H), 7.76 (d, *J* = 3.60 Hz, 1H), 7.83-7.90 (m, 4H), 8.00 (s, 1H), 8.28 (s, 1H), 8.88 (s, 1H), 8.88 (s, 1H), 10.30 (s, 1H).	**Example 660** ethyl 5-{2-({1-[(4-methylphenyl)sulfonyl]-1*H*-indol-5-yl}amino)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 668[n)]	 5-{2-(2,3-dihydro-1*H*-inden-5-ylamino)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 467 (M+1) for $C_{23}H_{17}F_3N_6O_2$ 400 MHz, DMSO-d_6: δ 2.00-2.04 (m, 2H), 2.80-2.88 (m, 4H), 6.98 (d, *J* = 2.60 Hz, 1H), 7.18 (d, *J* = 8.16 Hz, 1H), 7.50 (dd, *J* = 4.00, 10.00 Hz, 1H), 7.66 (s, 1H), 8.01 (s, 1H), 8.24 (d, *J* = 2.20 Hz, 1H), 8.44 (s, 1H), 8.70 (s, 1H), 8.95 (d, *J* = 1.72 Hz, 1H), 10.10 (s, 1H).	**Example 661** ethyl 5-{2-(2,3-dihydro-1*H*-inden-5-ylamino)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 669[o)]	 5-{2-(2,3-dihydro-1*H*-inden-5-ylamino)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 481 (M+1) for $C_{24}H_{19}F_3N_6O_2$ 400 MHz, DMSO-d_6: δ 2.01-2.04 (m, 2H), 2.34 (s, 3H), 2.80-2.87 (m, 4H), 6.72 (s, 1H), 7.18 (d, *J* = 8.16 Hz, 1H), 7.46 (d, *J* = 7.72 Hz, 1H), 7.63 (s, 1H), 7.89 (s, 1H), 8.12 (s, 1H), 8.84 (s, 1H), 8.88 (s, 1H), 10.14 (s, 1H).	**Example 662** ethyl 5-{2-(2,3-dihydro-1*H*-inden-5-ylamino)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 670[m)]	 5-{2-(1,3-benzodioxol-5-ylamino)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 471 (M+1) for $C_{21}H_{13}F_3N_6O_4$ 400 MHz, DMSO-d_6: δ 6.00 (d, J = 9.60 Hz, 2H), 6.92 (d, J = 8.40 Hz, 1H), 7.03 (d, J = 2.60 Hz, 1H), 7.17 (d, J = 8.44 Hz, 1H), 7.44 (s, 1H), 7.99 (s, 1H), 8.53 (s, 1H), 8.63 (d, J = 1.92 Hz, 1H), 8.75 (s, 1H), 8.99 (s, 1H), 10.13 (s, 1H), 13.39 (br s, 1H).	**Example 663** ethyl 5-{2-(1,3-benzodioxol-5-ylamino)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 671[m)]	 5-{2-(1,3-benzodioxol-5-ylamino)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 485 (M+1) for $C_{22}H_{15}F_3N_6O_4$ 400 MHz, DMSO-d_6: δ 2.39 (s, 3H), 6.00 (s, 2H), 6.74 (s, 1H), 6.91 (d, J = 8.44 Hz, 1H), 7.12 (t, J = 1.52 Hz, 1H), 7.39 (s, 1H), 7.86 (t, J = 79.00 Hz, 1H), 8.52 (d, J = 2.04 Hz, 1H), 8.91 (s, 1H), 8.94 (d, J = 1.72 Hz, 1H), 10.16 (s, 1H), 13.37 (br s, 1H).	**Example 664** ethyl 5-{2-(1,3-benzodioxol-5-ylamino)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 672[n)]	 5-(2-{[3-methoxy-5-(methylsulfonyl)phenyl]amino}-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylic acid	MS(ES): 535 (M+1) for $C_{22}H_{17}F_3N_6O_5S$. 400 MHz, DMSO-d_6: δ 3.24 (s, 3H), 3.87 (s, 3H), 7.05 (d, J = 2.64 Hz, 1H), 7.12 (t, J = 2.00 Hz, 1H), 7.70 (s, 1H), 8.03 (t, J = 1.88 Hz, 1H), 8.16 (s, 1H), 8.54-8.57 (m, 2H), 8.84 (s, 1H), 8.97 (d, J = 1.76 Hz, 1H), 10.63 (s, 1H).	**Example 665** ethyl 5-(2-{[3-methoxy-5-(methylsulfonyl)phenyl]amino}-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylate

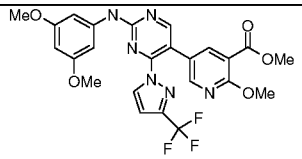
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 673[o)]	 5-(2-{[3-methoxy-5-(methylsulfonyl)phenyl]amino}-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylic acid	MS(ES): 549 (M+1) for $C_{23}H_{19}F_3N_6O_5S$. 400 MHz, DMSO-d_6: δ 2.47 (s, 3H), 3.23 (s, 3H), 3.86 (s, 3H), 6.79 (s, 1H), 7.14 (s, 1H), 7.73 (s, 1H), 7.86 (s, 1H), 8.03 (s, 1H), 8.51 (s, 1H), 8.96 (s, 1H), 9.04 (s, 1H), 10.65 (s, 1H), 13.49 (s, 1H).	**Example 666** ethyl 5-(2-{[3-methoxy-5-(methylsulfonyl)phenyl]amino}-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylate

[l)] NaOH (4 eq), THF-H_2O, RT, 4 h [m)] NaOH (2 eq), THF-H_2O, 40 °C 6-14 h [n)] $Ba(OH)_2$, dioxane-H_2O, RT, 12-24 h [o)] $Ba(OH)_2$, dioxane-H_2O, 55 °C, 1 h.

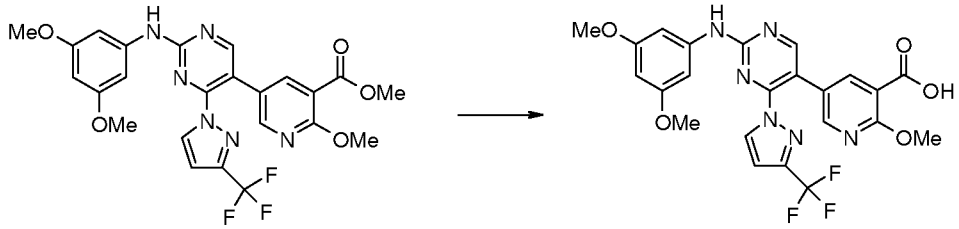
Example 674: methyl 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate



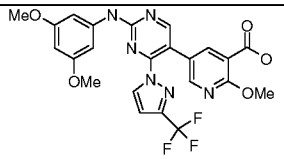
A suspension of 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 215**, 0.36 mmol, 160 mg), methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (0.36 mmol, 106 mg), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (0.073 mmol, 60 mg) and sodium carbonate (0.36 mmol, 40 mg) in acetonitrile/water (5 : 1) was degassed and heated to 100 °C for 45 min under an inert atmosphere. The reaction mass was passed through a celite bed. The solvent was concentrated *in vacuo* and the resultant crude mass was taken in EtOAc (50 mL), washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography to give the title compound (120 mg).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 674	 methyl 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 531 (M+1) for $C_{24}H_{21}F_3N_6O_5$. 400 MHz, DMSO-d_6: δ 3.73 (s, 6H), 3.76 (s, 3H), 3.93 (s, 3H), 6.20 (t, *J* = 2.20 Hz, 1H), 7.03 (d, *J* = 2.64 Hz, 1H), 7.09 (d, *J* = 2.20 Hz, 2H), 7.85 (d, *J* = 2.48 Hz, 1H), 8.27 (d, *J* = 2.48 Hz, 1H), 8.48 (t, *J* = 1.68 Hz, 1H), 8.77 (s, 1H), 10.18 (s, 1H).	**Intermediate 215** 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

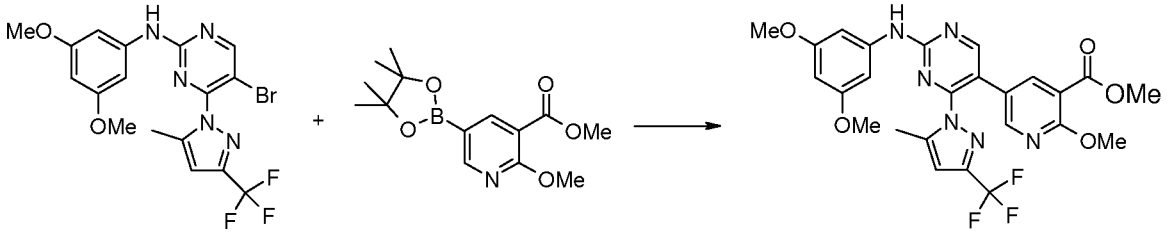
Example 675: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid



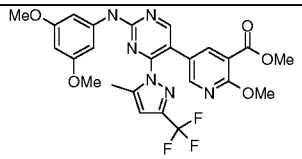
To 120 mg of methyl 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate (**Example 674**, 0.22 mmol) dissolved in a mixture of dioxane (1 mL) and water (0.33 mL), was added Barium hydroxide monohydrate (0.6 mmol, 114 mg) and allowed to stir overnight at room temperature. After completion of the reaction, the mixture was then carefully acidified with 1 N HCl and then diluted with ethyl acetate (50 mL), washed with water, brine, dried over Na_2SO_4 and concentrated to yield 70 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 675	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 517 (M+1) for $C_{23}H_{19}F_3N_6O_5$ 400 MHz, DMSO-d_6: δ 3.75 (s, 6H), 3.91 (s, 3H), 6.21 (t, J = 2.16 Hz, 1H), 7.02 (d, J = 2.64 Hz, 1H), 7.11 (d, J = 2.16 Hz, 2H), 7.77 (s, 1H), 8.16 (s, 1H), 8.43 (s, 1H), 8.76 (s, 1H), 10.17 (s, 1H).	**Example 674** methyl 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

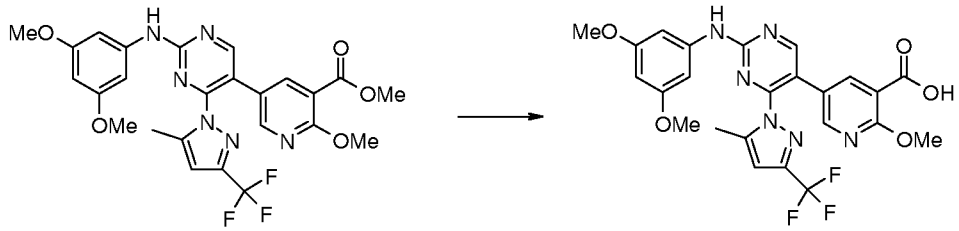
Example 676: methyl 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate



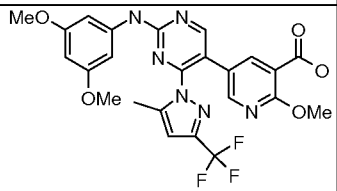
A suspension of 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 216**, 0.44 mmol, 200 mg) methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (0.48 mmol, 141 mg), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.087 mmol, 64 mg) and sodium carbonate (0.44 mmol, 46 mg) in acetonitrile/water (8:2) was degassed and heated to 90 °C for 15 min under an inert atmosphere. After completion of the reaction, the reaction mass was diluted with ethyl acetate (30 mL). The organic layer was separated, washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using ethyl acetate/hexanes (45:55) to obtain 150 mg of **Example 676**.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 676	 methyl 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 545 (M+1) for $C_{25}H_{23}F_3N_6O_5$. 400 MHz, DMSO-d_6: δ 2.29 (s, 3H), 3.71 (s, 6H), 3.74 (s, 3H), 3.91 (s, 3H), 6.21 (t, *J* = 2.16 Hz, 1H), 6.75 (s, 1H), 7.04 (d, *J* = 2.12 Hz, 2H), 7.60 (d, *J* = 2.52 Hz, 1H), 8.22 (d, *J* = 2.52 Hz, 1H), 8.93 (s, 1H), 10.21 (s, 1H).	**Intermediate 216** 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

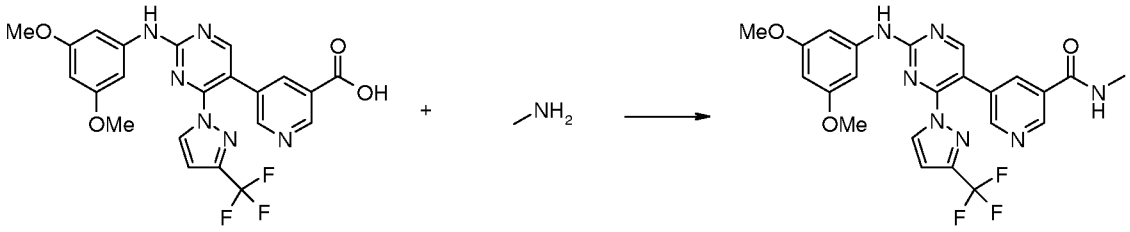
Example 677: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid



To 150 mg of methyl 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate (**Example 676**, 0.27 mmol) taken in a mixture of tetrahydrofuran (1.5 mL), was added 1 N aq. sodium hydroxide (1.07 mmol) and stirred in a room temperature for 4 h. After completion of reaction, reaction mixture was then carefully acidified with 1 N HCl and the solid that precipitated was filtered, washed with water and dried *in vacuo* to yield 120 mg **Example 677.**

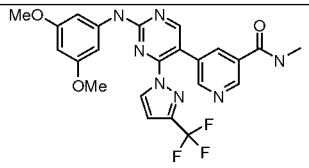
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 677	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 531 (M+1) for $C_{24}H_{21}F_3N_6O_5$. 400 MHz, DMSO-d_6: δ 2.30 (s, 3H), 3.71 (s, 6H), 3.89 (s, 3H), 6.20 (s, 1H), 6.74 (s, 1H), 7.04 (s, 2H), 7.61 (t, *J* = 1.52 Hz, 1H), 8.14 (d, *J* = 1.76 Hz, 1H), 8.92 (s, 1H), 10.20 (s, 1H), 13.10 (s, 1H).	**Example 676** methyl 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

Example 678: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-methylpyridine-3-carboxamide

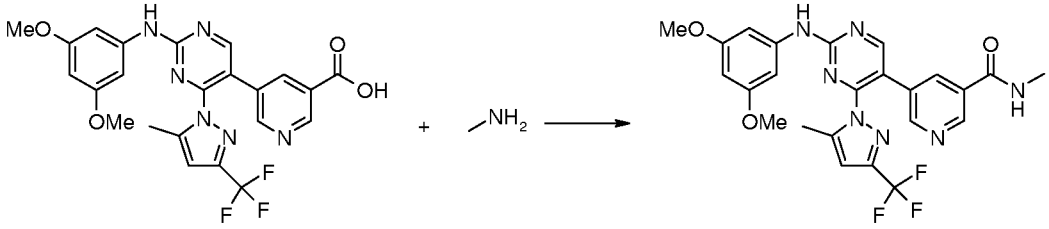


To a mixture of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid (**Example 635**, 0.56 mmol, 270 mg), triethylamine (1.67 mmol, 0.23 mL, 0.17 g) and methylamine hydrochloride (1.11 mmol, 75 mg) in dichloromethane was added T_3P in 50 % EtOAc (1.11mmol, 0.7 mL, 353 mg) at 0 °C. The reaction mixture was slowly raised to room temperature and stirred overnight. After completion of the reaction, the mixture was then diluted with dichloromethane (15 mL), and the organic layer was successively washed with water (2x20 mL), 10 % aq sodium bicarbonate solution (15 mL) and brine. The organic layer was dried over sodium sulphate and concentrated. The crude

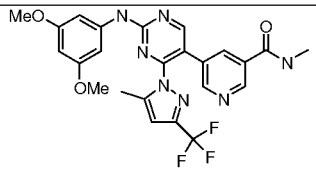
material was purified by silica gel column chromatography (230-400 mesh) using 8 % methanol/chloroform to yield 80 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 678	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-methylpyridine-3-carboxamide	MS(ES): 500 (M+1) for $C_{23}H_{20}F_3N_7O_3$. 400 MHz, DMSO-d_6: δ 2.79 (d, J = 4.44 Hz, 3H), 3.74 (s, 6H), 6.21 (t, J = 1.96 Hz, 1H), 7.04 (d, J = 2.52 Hz, 1H), 7.09 (d, J = 2.04 Hz, 2H), 8.06 (t, J = 1.88 Hz, 1H), 8.42 (d, J = 2.08 Hz, 1H), 8.50 (d, J = 1.12 Hz, 1H), 8.64 (m, J = 4.52 Hz, 1H), 8.80 (s, 1H), 8.91 (d, J = 1.84 Hz, 1H), 10.24 (s, 1H).	**Example 635** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

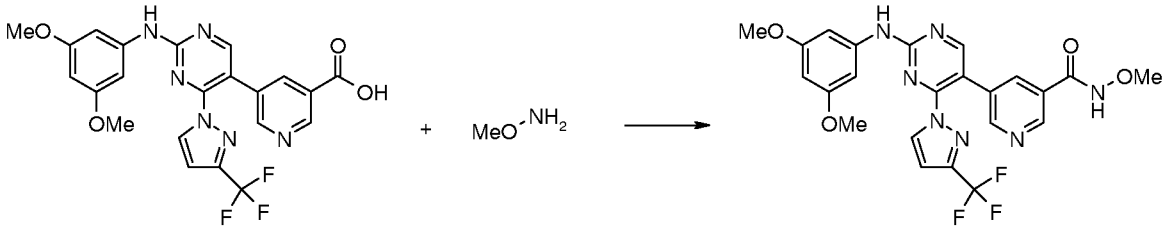
Example 679: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-methylpyridine-3-carboxamide



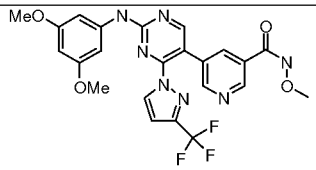
To a mixture of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid (**Example 636**, 0.35 mmol, 175 mg), triethylamine (1.05 mmol, 0.14 mL, 106 mg) and methylamine hydrochloride (0.70 mmol, 47 mg) in dichloromethane (10 mL) was added T_3P (50 % EtOAc) (0.70 mmol,0.45 mL, 223 mg) slowly at 0 °C. The reaction mixture was slowly raised to room temperature and stirred for 3 h. The reaction mixture was then diluted with dichloromethane (15 mL) and the dichloromethane layer was washed successively with water (2x20 mL), 10 % aq sodium bicarbonate solution (15 mL) and brine. The organic layer was dried over sodium sulphate, filtered, concentrated and dried to yield 120 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 679	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-methylpyridine-3-carboxamide	MS(ES): 514 (M+1) for $C_{24}H_{22}F_3N_7O_3$. 400 MHz, DMSO-d_6: δ 2.38 (s, 3H), 2.79 (d, *J* = 4.44 Hz, 3H), 3.73 (s, 6H), 6.23 (s, 1H), 6.76 (s, 1H), 7.05 (d, *J* = 1.72 Hz, 2H), 7.98 (s, 1H), 8.22 (d, *J* = 1.92 Hz, 1H), 8.63 (m, *J* = 4.56 Hz, 1H), 8.86 (d, *J* = 1.72 Hz, 1H), 8.96 (s, 1H), 10.26 (s, 1H).	**Example 636** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

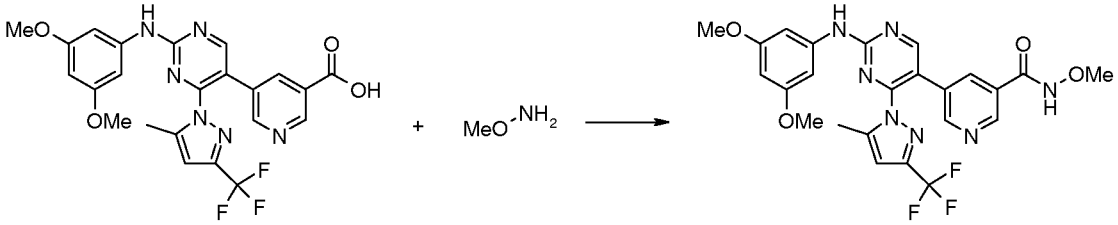
Example 680: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-methoxypyridine-3-carboxamide



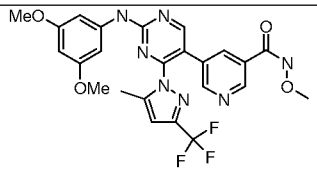
To a mixture of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid (**Example 635**, 0.41 mmol, 200 mg), triethylamine (0.82 mmol, 0.12 mL, 80 mg) and methoxylamine hydrochloride (0.5 mmol, 42 mg) in dichloromethane, was added. TBTU (0.49 mmol, 158 mg) slowly at 0 °C. The reaction mixture was slowly raised to room temperature and stirred overnight. The reaction mixture was then diluted with dichloromethane (15 mL) and the dichloromethane solution was washed successively with water (2x20 mL), 10 % aq sodium bicarbonate solution (20 mL) and brine. The organic layer was dried over sodium sulphate, and concentrated. The crude material was purified by silica gel column chromatography using 8 % methanol/chloroform to yield 90 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 680	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-methoxypyridine-3-carboxamide	MS(ES): 516 (M+1) for $C_{23}H_{20}F_3N_7O_4$. 400 MHz, DMSO-d_6: δ 3.73 (s, 3H), 3.75 (s, 6H), 6.23 (t, *J* = 2.16 Hz, 1H), 7.06 (d, *J* = 2.60 Hz, 1H), 7.11 (d, *J* = 2.16 Hz, 2H), 8.00 (s, 1H), 8.50 (d, *J* = 2.12 Hz, 1H), 8.53 (d, *J* = 1.60 Hz, 1H), 8.81 (s, 1H), 8.84 (d, *J* = 1.96 Hz, 1H), 10.26 (s, 1H), 11.97 (s, 1H).	**Example 635** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

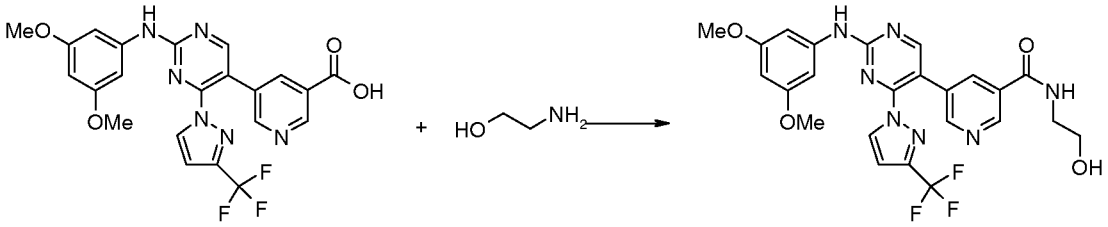
Example 681: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-methoxypyridine-3-carboxamide



To a mixture of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid (**Example 636**, 0.34 mmol, 170 mg), triethylamine (0.68 mmol, 0.1 mL) and methoxylamine hydrochloride (0.51 mmol, 43 mg) in dichloromethane, was added TBTU (131 mg, 0.41 mmol, 1.2 eq) at 0 °C. The reaction mixture was slowly raised to room temperature and stirred overnight. The reaction mixture was then diluted with dichloromethane (15 mL) and the dichloromethane solution was washed successively with water (2x20 mL), 10 % aq. sodium bicarbonate solution (20 mL) and brine. The organic layer was dried over sodium sulphate, filtered, concentrated and dried to yield 120 mg of the title compound.

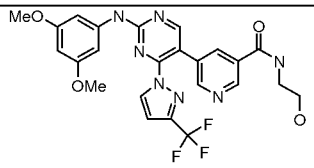
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 681	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-methoxypyridine-3-carboxamide	MS(ES): 530 (M+1) for $C_{24}H_{22}F_3N_7O_4$. 400 MHz, DMSO-d_6: δ 2.41 (s, 3H), 3.72 (s, 3H), 3.74 (s, 6H), 6.24 (t, J = 2.08 Hz, 1H), 6.78 (s, 1H), 7.06 (d, J = 1.96 Hz, 2H), 7.86 (s, 1H), 8.32 (d, J = 1.80 Hz, 1H), 8.79 (d, J = 1.84 Hz, 1H), 8.97 (s, 1H), 10.28 (s, 1H), 11.96 (s, 1H).	**Example 636** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

Example 682: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(2-hydroxyethyl)pyridine-3-carboxamide

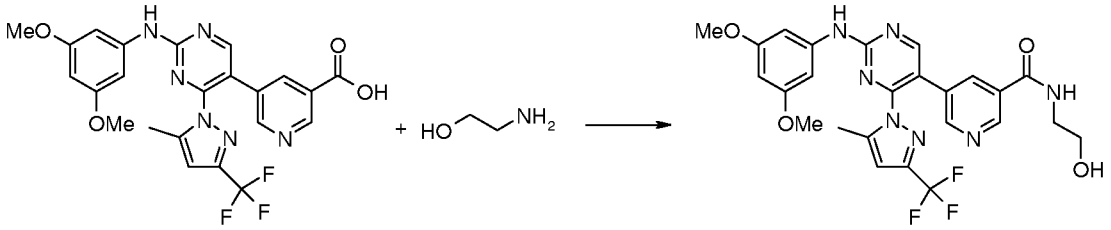


To a mixture of T_3P (4.11 mmol, 1.3 g) and Et_3N (5.14 mmol, 520 mg) taken in dry dichloromethane (20 mL), was added ethanolamine (2.03 mmol, 128 mg). Then 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid (**Example 635**, 1.03 mmol, 500 mg) in dry THF (20 mL) was added slowly for 15 min. The reaction mixture was stirred overnight at room temperature. The solvent was removed *in vacuo,* water was added and extracted with EtOAc. The organic layer was further washed with brine, dried over Na_2SO_4 and concentrated. The crude mass was purified by column chromatography (230-400 mesh) using 10 % MeOH/dichloromethane as an eluent to yield 120 mg product. The compound was further purified by RP-HPLC (Atlantis C18 column(19x250mm;10μm); using a binary solvent mixture of 0.1 % TFA in water (A)/ MeOH (B) (0-20 min: 10-65 % B, 20-30 min: 65-75 % B and 30-40 min: 75-100 % B; flow rate of 15

mL/min; Separation was monitored at 210 and 290 nm) to get 0.057 g of the pure title compound .

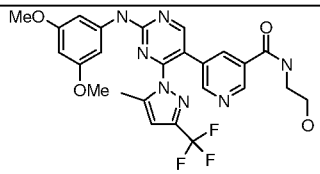
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 682	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(2-hydroxyethyl)pyridine-3-carboxamide	MS(ES): 530 (M+1) for $C_{24}H_{22}F_3N_7O_4$. 400 MHz, DMSO-d_6: δ 3.34 (q, J = 6.00 Hz, 2H), 3.51 (t, J = 6.04 Hz, 2H), 3.74 (s, 6H), 6.21 (t, J = 1.92 Hz, 1H), 7.04 (d, J = 2.52 Hz, 1H), 7.10 (d, J = 2.04 Hz, 2H), 8.14 (t, J = 1.72 Hz, 1H), 8.41 (d, J = 1.92 Hz, 1H), 8.50 (s, 1H), 8.67 (t, J = 5.48 Hz, 1H), 8.81 (s, 1H), 8.93 (d, J = 1.80 Hz, 1H), 10.25 (s, 1H).	**Example 635** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

Example 683: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(2-hydroxyethyl)pyridine-3-carboxamide

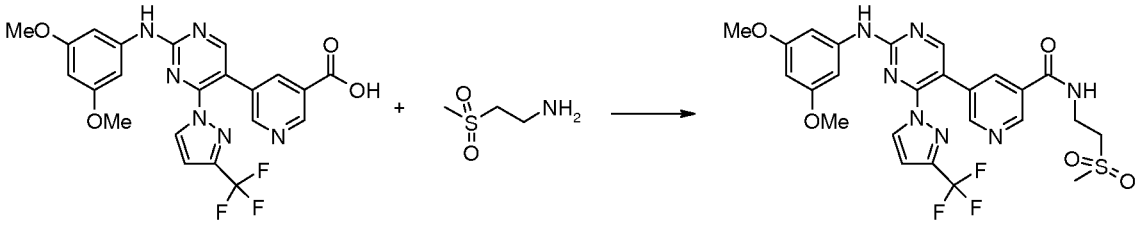


To 100 mg of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid (**Example 636**, 0.19 mmol) in dry dichloromethane (1 mL), was added Et_3N (1.19 mmol, 0.121 g) with constant stirring. To this solution, TBTU (0.51 mmol, 0.167 g) and HOBt (0.51 mmol, 0.070 g) were added and the reaction mixture was stirred for 15 min. Then ethanolamine (0.47 mmol, 0.029 g) was added and allowed to stir for 12 h. The reaction mixture was diluted with dichloromethane and the organic layer was further washed with brine and 10 % $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated. The crude mass was purified by column chromatography (230-400 mesh) using 2 % MeOH/$CHCl_3$ as an eluent to yield a solid. The solid obtained was dissolved in minimum

amount of dry dichloromethane and n-hexane was added to it and stirred for 1 h. The precipitate was filtered and dried under vacuum to give the title compound as a brown solid (20 mg).

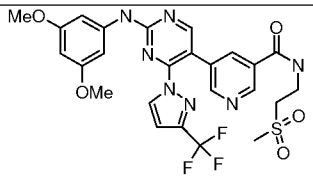
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 683	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(2-hydroxyethyl)pyridine-3-carboxamide	MS(ES): 544 (M+1) and 545 (M+2) for $C_{25}H_{24}F_3N_7O_4$. 400 MHz, DMSO-d_6: δ 2.38 (s, 3H), 3.34 (m, 2H, merges with water peak), 3.51 (q, J = 5.84 Hz, 2H), 3.72 (s, 6H), 4.76 (t, J = 5.60 Hz, 1H), 6.22 (d, J = 2.00 Hz, 1H), 6.76 (s, 1H), 7.05 (d, J = 1.80 Hz, 2H), 8.04 (d, J = 1.84 Hz, 1H), 8.18 (d, J = 1.96 Hz, 1H), 8.66 (t, J = 5.48 Hz, 1H), 8.88 (d, J = 1.80 Hz, 1H), 8.97 (s, 1H), 10.26 (s, 1H).	**Example 636** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

Example 684: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-[2-(methylsulfonyl)ethyl]pyridine-3-carboxamide

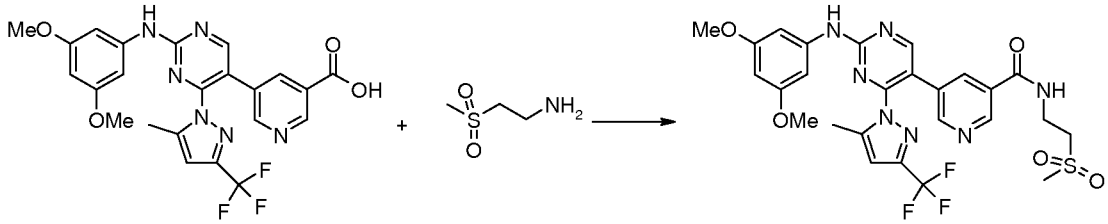


To 100 mg of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid (**Example 635**, 0.21 mmol) taken in dry dichloromethane (1 mL), was added Et_3N (1.23 mmol, 0.125 g) with constant stirring. To this solution, TBTU (0.53 mmol, 0.171 g) followed by HOBt (0.53 mmol, 0.072 g) were added and the reaction mixture was left for stirring for 15 min. Then 2-aminoethylmethylsulfone hydrochloride (0.38 mmol, 61 mg) was added and allowed to stir for 12 h. The reaction mixture was diluted with dichloromethane and the organic layer was further washed with brine and 10 % $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated. The crude mass was purified by column

chromatography (230-400 mesh) using 1.5 % MeOH/$CHCl_3$ as an eluent to yield a solid. The solid obtained was dissolved in minimum amount of dry dichloromethane and n-hexane was added to it and stirred for 1 h. The precipitate was filtered and dried under vacuum to yield the title compound as a fine white solid (30 mg).

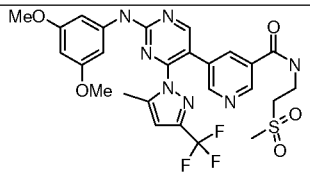
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 684	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-[2-(methylsulfonyl)ethyl]pyridine-3-carboxamide	MS(ES): 592 (M+1) for $C_{25}H_{24}F_3N_7O_5S$. 400 MHz, DMSO-d_6: δ 3.05 (s, 3H), 3.39 (t, *J* = 6.72 Hz, 2H), 3.70 (q, *J* = 6.12 Hz, 2H), 3.75 (s, 6H), 6.23 (t, *J* = 2.04 Hz, 1H), 7.06 (d, *J* = 2.52 Hz, 1H), 7.11 (d, *J* = 2.08 Hz, 2H), 8.10 (t, *J* = 2.00 Hz, 1H), 8.46 (d, *J* = 2.00 Hz, 1H), 8.52 (s, 1H), 8.81 (s, 1H), 8.93 (d, *J* = 1.88 Hz, 1H), 8.97 (t, 1H), 10.26 (s, 1H).	**Example 635** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

Example 685: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-[2-(methylsulfonyl)ethyl]pyridine-3-carboxamide

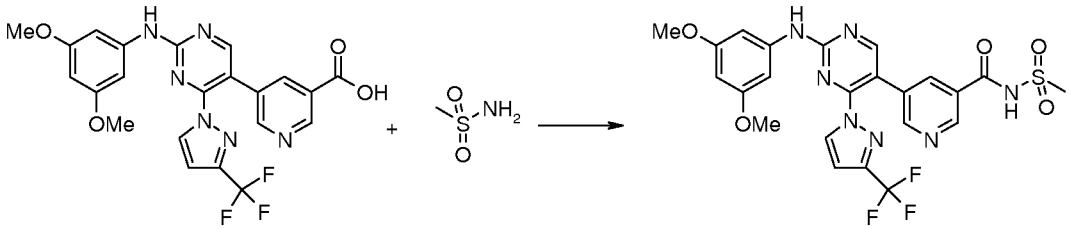


To 100 mg of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid (**Example 636**, 0.19 mmol) taken in dry dichloromethane (1mL), was added Et_3N (0.49 mmol, 0.051 g,) with constant stirring. To this HATU (0.25 mmol, 0.099 g) followed by HOAt (0.25 mmol, 0.035 g) were added and stirred for 15 min. Then 2-aminoethylmethylsulfone hydrochloride (0.19 mmol, 0.03 g) was added and the reaction mixture allowed to stir for 12 h. The reaction mixture was diluted with dichloromethane and the organic layer was further washed with brine and 10 % $NaHCO_3$ solution, dried over

Na_2SO_4 and concentrated. The crude mass was purified by column chromatography (230-400 mesh) using 3 % MeOH/$CHCl_3$ as an eluent to yield a solid. The solid obtained was dissolved in minimum amount of dry dichloromethane and n-hexane was added to it and stirred for 1 h. The precipitate was filtered and dried under vacuum to get the title compound as an off-white solid (60 mg).

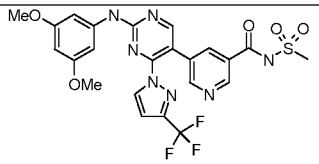
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 685	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-[2-(methylsulfonyl)ethyl]pyridine-3-carboxamide	MS(ES): 606 (M+1) for $C_{26}H_{26}F_3N_7O_5S$. 400 MHz, DMSO-d_6: δ 2.41 (s, 3H), 3.05 (s, 3H), 3.38 (t, *J* = 6.88 Hz, 2H), 3.69 (q, *J* = 6.60 Hz, 2H), 3.73 (s, 6H), 6.24 (t, *J* = 2.20 Hz, 1H), 6.78 (s, 1H), 7.06 (d, *J* = 2.08 Hz, 2H), 8.00 (t, *J* = 2.04 Hz, 1H), 8.25 (d, *J* = 2.12 Hz, 1H), 8.88 (d, *J* = 1.92 Hz, 1H), 8.96 (t, *J* = 5.44 Hz, 2H), 10.26 (s, 1H).	**Example 636** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

Example 686: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(methylsulfonyl)pyridine-3-carboxamide

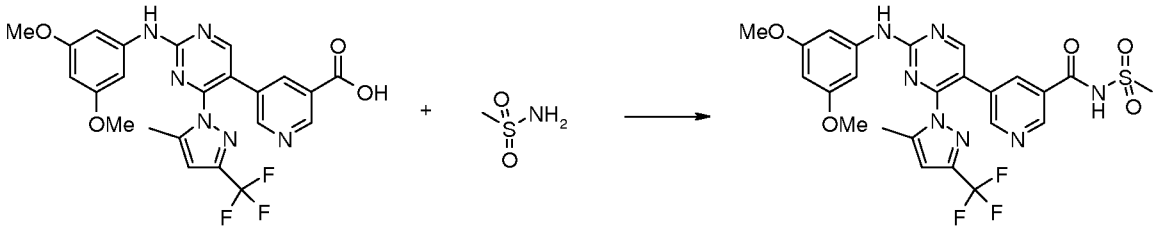


A suspension of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid (**Example 635,** 0.41 mmol, 0.2 g), methane sulfonamide (1.02 mmol, 0.097 g), HATU (0.533 mmol, 0.2 g) HOAt (0.533 mmol, 0.072 g) and triethylamine (1.23 mmol, 0.124 g) in dichloromethane (2 mL) was stirred at room temperature for 4 h. The reaction mixture was diluted with dichloromethane (5 mL), washed with 10 % sodium bicarbonate solution (5x2 mL), water (5 mL) and brine (5 mL), dried over anhydrous

Na_2SO_4 and concentrated under reduced pressure. Then the crude mass was purified by RP-HPLC (Sunfire C18 column(19x250mm;10µm); using a binary solvent mixture of 10 mM aq. NH_4OAc (A)/ MeCN (B) (0-20 min: 10-60 % B, 20-30 min: 60 % B; 30-40 min: 60-70 % B and 40-50 min: 70-100 % B; flow rate of 15 mL/min; Separation was monitored at 210 and 300 nm) to get 0.04 g of **Example 686.**

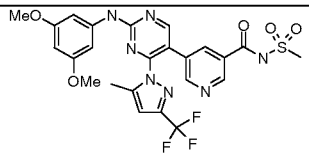
Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 686	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(methylsulfonyl)pyridine-3-carboxamide	MS(ES): 564 (M+1) for $C_{23}H_{20}F_3N_7O_5S$. 400 MHz, DMSO-d_6: δ 3.16 (s, 3H), 3.75 (s, 6H), 6.22 (d, *J* = 2.00 Hz, 1H), 7.04 (d, *J* = 2.44 Hz, 1H), 7.11 (d, *J* = 2.12 Hz, 2H), 8.18 (s, 1H), 8.42 (s, 1H), 8.49 (s, 1H), 8.80 (s, 1H), 8.98 (d, *J* = 1.80 Hz, 1H), 10.24 (s, 1H), 12.43 (s, 1H) .	**Example 635** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

Example 687: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(methylsulfonyl)pyridine-3-carboxamide

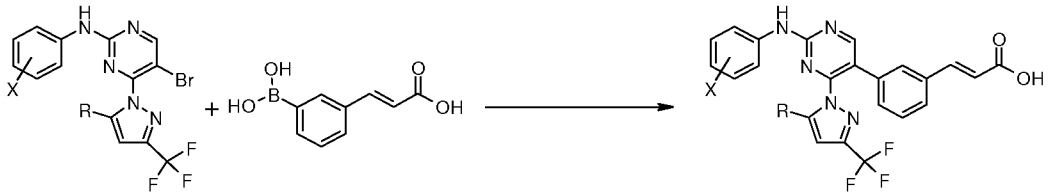


A suspension of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid (**Example 636**, 0.1 g, 0.2 mmol), methane sulfonamide (0.5 mmol, 0.047 g), HATU (0.26 mmol, 0.099 g), HOAt (0.26 mmol, 0.035 g) and triethylamine (0.6 mmol, 0.061 g) in dichloromethane (1 mL) was stirred at room temperature for 4 h. After completion of reaction, the reaction mixture was diluted with dichloromethane (2 mL) and washed with 10 % sodium bicarbonate solution (2x2 mL), water (2

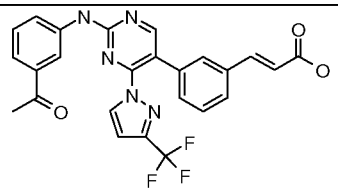
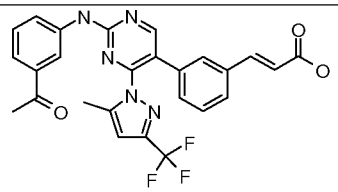
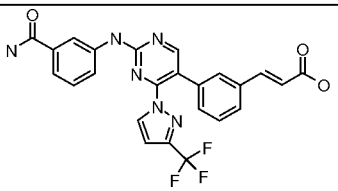
mL) and brine (2 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Then the crude mass was purified by column chromatography (230-400 mesh) using 3 % MeOH/$CHCl_3$ as an eluent to yield to get 0.04 g of **Example 687**.

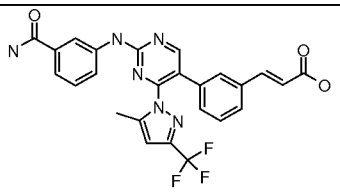
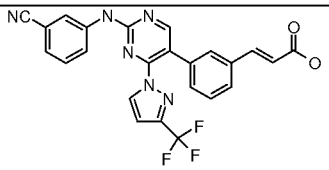
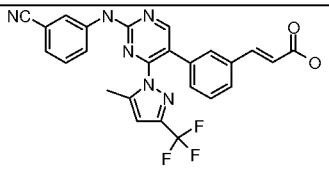
Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 687	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(methylsulfonyl)pyridine-3-carboxamide	MS(ES): 578 (M+1) for $C_{24}H_{22}F_3N_7O_5S$ 400 MHz, DMSO-d_6: δ 2.32 (s, 3H), 2.95 (s, 3H), 3.72 (s, 6H), 6.21 (t, *J* = 2.16 Hz, 1H), 6.73 (s, 1H), 7.05 (d, *J* = 2.08 Hz, 2H), 8.06 (d, *J* = 1.96 Hz, 1H), 8.10 (d, *J* = 2.04 Hz, 1H), 8.92 (m, 2H), 10.23 (s, 1H).	**Example 636** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

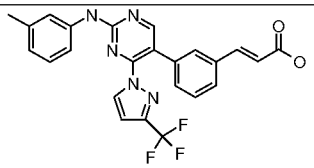
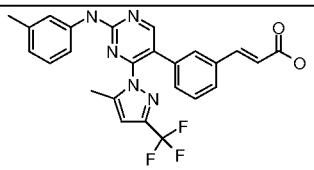
General method for the synthesis of (2*E*)-3-(3-{2-[arylamino]-4-[1*H*-azol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid derivatives



A suspension of 5-bromo-*N*-(aryl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine or 5-bromo-*N*-(aryl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (1 eq), 3-(*trans*-2-carboxyvinyl)phenylboronic acid (1.1 – 1.5 eq), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (20 mol%) and sodium carbonate (1.5-2 eq) in acetonitrile/water (4 : 1) was degassed and heated to 90 °C for 15-30 min under inert atmosphere. The solvent was removed *in vacuo* and the crude mixture taken in $CHCl_3$ was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using chloroform: methanol (9:1) as eluent to give the product. The compounds in the below table were prepared using this procedure and the starting material indicated.

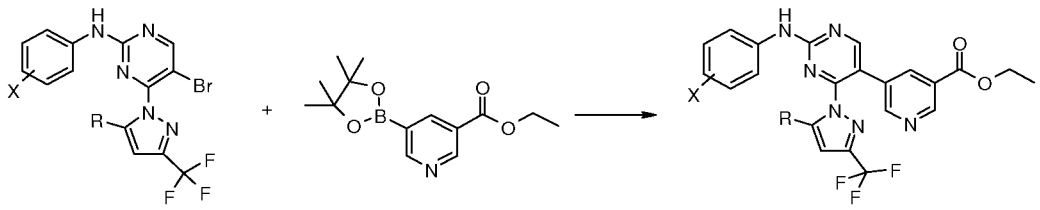
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 688	 (2*E*)-3-(3-{2-[(3-acetylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 494 (M+1) for $C_{25}H_{18}F_3N_5O_3$. 400 MHz, DMSO-d_6: δ 2.60 (s, 3H), 6.50 (d, *J* = 16.04 Hz, 1H), 7.02 (d, *J* = 1.76 Hz, 1H), 7.17 (d, *J* = 7.48 Hz, 1H), 7.38 (t, *J* = 7.68 Hz, 1H), 7.54 (m, 3H), 7.65 (d, *J* = 6.80 Hz, 2H), 7.98 (d, *J* = 8.04 Hz, 1H), 8.46 (s, 1H), 8.55 (s, 1H), 8.83 (s, 1H), 10.46 (s, 1H), 12.43 (s, 1H).	**Intermediate 257** 1-[3-({5-bromo-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)phenyl]ethanone
Example 689	 (2*E*)-3-(3-{2-[(3-acetylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 508 (M+1) for $C_{26}H_{20}F_3N_5O_3$. 400 MHz, DMSO-d_6: δ 2.24 (s, 3H), 2.56 (s, 3H), 6.44 (d, *J* = 16.04 Hz, 1H), 6.72 (s, 1H), 7.04 (d, *J* = 7.72 Hz, 1H), 7.33-7.37 (m, 2H), 7.48-7.51 (m, 2H), 7.59-7.65 (m, 2H), 7.96 (d, *J* = 7.64 Hz, 1H), 8.43 (s, 1H), 8.97 (s, 1H), 10.46 (s, 1H), 12.43 (br s, 1H).	**Intermediate 258** 1-[3-({5-bromo-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)phenyl]ethanone
Example 690	 (2*E*)-3-(3-{2-[(3-carbamoylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 495 (M+1) for $C_{24}H_{17}F_3N_6O_3$. 400 MHz, DMSO-d_6: δ 6.48 (d, *J* = 16.04 Hz, 1H), 7.00 (d, *J* = 2.44 Hz, 1H), 7.16 (d, *J* = 7.72 Hz, 1H), 7.34-7.43 (m, 4H), 7.53-7.62 (m, 3H), 7.86 (d, *J* = 8.24 Hz, 1H), 7.94 (br s, 1H), 8.38 (s, 1H), 8.51 (br s, 1H), 8.79 (s, 1H), 10.35 (s, 1H), 12.41 (s, 1H).	**Intermediate 262** 3-({5-bromo-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)benzamide

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 691	 (2*E*)-3-(3-{2-[(3-carbamoylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 509 (M+1) for $C_{25}H_{19}F_3N_6O_3$. 400 MHz, DMSO-d_6: δ 2.29 (s, 3H), 6.44 (d, J = 16.00 Hz, 1H), 6.72 (s, 1H), 7.03 (d, J = 7.76 Hz, 1H), 7.32-7.47 (m, 4H), 7.51-7.61 (m, 2H), 7.86 (d, J = 7.84 Hz, 1H), 7.93 (br s, 1H), 8.26 (s, 1H), 8.94 (s, 1H), 10.36 (s, 1H), 12.45 (br s, 1H).	**Intermediate 263** 3-({5-bromo-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)benzamide
Example 692[c)]	 (2*E*)-3-(3-{2-[(3-cyanophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 477 (M+1) for $C_{24}H_{15}F_3N_6O_2$. 400 MHz, DMSO-d_6: δ 6.48 (d, J = 16.00 Hz, 1H), 7.01 (d, J = 2.24 Hz, 1H), 7.14 (d, J = 7.56 Hz, 1H), 7.38 (t, J = 7.68 Hz, 1H), 7.47 (d, J = 7.56 Hz, 1H), 7.52-7.58 (m, 3H), 7.64 (d, J = 7.60 Hz, 1H), 8.05 (d, J = 8.08 Hz, 1H), 8.31 (s, 1H), 8.38 (s, 1H), 8.86 (s, 1H), 10.59 (s, 1H), 12.42 (s, 1H).	**Intermediate 266** 3-({5-bromo-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)benzonitrile
Example 693[c)]	 (2*E*)-3-(3-{2-[(3-cyanophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 491 (M+1) for $C_{25}H_{17}F_3N_6O_2$. 400 MHz, DMSO-d_6: δ 2.26 (s, 3H), 6.45 (d, J = 16.00 Hz, 1H), 6.73 (s, 1H), 7.05 (d, J = 7.76 Hz, 1H), 7.34-7.36 (m, 2H), 7.47-7.62 (m, 4H), 8.00 (d, J = 8.12 Hz, 1H), 8.29 (s, 1H), 9.02 (s, 1H), 10.63 (s, 1H), 12.45-12.46 (m, 1H).	**Intermediate 267** 3-({5-bromo-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)benzonitrile

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 694	 (2*E*)-3-(3-{2-[(3-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 466 (M+1) for $C_{24}H_{18}F_3N_5O_2$. 400 MHz, DMSO-d_6: δ 2.31 (s, 3H), 6.47 (d, *J* = 16.00 Hz, 1H), 6.85 (d, *J* = 7.56 Hz, 1H), 6.99 (d, *J* = 2.40 Hz, 1H), 7.14 (d, *J* = 7.96 Hz, 1H), 7.22 (t, *J* = 7.80 Hz, 1H), 7.36 (t, *J* = 7.80 Hz, 1H), 7.52 (m, 2H), 7.56-7.59 (m, 4H), 8.38 (s, 1H), 8.78 (s, 1H), 10.15 (s, 1H).	**Intermediate 259** 5-bromo-*N*-(3-methylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 695	 (2*E*)-3-(3-{2-[(3-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 480 (M+1) for $C_{25}H_{20}F_3N_5O_2$. 400 MHz, DMSO-d_6: δ 2.23 (s, 3H), 2.29 (s, 3H), 6.44 (s, 1H), 6.71 (s, 1H), 6.86 (d, *J* = 7.52 Hz, 1H), 7.04 (d, *J* = 8.04 Hz, 1H), 7.22 (t, *J* = 7.72 Hz, 1H), 7.33-7.36 (m, 2H), 7.49 (d, *J* = 16.00 Hz, 1H), 7.55-7.61 (m, 3H), 8.92 (s, 1H), 10.19 (s, 1H), 12.42 (s, 1H).	**Intermediate 260** 5-bromo-*N*-(3-methylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

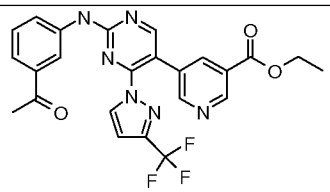
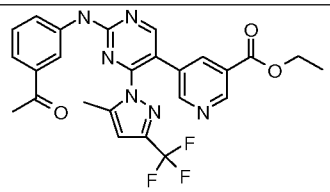
[c] 35 mol% XPHOS was also used.

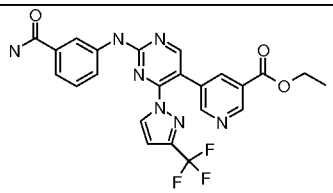
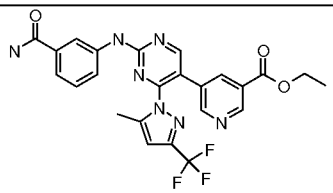
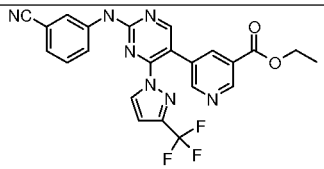
General method for the synthesis of ethyl 5-(2-{arylamino}-4-[1*H*-azol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylate

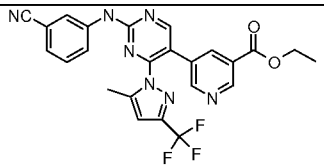
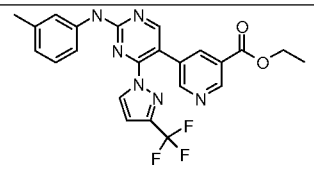
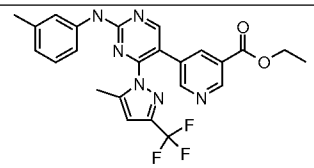


A suspension of 5-bromo-*N*-(aryl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine or 5-bromo-*N*-(aryl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (1 eq), ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (1.1–1.2 eq), [1,1′-

bis(diphenylphosphino)ferrocene]dichloropalladium(II) (10-20 mol%) and sodium carbonate (1-2 eq) in acetonitrile/water (4:1) was degassed and heated to 90 °C for 15-30 min under inert atmosphere. The solvent was removed *in vacuo* and the crude mixture taken in $CHCl_3$ was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using 30 % ethyl acetate / hexanes as eluent to give the product. The compounds in the below table were prepared using this method and the specified starting material.

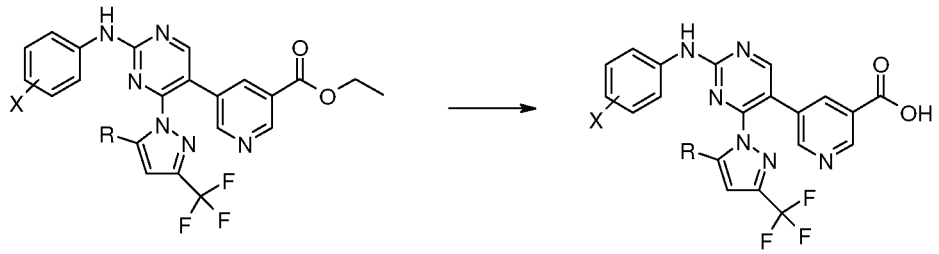
Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 696	 ethyl 5-{2-[(3-acetylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 497 (M+1) for $C_{24}H_{19}F_3N_6O_3$. 400 MHz, DMSO-d_6: δ 1.30 (t, *J* = 7.12 Hz, 3H), 2.59 (s, 3H), 4.33 (q, *J* = 7.12 Hz, 2H), 7.07 (d, *J* = 2.56 Hz, 1H), 7.52 (t, *J* = 7.76 Hz, 1H), 7.67 (d, *J* = 7.36 Hz, 1H), 7.96 (d, *J* = 8.28 Hz, 1H), 8.07 (m, 1H), 8.52 (s, 1H), 8.65 (s, 1H), 8.70 (dd, *J* = 0.76, 2.14 Hz, 1H), 8.83 (d, *J* = 0.92 Hz, 1H), 9.02 (dd, *J* = 0.84, 1.92 Hz, 1H), 10.49 (s, 1H).	**Intermediate 257** 1-[3-({5-bromo-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)phenyl]ethanone
Example 697	 ethyl 5-{2-[(3-acetylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 511 (M+1) for $C_{25}H_{21}F_3N_6O_3$. 400 MHz, DMSO-d_6: δ 1.29 (t, *J* = 7.08 Hz, 3H), 2.44 (s, 3H), 2.57 (s, 3H), 4.31 (q, *J* = 7.12 Hz, 2H), 6.78 (s, 1H), 7.51 (t, *J* = 7.84 Hz, 1H), 7.67 (d, *J* = 7.72 Hz, 1H), 7.80 (t, *J* = 1.96 Hz, 1H), 7.96 (d, *J* = 8.04 Hz, 1H), 8.41 (s, 1H), 8.61 (d, *J* = 2.08 Hz, 1H), 8.97 (d, *J* = 1.68 Hz, 1H), 9.01 (s, 1H), 10.50 (s, 1H).	**Intermediate 258** 1-[3-({5-bromo-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)phenyl]ethanone

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 698	 ethyl 5-{2-[(3-carbamoylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 498 (M+1) for $C_{23}H_{18}F_3N_7O_3$. 300 MHz, DMSO-d_6: δ 1.29 (t, J = 7.05 Hz, 3H), 4.32 (q, J = 7.05 Hz, 2H), 7.04 (d, J = 2.58 Hz, 1H), 7.38 (d, J = 4.77 Hz, 1H), 7.43 (d, J = 7.89 Hz, 1H), 7.54 (d, J = 7.86 Hz, 1H), 7.82 (d, J = 7.62 Hz, 1H), 7.96 (s, 1H), 8.06 (t, J = 2.04 Hz, 1H), 8.43 (s, 1H), 8.70 (d, J = 2.13 Hz, 2H), 8.79 (s, 1H), 9.02 (d, J = 1.92 Hz, 1H), 10.40 (s, 1H).	**Intermediate 262** 3-({5-bromo-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)benzamide
Example 699	 ethyl 5-{2-[(3-carbamoylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 512 (M+1) for $C_{24}H_{20}F_3N_7O_3$. 300 MHz, DMSO-d_6: δ 1.29 (t, J = 7.05 Hz, 3H), 2.46 (s, 3H), 4.30 (q, J = 6.99 Hz, 2H), 6.76 (s, 1H), 7.35 (br s, 1H), 7.41 (t, J = 8.13 Hz, 1H), 7.53 (d, J = 8.07 Hz, 1H), 7.78-7.85 (m, 2H), 7.93 (br s, 1H), 8.27 (s, 1H), 8.59 (d, J = 2.19 Hz, 1H), 8.97 (d, J = 3.06 Hz, 2H), 10.40 (s, 1H)	**Intermediate 263** 3-({5-bromo-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)benzamide
Example 700[d)]	 ethyl 5-{2-[(3-cyanophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 480 (M+1) for $C_{23}H_{16}F_3N_7O_2$. 400 MHz, DMSO-d_6: δ 1.30 (t, J = 7.04 Hz, 3H), 4.33 (q, J = 7.12 Hz, 2H), 7.07 (d, J = 2.60 Hz, 1H), 7.50 (dd, J = 1.04, 7.62 Hz, 1H), 7.59 (t, J = 8.12 Hz, 1H), 8.04-8.08 (m, 2H), 8.27 (s, 1H), 8.59 (s, 1H), 8.70 (m, 1H), 8.88 (s, 1H), 9.03-9.04 (m, 1H), 10.63 (s, 1H).	**Intermediate 266** 3-({5-bromo-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)benzonitrile

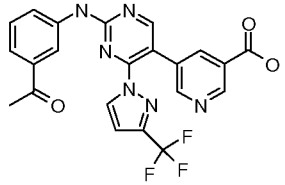
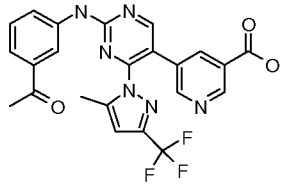
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 701[d]	 ethyl 5-{2-[(3-cyanophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 494 (M+1) for $C_{24}H_{18}F_3N_7O_2$. 400 MHz, DMSO-d_6: δ 1.31 (t, J = 7.08 Hz, 3H), 2.44 (s, 3H), 4.32 (q, J = 7.12 Hz, 2H), 6.81 (s, 1H), 7.50-7.52 (m, 1H), 7.59 (t, J = 8.04 Hz, 1H), 7.82 (t, J = 2.08 Hz, 1H), 8.00-8.02 (m, 1H), 8.29 (s, 1H), 8.63 (d, J = 2.20 Hz, 1H), 9.00 (d, J = 1.96 Hz, 1H), 9.06 (s, 1H), 10.67 (s, 1H).	**Intermediate 267** 3-({5-bromo-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)benzonitrile
Example 702	 ethyl 5-{2-[(3-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	Taken to the next step on the basis of LCMS. MS(ES): 469 (M+1) for $C_{23}H_{19}F_3N_6O_2$.	**Intermediate 259** 5-bromo-*N*-(3-methylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 703	 ethyl 5-{2-[(3-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 483 (M+1) for $C_{24}H_{21}F_3N_6O_2$. 400 MHz, DMSO-d_6: δ 1.31 (t, J = 7.12 Hz, 3H), 2.31 (s, 3H), 2.43 (s, 3H), 4.28 (q, J = 7.08 Hz, 2H), 6.78 (s, 1H), 6.89 (d, J = 7.36 Hz, 1H), 7.24 (t, J = 7.72 Hz, 1H), 7.55 (s, 1H), 7.57 (s, 1H), 7.79 (t, J = 2.12 Hz, 1H), 8.61 (d, J = 2.24 Hz, 1H), 8.97 (s, 1H), 8.98 (d, J = 2.00 Hz, 1H), 10.25 (s, 1H).	**Intermediate 260** 5-bromo-*N*-(3-methylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

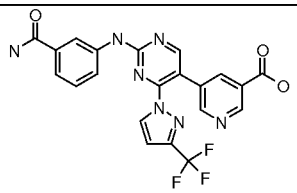
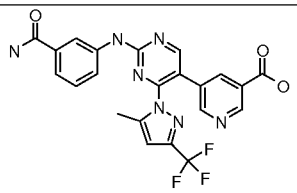
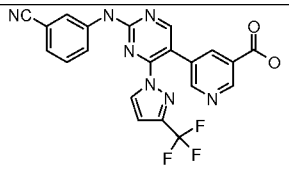
[d] 35 mol% XPHOS was also used.

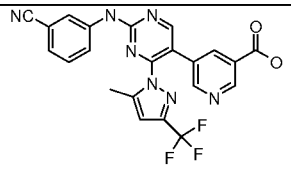
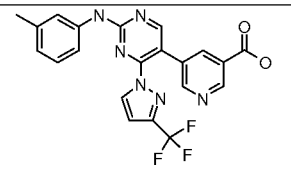
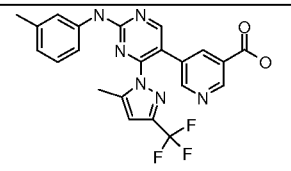
General method for the synthesis of 5-{2-(arylamino)-4-[1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid



To 1 eq of ethyl 5-(2-{arylamino}-4-[1*H*-azol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylate taken in dioxane and water, was added sodium hydroxide (2- 2.5 eq) and stirred at RT for 4 h. The reaction mixture was carefully acidified with 1 N HCl and the solid that precipitated was filtered, washed with water and dried *in vacuo* to yield the desired carboxylic acid.

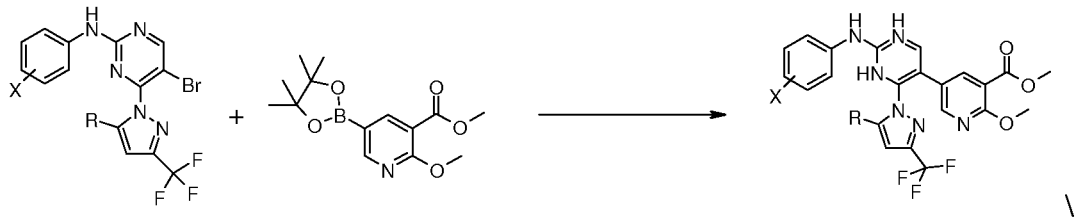
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 704	 5-{2-[(3-acetylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 469 (M+1) for $C_{22}H_{15}F_3N_6O_3$. 400 MHz, DMSO-d_6: δ 2.59 (s, 3H), 7.06 (d, *J* = 2.56 Hz, 1H), 7.52 (t, *J* = 7.84 Hz, 1H), 7.66 (d, *J* = 7.64 Hz, 1H), 7.97 (d, *J* = 7.88 Hz, 1H), 8.05 (s, 1H), 8.52 (s, 1H), 8.64 (s, 1H), 8.66 (d, *J* = 2.08 Hz, 1H), 8.82 (s, 1H), 9.00 (d, *J* = 1.68 Hz, 1H), 10.48 (s, 1H), 13.41 (br s, 1H).	**Example 696** ethyl 5-{2-[(3-acetylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 705[e)]	 5-{2-[(3-acetylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 483 (M+1) for $C_{23}H_{17}F_3N_6O_3$. 400 MHz, DMSO-d_6: δ 2.44 (s, 3H), 2.57 (s, 3H), 6.77 (s, 1H), 7.52 (t, *J* = 7.88 Hz, 1H), 7.67 (d, *J* = 7.80 Hz, 1H), 7.84 (t, *J* = 2.00 Hz, 1H), 7.97 (d, *J* = 6.84 Hz, 1H), 8.41 (s, 1H), 8.49 (s, 1H), 8.95 (d, *J* = 1.84 Hz, 1H), 8.98 (s, 1H), 10.49 (s, 1H), 13.60 (br s, 1H).	**Example 697** ethyl 5-{2-[(3-acetylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 706	 5-{2-[(3-carbamoylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 470 (M+1) for $C_{21}H_{14}F_3N_7O_3$. 400 MHz, DMSO-d_6: δ 7.04 (s, 1H), 7.38 (s, 1H), 7.43 (t, J = 7.84 Hz, 1H), 7.55 (d, J = 7.84 Hz, 1H), 7.84 (d, J = 7.76 Hz, 1H), 7.96 (s, 1H), 8.06 (s, 1H), 8.43 (s, 1H), 8.68 (d, J = 7.52 Hz, 2H), 8.79 (s, 1H), 9.01 (s, 1H), 10.39 (s, 1H).	**Example 698** ethyl 5-{2-[(3-carbamoylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 707[f]	 5-{2-[(3-carbamoylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 484 (M+1) for $C_{22}H_{16}F_3N_7O_3$. 400 MHz, DMSO-d_6: δ 2.48 (s, 3H), 6.76 (s, 1H), 7.36 (br s, 1H), 7.42 (t, J = 7.88 Hz, 1H), 7.54 (d, J = 7.60 Hz, 1H), 7.82-7.86 (m, 2H), 7.94 (s, 1H), 8.27 (s, 1H), 8.53 (d, J = 2.00 Hz, 1H), 8.95 (m, 2H), 10.40 (s, 1H), 13.47 (br s, 1H) .	**Example 699** ethyl 5-{2-[(3-carbamoylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 708[f]	 5-{2-[(3-cyanophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 452 (M+1) for $C_{21}H_{12}F_3N_7O_2$. 400 MHz, DMSO-d_6: δ 7.07 (d, J = 1.84 Hz, 1H), 7.50 (d, J = 7.48 Hz, 1H), 7.59 (t, J = 8.04 Hz, 1H), 8.04 (s, 1H), 8.08 (d, J = 8.16 Hz, 1H), 8.28 (s, 1H), 8.59 (s, 1H), 8.67 (s, 1H), 8.88 (s, 1H), 9.02 (s, 1H), 10.63 (s, 1H), 13.46 (br s, 1H).	**Example 700** ethyl 5-{2-[(3-cyanophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

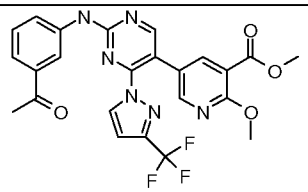
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 709[g)]	 5-{2-[(3-cyanophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES):466 (M+1) for $C_{22}H_{14}F_3N_7O_2$. 400 MHz, DMSO-d_6: δ 2.44 (s, 3H), 6.78 (s, 1H), 7.49 (d, *J* = 7.64 Hz, 1H), 7.57 (t, *J* = 8.08 Hz, 1H), 7.84 (d, *J* = 1.84 Hz, 1H), 8.00 (d, *J* = 8.40 Hz, 1H), 8.27 (s, 1H), 8.55 (s, 1H), 8.96 (s, 1H), 9.03 (s, 1H), 10.64 (s, 1H), 13.46 (br s, 1H).	**Example 701** ethyl 5-{2-[(3-cyanophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 710[g)]	 5-{2-[(3-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 441 (M+1) for $C_{21}H_{15}F_3N_6O_2$. 400 MHz, DMSO-d_6: δ 2.33 (s, 3H), 6.88 (d, *J* = 7.40 Hz, 1H), 7.04 (d, *J* = 2.64 Hz, 1H), 7.25 (t, *J* = 7.68 Hz, 1H), 7.60 (s, 1H), 7.62 (s, 1H), 8.02 (t, *J* = 2.04 Hz, 1H), 8.56 (s, 1H), 8.64 (s, 1H), 8.79 (s, 1H), 9.00 (d, *J* = 1.92 Hz, 1H), 10.21 (s, 1H), 13.44 (s, 1H).	**Example 702** ethyl 5-{2-[(3-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 711[f)]	 5-{2-[(3-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 455 (M+1) for $C_{22}H_{17}F_3N_6O_2$. 400 MHz, DMSO-d_6: δ 2.31 (s, 3H), 2.44 (s, 3H), 6.77 (s, 1H), 6.88 (d, *J* = 7.44 Hz, 1H), 7.24 (t, *J* = 8.12 Hz, 1H), 7.55 (s, 1H), 7.57 (s, 1H), 7.82 (t, *J* = 1.84 Hz, 1H), 8.54 (d, *J* = 1.96 Hz, 1H), 8.95-8.96 (m, 2H), 10.23 (s, 1H), 13.42 (s, 1H).	**Example 703** ethyl 5-{2-[(3-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

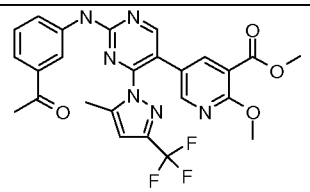
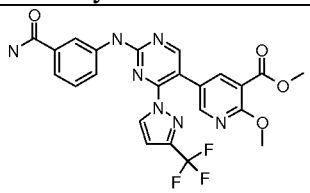
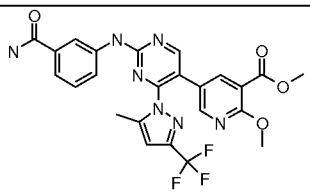
[e)] NaOH (2.5 eq), MeCN-H_2O, reflux, 15 min [f)] NaOH (2.5 eq), THF-H_2O, RT, 5 h [g)] $Ba(OH)_2$ (2 eq), dioxane-H_2O, RT.

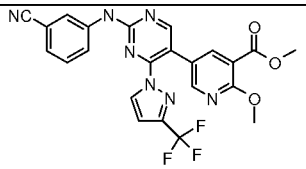
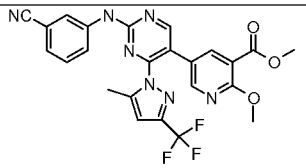
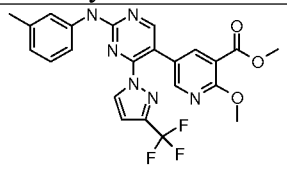
General method for the synthesis of methyl 5-(2-{arylamino}-4-[1*H*-azol-1-yl]pyrimidin-5-yl)-2-methoxypyridine-3-carboxylate

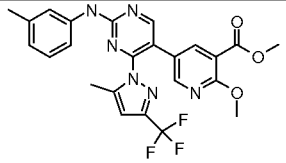


A suspension of 5-bromopyrimidine derivative (1 eq), methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (1.1–1.2 eq), [1,1′-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (10-20 mol%) and sodium carbonate (1-2 eq) in acetonitrile/water (4:1) was degassed and heated to 90 °C for 15-30 min under inert atmosphere. The solvent was removed *in vacuo* and the crude mixture taken in $CHCl_3$ was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using 50 % ethyl acetate / hexanes as eluent to give the product. The compounds in the below table were prepared using this method and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 712	 methyl 5-{2-[(3-acetylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 513 (M+1) for $C_{24}H_{19}F_3N_6O_4$. 300 MHz, DMSO-d_6: δ 2.58 (s, 3H), 3.76 (s, 3H), 3.94 (s, 3H), 7.04 (s, 1H), 7.50 (t, *J* = 7.80 Hz, 1H), 7.65 (d, *J* = 7.95 Hz, 1H), 7.88 (d, *J* = 2.43 Hz, 1H), 7.95 (d, *J* = 8.04 Hz, 1H), 8.28 (d, *J* = 2.43 Hz, 1H), 8.51 (s, 1H), 8.59 (s, 1H), 8.78 (s, 1H), 10.41 (s, 1H).	**Intermediate 257** 1-[3-({5-bromo-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)phenyl]ethanone

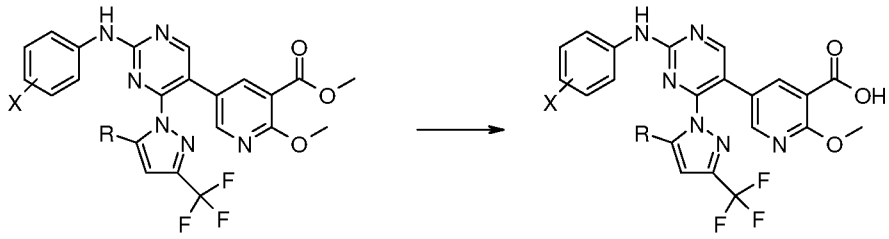
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 713	 methyl 5-{2-[(3-acetylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 527 (M+1) for $C_{25}H_{21}F_3N_6O_4$. 300 MHz, DMSO-d_6: δ 2.34 (s, 3H), 2.56 (s, 3H), 3.74 (s, 3H), 3.91 (s, 3H), 7.49 (t, J = 7.95 Hz, 1H), 7.60 (d, J = 2.31 Hz, 1H), 7.64 (d, J = 7.86 Hz, 1H), 7.95 (d, J = 8.10 Hz, 1H), 8.22 (d, J = 2.34 Hz, 1H), 8.30 (s, 1H), 8.40 (s, 1H), 8.95 (s, 1H), 10.44 (s, 1H).	**Intermediate 258** 1-[3-({5-bromo-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)phenyl]ethanone
Example 714	 methyl 5-{2-[(3-carbamoylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 514 (M+1) for $C_{23}H_{18}F_3N_7O_4$. 300 MHz, DMSO-d_6: δ 3.76 (s, 3H), 3.93 (s, 3H), 7.02 (d, J = 2.55 Hz, 1H), 7.37 (d, J = 4.26 Hz, 1H), 7.42 (d, J = 7.71 Hz, 1H), 7.53 (d, J = 7.89 Hz, 1H), 7.82 (d, J = 8.58 Hz, 1H), 7.88 (d, J = 2.40 Hz, 1H), 7.95 (s, 1H), 8.28 (d, J = 2.46 Hz, 1H), 8.40 (s, 1H), 8.64 (s, 1H), 8.75 (s, 1H), 10.33 (s, 1H).	**Intermediate 262** 3-({5-bromo-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)benzamide
Example 715	 methyl 5-{2-[(3-carbamoylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 528 (M+1) for $C_{24}H_{20}F_3N_7O_4$. 400 MHz, DMSO-d_6: δ 2.39 (s, 3H), 3.75 (s, 3H), 3.91 (s, 3H), 6.68 (d, J = 8.28 Hz, 1H), 6.77 (s, 1H), 7.36 (br s, 1H), 7.42 (t, J = 7.76 Hz, 1H), 7.61 (d, J = 2.48 Hz, 1H), 7.85 (d, J = 8.68 Hz, 1H), 7.94 (br s, 1H), 8.23 (d, J = 2.48 Hz, 1H), 8.27 (s, 1H), 8.94 (s, 1H), 10.37 (s, 1H).	**Intermediate 263** 3-({5-bromo-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)benzamide

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 716[h)]	 methyl 5-{2-[(3-cyanophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 496 (M+1) for $C_{23}H_{16}F_3N_7O_3$. 400 MHz, DMSO-d_6: δ 3.76 (s, 3H), 3.94 (s, 3H), 7.05 (d, J = 2.48 Hz, 1H), 7.46-7.49 (m, 1H), 7.57 (t, J = 8.16 Hz, 1H), 7.86 (d, J = 2.48 Hz, 1H), 8.04-8.06 (m, 1H), 8.27-8.31 (m, 2H), 8.53 (s, 1H), 8.83 (s, 1H), 10.57 (s, 1H).	**Intermediate 266** 3-({5-bromo-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)benzonitrile
Example 717[h)]	 methyl 5-{2-[(3-cyanophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 510 (M+1) for $C_{24}H_{18}F_3N_7O_3$. 400 MHz, DMSO-d_6: δ 2.33 (s, 3H), 3.74 (s, 3H), 3.91 (s, 3H), 6.77 (s, 1H), 7.48 (dd, J = 1.16, 7.60 Hz, 1H), 7.56 (t, J = 8.12 Hz, 1H), 7.61 (d, J = 2.52 Hz, 1H), 7.97-8.00 (m, 1H), 8.23 (d, J = 2.52 Hz, 1H), 8.27 (s, 1H), 9.00 (s, 1H), 10.61 (s, 1H).	**Intermediate 267** 3-({5-bromo-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-yl}amino)benzonitrile
Example 718	 methyl 2-methoxy-5-{2-[(3-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	Taken to the next step on the basis of LCMS. MS(ES): 485 (M+1) for $C_{23}H_{19}F_3N_6O_3$.	**Intermediate 259** 5-bromo-*N*-(3-methylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 719	 methyl 2-methoxy-5-{2-[(3-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 499 (M+1) for $C_{24}H_{21}F_3N_6O_3$. 400 MHz, DMSO-d_6: δ 2.29 (s, 3H), 2.32 (s, 3H), 3.74 (s, 3H), 3.91 (s, 3H), 6.74 (s, 1H), 6.86 (d, J = 7.68 Hz, 1H), 7.22 (t, J = 8.80 Hz, 1H), 7.53-7.59 (m, 3H), 8.21 (d, J = 2.52 Hz, 1H), 8.90 (s, 1H), 10.18 (s, 1H).	**Intermediate 260** 5-bromo-*N*-(3-methylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

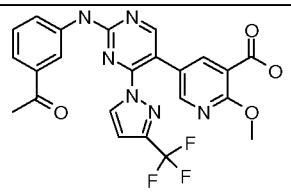
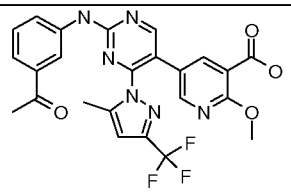
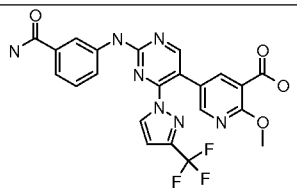
[h)] 35 mol% XPHOS was also used.

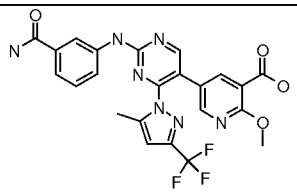
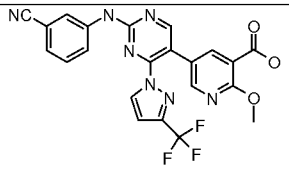
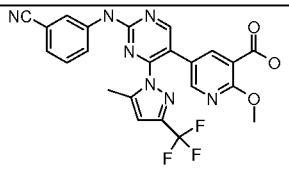
General procedure for the synthesis of 5-{2-(arylamino)-4-[1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

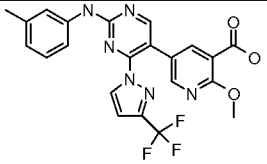
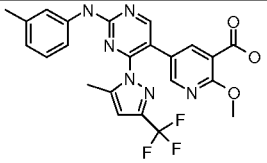


To 1 eq of methyl 5-(2-{arylamino}-4-[1*H*-azol-1-yl]pyrimidin-5-yl)-2-methoxypyridine-3-carboxylate taken in dioxane (5 mL), was added 1 N aq. sodium hydroxide or Barium hydroxide (2- 6 eqs) and was heated to 60 °C for 1 h. The reaction mixture was carefully acidified with 1 N HCl and the solid that precipitated was filtered, washed with water and dried *in vacuo* to yield the desired carboxylic acid. The compounds in the below table were prepared using this method and the specified starting material.

5

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 720	 5-{2-[(3-acetylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 499 (M+1) for $C_{23}H_{17}F_3N_6O_4$. 400 MHz, DMSO-d_6: δ 2.60 (s, 3H), 3.93 (s, 3H), 7.05 (d, J = 2.44 Hz, 1H), 7.52 (t, J = 7.88 Hz, 1H), 7.66 (d, J = 7.68 Hz, 1H), 7.83 (d, J = 2.04 Hz, 1H), 7.97 (d, J = 7.76 Hz, 1H), 8.22 (s, 1H), 8.53 (s, 1H), 8.58 (s, 1H), 8.79 (s, 1H), 10.43 (s, 1H), 12.96 (br s, 1H).	**Example 713** methyl 5-{2-[(3-acetylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate
Example 721	 5-{2-[(3-acetylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 513 (M+1) for $C_{24}H_{19}F_3N_6O_4$. 400 MHz, DMSO-d_6: δ 2.34 (s, 3H), 2.57 (s, 3H), 3.88 (s, 3H), 6.76 (s, 1H), 7.51 (t, J = 7.88 Hz, 1H), 7.58 (d, J = 2.28 Hz, 1H), 7.65 (d, J = 7.72 Hz, 1H), 7.97 (d, J = 7.56 Hz, 1H), 8.04 (s, 1H), 8.42 (s, 1H), 8.94 (s, 1H), 10.45 (s, 1H), 13.19 (s, 1H).	**Example 714** methyl 5-{2-[(3-acetylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate
Example 722[1)]	 5-{2-[(3-carbamoylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 500 (M+1) for $C_{22}H_{16}F_3N_7O_4$. 400 MHz, DMSO-d_6: δ 3.93 (s, 3H), 7.03 (s, 1H), 7.38- 7.43 (m, 2H), 7.53 (d, J = 7.52 Hz, 1H), 7.82-7.85 (m, 2H), 7.96 (s, 1H), 8.25 (s, 1H), 8.40 (s, 1H), 8.63 (s, 1H), 8.75 (s, 1H), 10.34 (s, 1H), 12.91 (br s, 1H).	**Example 715** methyl 5-{2-[(3-carbamoylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

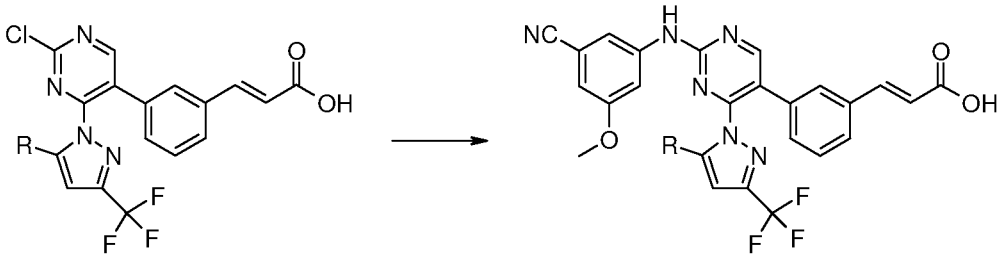
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 723[i)]	 5-{2-[(3-carbamoylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 514 (M+1) for $C_{23}H_{18}F_3N_7O_4$. 400 MHz, DMSO-d_6: δ 2.39 (s, 3H), 3.89 (s, 3H), 6.74 (s, 1H), 7.35 (br s, 1H), 7.40 (t, J = 7.88 Hz, 1H), 7.52 (d, J = 7.80 Hz, 1H), 7.61 (d, J = 2.52 Hz, 1H), 7.84 (d, J = 7.84 Hz, 1H), 7.93 (br s, 1H), 8.15 (d, J = 2.44 Hz, 1H), 8.25 (t, J = 1.76 Hz, 1H), 8.91 (s, 1H), 10.34 (s, 1H), 12.96 (br s, 1H) .	**Example 716** methyl 5-{2-[(3-carbamoylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate
Example 724[j)]	 5-{2-[(3-cyanophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 482 (M+1) for $C_{22}H_{14}F_3N_7O_3$. 400 MHz, DMSO-d_6: δ 3.93 (s, 3H), 7.04 (d, J = 2.52 Hz, 1H), 7.48 (d, J = 7.64 Hz, 1H), 7.57 (t, J = 8.12 Hz, 1H), 7.83 (d, J = 2.48 Hz, 1H), 8.05 (d, J = 7.68 Hz, 1H), 8.25 (d, J = 2.44 Hz, 1H), 8.28 (s, 1H), 8.53 (s, 1H), 8.83 (s, 1H), 10.57 (s, 1H), 12.96 (br s, 1H).	**Example 717** methyl 5-{2-[(3-cyanophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate
Example 725[j)]	 5-{2-[(3-cyanophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 496 (M+1) for $C_{23}H_{16}F_3N_7O_3$. 400 MHz, DMSO-d_6: δ 2.34 (s, 3H), 3.90 (s, 3H), 6.77 (s, 1H), 7.48 (d, J = 7.52 Hz, 1H), 7.57 (t, J = 8.12 Hz, 1H), 7.62 (d, J = 2.08 Hz, 1H), 7.99 (d, J = 8.80 Hz, 1H), 8.16 (d, J = 1.76 Hz, 1H), 8.27 (s, 1H), 9.00 (s, 1H), 10.60 (s, 1H), 13.00 (br s, 1H).	**Example 718** methyl 5-{2-[(3-cyanophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 726	 2-methoxy-5-{2-[(3-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 471 (M+1) for $C_{22}H_{17}F_3N_6O_3$. 400 MHz, DMSO-d_6: δ 2.31 (s, 3H), 3.92 (s, 3H), 6.85 (d, J = 7.68 Hz, 1H), 7.01 (s, 1H), 7.23 (t, J = 8.16 Hz, 1H), 7.58 (s, 1H), 7.60 (s, 1H), 7.81 (s, 1H), 8.22 (s, 1H), 8.50 (s, 1H), 8.74 (s, 1H), 10.13 (s, 1H), 12.92 (s, 1H).	**Example 719** methyl 2-methoxy-5-{2-[(3-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 727[k)]	 2-methoxy-5-{2-[(3-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 485 (M+1) for $C_{23}H_{19}F_3N_6O_3$. 400 MHz, DMSO-d_6: δ 2.29 (s, 3H), 2.34 (s, 3H), 3.90 (s, 3H), 6.74 (s, 1H), 6.86 (d, J = 7.52 Hz, 1H), 7.22 (t, J = 8.68 Hz, 1H), 7.54-7.55 (m, 2H), 7.61 (d, J = 2.52 Hz, 1H), 8.15 (d, J = 2.48 Hz, 1H), 8.89 (s, 1H), 10.16 (s, 1H), 12.95 (s, 1H).	**Example 720** methyl 2-methoxy-5-{2-[(3-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

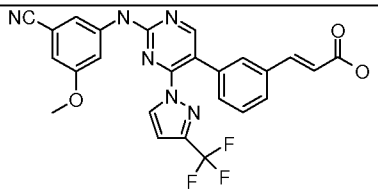
[i)] NaOH (2 eq), THF-H_2O, RT, 5 h [j)] $Ba(OH)_2$ (2 eq), dioxane-H_2O, RT [k)] NaOH (4 eq), THF-H_2O, RT, 4 h.

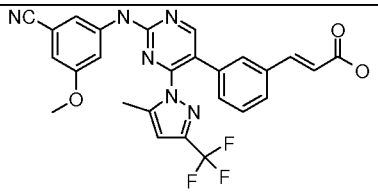
Example 728: (2*E*)-3-(3-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid

Example 729: (2*E*)-3-(3-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid



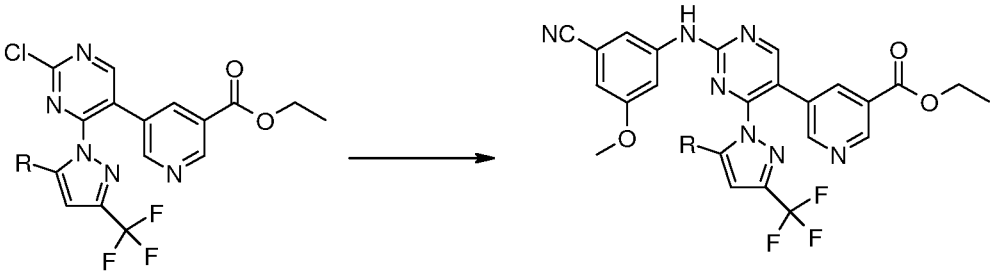
A suspension of (2*E*)-3-(3-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid (**Intermediate 268**, 1 eq) or (2*E*)-3-(3-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid (**Intermediate 269**, 1 eq), 3-amino-5-methoxybenzonitrile (1 eq), tris(dibenzylideneacetone)dipalladium(0) (10 mol%), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (20 mol%) and sodium carbonate (2 eq) in acetonitrile/water (5:1) was heated to 90 °C for 30 min. The reaction mixture was concentrated, the residue was taken in ethyl acetate and washed with water and brine. The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using MeOH/$CHCl_3$ as an eluent to give the product. The compounds in the below table were prepared using this method and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 728	 (2*E*)-3-(3-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 507 (M+1) for $C_{25}H_{17}F_3N_6O_3$. 400 MHz, DMSO-d_6: δ 3.82 (s, 3H), 6.48 (d, *J* = 16.04 Hz, 1H), 7.00 (d, *J* = 2.56 Hz, 1H), 7.09 (t, *J* = 1.80 Hz, 1H), 7.14 (d, *J* = 7.96 Hz, 1H), 7.38 (t, *J* = 7.72 Hz, 1H), 7.52-7.56 (m, 2H), 7.64 (d, *J* = 7.72 Hz, 1H), 7.83 (m, 2H), 8.32 (d, *J* = 1.72 Hz, 1H), 8.87 (s, 1H), 10.56 (s, 1H), 12.43 (br s, 1H).	**Intermediate 268** (2*E*)-3-(3-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 729	 (2*E*)-3-(3-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid	MS(ES): 521 (M+1)for $C_{26}H_{19}F_3N_6O_3$. 400 MHz, DMSO-d_6: δ 2.21 (s, 3H), 3.81 (s, 3H), 6.45 (d, *J* = 16.04 Hz, 1H), 6.74 (s, 1H), 7.06 (d, *J* = 7.88 Hz, 1H), 7.11 (dd, *J* = 1.24, 2.16 Hz, 1H), 7.35-7.39 (m, 2H), 7.51 (d, *J* = 16.04 Hz, 1H), 7.63 (d, *J* = 7.88 Hz, 1H), 7.75 (t, *J* = 2.12 Hz, 1H), 7.83 (s, 1H), 9.04 (s, 1H), 10.61 (s, 1H), 12.46 (br s, 1H).	**Intermediate 269** (2*E*)-3-(3-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}phenyl)prop-2-enoic acid

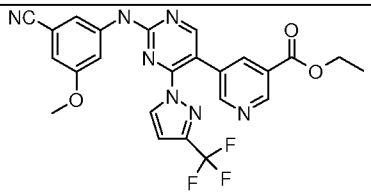
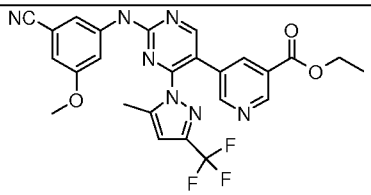
Example 730: ethyl 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

Example 731: ethyl 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate



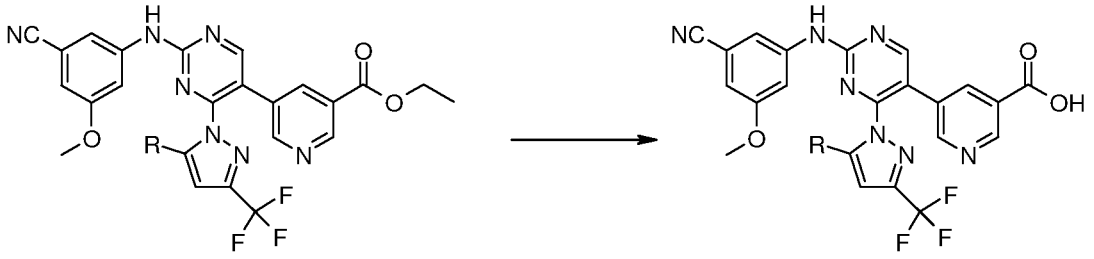
A suspension of ethyl 5-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate (**Intermediate 270**, 1 eq) or ethyl 5-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate (**Intermediate 271**, 1 eq), 3-amino-5-methoxybenzonitrile (1.2 eq), tris(dibenzylideneacetone)dipalladium(0) (10 mol%), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (20 mol%) and sodium carbonate (1 eq) in acetonitrile/water (5:1) was heated to 90 °C for 30 minutes. The reaction mixture was concentrated. The residue taken in ethyl acetate was washed with water and brine.

The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using ethyl acetate/hexanes as an eluent to give the product. The compounds in the below table were prepared using this method and the specified starting material.

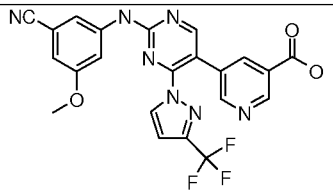
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 730	 ethyl 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 510 (M+1) for $C_{24}H_{18}F_3N_7O_3$. 400 MHz, DMSO-d_6: δ 1.29 (t, J = 7.08 Hz, 3H), 3.82 (s, 3H), 4.32 (q, J = 7.08 Hz, 2H), 7.06 (d, J = 2.58 Hz, 1H), 7.11 (t, J = 1.26 Hz, 1H), 7.78 (d, J = 2.22 Hz, 1H), 7.82 (s, 1H), 8.04 (t, J = 2.13 Hz, 1H), 8.54 (d, J = 1.62 Hz, 1H), 8.69 (d, J = 2.19 Hz, 1H), 8.88 (s, 1H), 9.03 (d, J = 1.98s Hz, 1H), 10.59 (s, 1H).	**Intermediate 270** ethyl 5-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 731	 ethyl 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 524 (M+1) for $C_{25}H_{20}F_3N_7O_3$. 400 MHz, DMSO-d_6: δ 1.30 (t, J = 7.04 Hz, 3H), 2.41 (s, 3H), 3.81 (s, 3H), 4.31 (q, J = 6.92 Hz, 2H), 6.79 (s, 1H), 7.12 (d, J = 1.16 Hz, 1H), 7.71 (d, J = 1.88 Hz, 1H), 7.82 (d, J = 1.96 Hz, 1H), 7.83 (s, 1H), 8.62 (s, 1H), 8.99 (s, 1H), 9.05 (s, 1H), 10.61 (s, 1H).	**Intermediate 271** ethyl 5-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

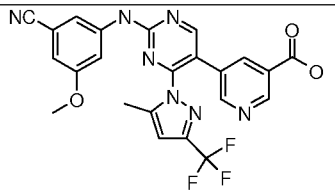
Example 732: 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

Example 733: 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid



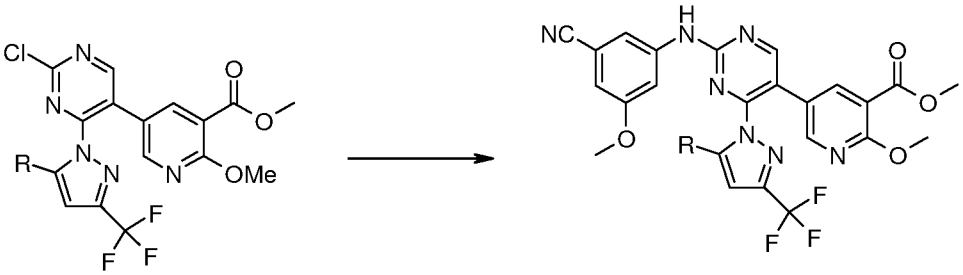
To ethyl 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate (**Example 730**, 1 eq) or ethyl 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate (**Example 731**, 1 eq) taken in a mixture of dioxane (5 mL) and water (5 mL), was added sodium hydroxide (2.5 eq) and stirred at room temperature for 3-5 h. The reaction mixture was carefully acidified with 1 N HCl and further extracted with ethyl acetate (50 mL). The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated to give the product. The compounds in the below table were prepared using this method and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 732	 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 482 (M+1) for $C_{22}H_{14}F_3N_7O_3$. 400 MHz, DMSO-d_6: δ 3.83 (s, 3H), 7.07 (d, *J* = 2.60 Hz, 1H), 7.12 (dd, *J* = 1.32, 2.18 Hz, 1H), 7.80 (t, *J* = 2.00 Hz, 1H), 7.83 (s, 1H), 8.03 (t, *J* = 2.04 Hz, 1H), 8.53 (d, *J* = 1.64 Hz, 1H), 8.62 (s, 1H), 8.89 (s, 1H), 9.01 (d, *J* = 1.84 Hz, 1H), 10.60 (s, 1H), 13.53 (s, 1H) .	**Example 730** ethyl 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 733	 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 496 (M+1) for $C_{23}H_{16}F_3N_7O_3$. 400 MHz, DMSO-d_6: δ 2.43 (s, 3H), 3.82 (s, 3H), 6.80 (s, 1H), 7.14 (dd, J = 1.28, 2.16 Hz, 1H), 7.71 (t, J = 2.12 Hz, 1H), 7.85 (t, J = 2.16 Hz, 2H), 8.56 (d, J = 2.20 Hz, 1H), 8.98 (s, 1H), 9.05 (s, 1H), 10.61 (s, 1H).	**Example 731** ethyl 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

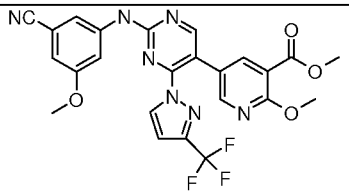
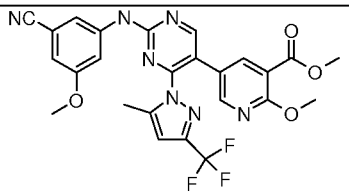
Example 734: methyl 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

Example 735: methyl 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate



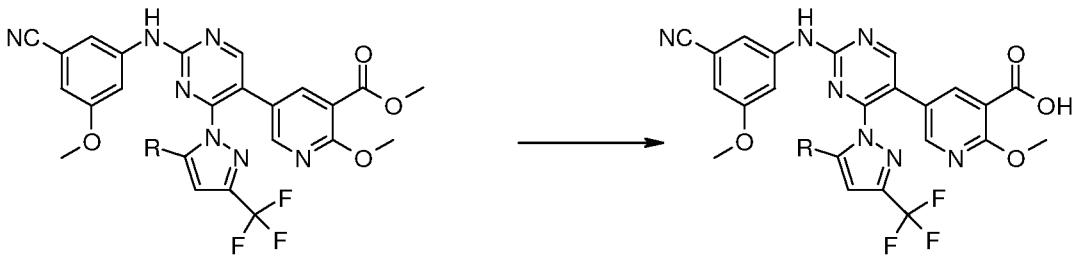
A suspension of methyl 5-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate (**Intermediate 325**, 1 eq) or methyl 5-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate (**Intermediate 273**, 1 eq), 3-amino-5-methoxybenzonitrile (1.0 eq), tris(dibenzylideneacetone)dipalladium(0) (10 mol%), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (20 mol%) and sodium carbonate (1 eq) in acetonitrile/water (5:1) was heated to 90 °C for 30 min. The reaction mixture was concentrated. The residue was taken in ethyl acetate, washed with water and brine. The organic layer was separated, dried over sodium

sulfate, filtered and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using ethyl acetate/hexanes as an eluent to give the product. The compounds in the below table were prepared using this method and the specified starting material.

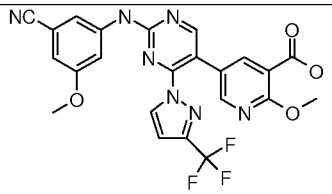
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 734	 methyl 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 526 (M+1) for $C_{24}H_{18}F_3N_7O_4$. 400 MHz, DMSO-d_6: δ 3.77 (s, 3H), 3.83 (s, 3H), 3.95 (s, 3H), 7.06 (d, J = 2.68 Hz, 1H), 7.11 (dd, J = 1.28, 2.30 Hz, 1H), 7.79 (t, J = 1.80 Hz, 1H), 7.83 (s, 1H), 7.87 (d, J = 2.48 Hz, 1H), 8.29 (d, J = 2.48 Hz, 1H), 8.50 (t, J = 1.76 Hz, 1H), 8.85 (s, 1H), 10.55 (s, 1H) .	**Intermediate 325** methyl 5-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate
Example 735	 methyl 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 540 (M+1) for $C_{25}H_{20}F_3N_7O_4$. 400 MHz, DMSO-d_6: δ 2.31 (s, 3H), 3.75 (s, 3H), 3.80 (s, 3H), 3.92 (s, 3H), 6.77 (s, 1H), 7.11 (s, 1H), 7.62 (d, J = 2.48 Hz, 1H), 7.71 (d, J = 2.00 Hz, 1H), 7.82 (s, 1H), 8.24 (d, J = 2.84 Hz, 1H), 9.01 (s, 1H), 10.57 (s, 1H).	**Intermediate 273** methyl 5-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

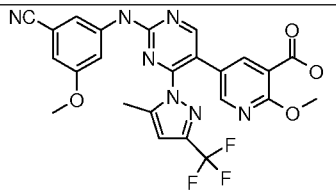
Example 736: 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

Example 737: 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid



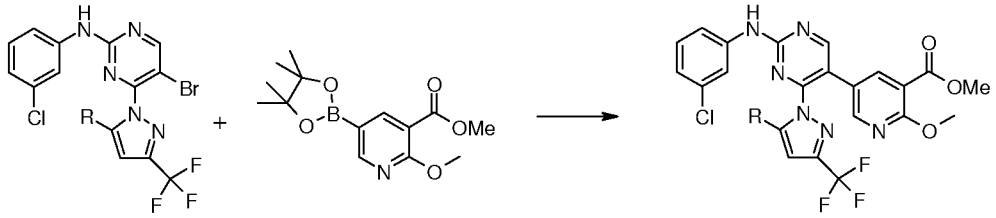
To methyl 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate (**Example 734**, 1 eq) or methyl 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate (**Example 735**, 1 eq) dissolved in a mixture of dioxane (5 mL) and water (5 mL), was added sodium hydroxide (2.5 eq) and stirred at room temperature for 3-5 h. The reaction mixture was carefully acidified with 1 N HCl and further extracted with ethyl acetate (50 mL). The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The compounds in the below table were prepared using this method and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 736	 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 512 (M+1) for $C_{23}H_{16}F_3N_7O_4$. 400 MHz, DMSO-d_6: δ 3.81 (s, 3H), 3.92 (s, 3H), 7.04 (d, J = 2.32 Hz, 1H), 7.09 (d, J = 1.08 Hz, 1H), 7.79 (d, J = 1.84 Hz, 2H), 7.81 (s, 1H), 8.22 (s, 1H), 8.47 (s, 1H), 8.83 (s, 1H), 10.54 (s, 1H), 12.95 (s, 1H).	**Example 734** methyl 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 737	 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 526 (M+1) for $C_{24}H_{18}F_3N_7O_4$. 400 MHz, DMSO-d_6: δ 2.33 (s, 3H), 3.81 (s, 3H), 3.91 (s, 3H), 6.77 (s, 1H), 7.11 (s, 1H), 7.63 (d, J = 2.40 Hz, 1H), 7.72 (t, J = 1.92 Hz, 1H), 7.83 (s, 1H), 8.14 (s, 1H), 9.00 (s, 1H), 10.57 (s, 1H), 13.02 (br s, 1H).	**Example 735** methyl 5-{2-[(3-cyano-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

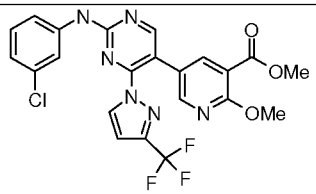
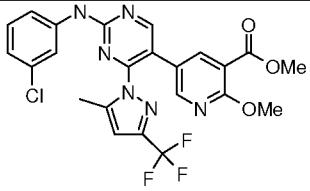
Example 738: methyl 5-{2-[(3-chlorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

Example 739: methyl 5-{2-[(3-chlorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate



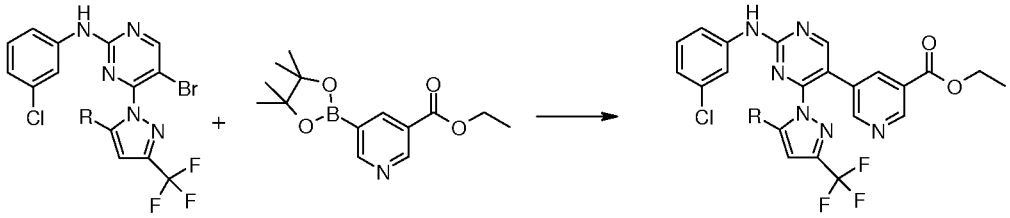
A suspension of 5-bromo-*N*-(3-chlorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 276** or 5-bromo-*N*-(3-chlorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 277** (1 eq), methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (1.1 eq), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (10 mol%) and sodium carbonate (1.1eq) in acetonitrile/water (4:1) was degassed and heated to 100 °C for 45 minutes under an inert atmosphere. The reaction mass was passed through a celite bed. The solvent was concentrated *in vacuo* and the resultant crude mass was taken in $CHCl_3$ (50 mL), washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was

purified by silica gel column chromatography using 1:1 ethyl acetate/hexanes as an eluent to give the product. The compounds in the below table were prepared using this method and the specified starting material.

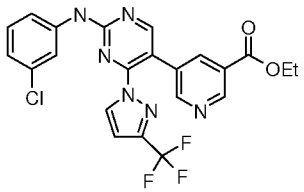
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 738	 methyl 5-{2-[(3-chlorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS (ES): 505 (M+1) for $C_{22}H_{16}ClF_3N_6O_3$. 300 MHz, DMSO-d_6: δ 3.75 (s, 3H), 3.93 (s, 3H), 7.04 (m, 1H), 7.10 (s, 1H), 7.36 (t, *J* = 8.19 Hz, 1H), 7.70 (d, *J* = 6.75 Hz, 1H), 7.85 (d, *J* = 2.43 Hz, 1H), 7.96 (s, 1H), 8.27 (d, *J* = 2.40 Hz, 1H), 8.50 (s, 1H), 8.80 (s, 1H), 10.41 (s, 1H).	**Intermediate 276** 5-bromo-*N*-(3-chlorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 739	 methyl 5-{2-[(3-chlorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS (ES): 519 (M+1) for $C_{23}H_{18}ClF_3N_6O_3$. 300 MHz, DMSO-d_6: δ 2.33 (s, 3H), 3.73 (s, 3H), 3.96 (s, 3H), 6.76 (s, 1H), 7.07 (d, *J* = 8.01 Hz, 1H), 7.36 (t, *J* = 8.13 Hz, 1H), 7.60 (d, *J* = 2.46 Hz, 1H), 7.64 (d, *J* = 9.6 Hz, 1H),7.97 (s, 1H), 8.22 (d, *J* = 2.10 Hz, 1H), 8.97 (s, 1H), 10.45 (s, 1H).	**Intermediate 277** 5-bromo-*N*-(3-chlorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

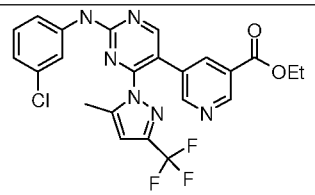
Example 740: ethyl 5-{2-[(3-chlorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

Example 741: ethyl 5-{2-[(3-chlorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

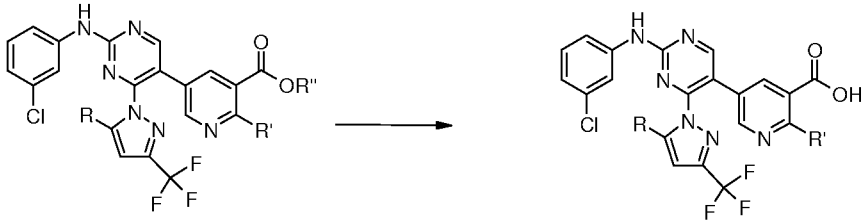


A suspension of 5-bromo-*N*-(3-chlorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine or 5-bromo-*N*-(3-chlorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (1 eq), (1 eq), ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (1.1 eq), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)complex with CH_2Cl_2 (10 mol%) and sodium carbonate (1.1 eq) in acetonitrile/water (4:1) was degassed and heated to 100 °C for 45 min. The reaction mass was passed through a celite bed. The solvent was concentrated *in vacuo* and the resultant crude mass was taken in $CHCl_3$ (50 mL), washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using 1:1 ethyl acetate/hexanes as an eluent to give the product. The compounds in the below table were prepared using this method and the specified starting material.

Compound	**Structure**	**Mass spectrum and ^{1}H NMR**	**SM**
Example 740	 ethyl 5-{2-[(3-chlorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS (ES): 489 (M+1) for $C_{22}H_{16}ClF_3N_6O_2$. 300 MHz, DMSO-d_6: δ 1.29 (m, 3H), 4.30 (q, *J* = 7.14 Hz, 2H), 7.03 (d, *J* = 1.32 Hz, 1H), 7.08 (d, *J* = 5.64 Hz, 1H), 7.38 (t, *J* = 8.10 Hz, 1H), 7.72 (d, *J* = 8.85 Hz, 1H), 7.97 (s, 1H), 8.03 (s, 1H), 8.55 (s, 1H), 8.69 (s, 1H), 8.85 (d, *J* = 2.22 Hz, 1H), 9.01 (s, 1H), 10.49 (s, 1H).	**Intermediate 276** 5-bromo-*N*-(3-chlorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

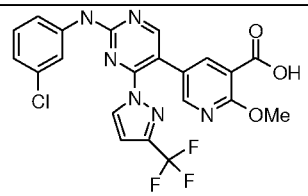
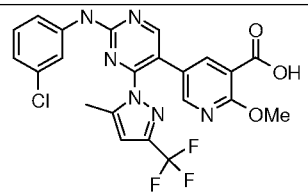
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 741	 ethyl 5-{2-[(3-chlorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS (ES): 503 (M+1) for $C_{23}H_{18}ClF_3N_6O_2$. 300 MHz, DMSO-d_6: δ 1.29 (t, *J* = 7.08 Hz, 3H), 2.43 (s, 3H), 4.30 (q, *J* = 7.08 Hz, 2H), 6.77 (s, 1H), 7.09 (d, *J* = 8.01 Hz, 1H), 7.37 (t, *J* = 8.13 Hz, 1H), 7.64 (d, *J* = 7.92 Hz, 1H), 7.80 (s, 1H), 7.98 (s, 1H), 8.60 (s, 1H), 8.97 (d, *J* = 1.83 Hz, 1H), 9.01 (s, 1H), 10.50 (s, 1H).	**Intermediate 277** 5-bromo-*N*-(3-chlorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

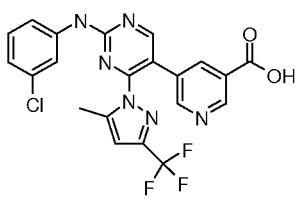
General methods for carboxylic ester hydrolysis



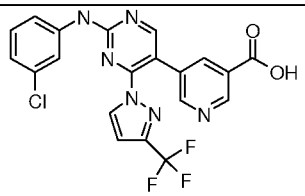
To a suspension of ester derivative (100 mg, 1 eq) taken in a mixture of dioxane (1 mL) and water (0.33 mL), was added Barium hydroxide (2 eq) and the mixture was allowed to stir at 45°C for 2 h. The mixture was carefully acidified with 1 N HCl and the precipitate formed was filtered, washed with water and dried to yield the product. The compounds in the below table were prepared using this method and the specified starting material.

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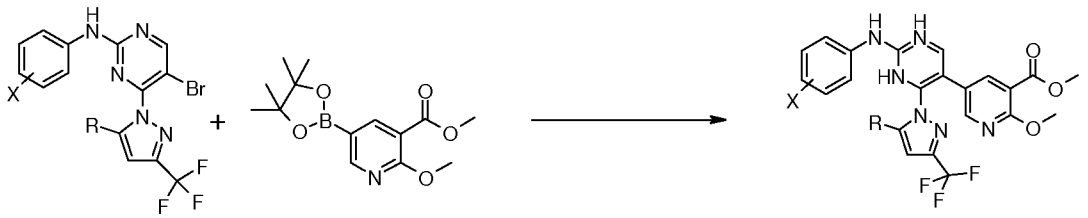
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 742	 5-{2-[(3-chlorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS (ES): 491 (M+1) for $C_{21}H_{14}ClF_3N_6O_3$. 400 MHz, DMSO-d_6: δ 3.90 (s, 3H), 7.03 (d, J = 2.40 Hz, 1H), 7.06-7.08 (m, 1H), 7.37 (t, J = 8.20 Hz, 1H), 7.71 (d, J = 8.40 Hz, 1H), 7.82 (d, J = 2.40 Hz, 1H), 7.98 (s, 1H), 8.23 (d, J = 2.32 Hz, 1H), 8.49 (d, J = 1.04 Hz, 1H), 8.80 (s, 1H), 10.41 (s, 1H), 12.94 (s, 1H).	**Example 738** methyl 5-{2-[(3-chlorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate
Example 743	 5-{2-[(3-chlorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS (ES): 505 (M+1) for $C_{22}H_{16}ClF_3N_6O_3$. 400 MHz, DMSO-d_6: δ 2.35 (s, 3H), 3.90 (s, 3H), 6.76 (s, 1H), 7.08 (dd, J = 1.32, 7.96 Hz, 1H), 7.37 (t, J = 8.16 Hz, 1H), 7.62 (d, J = 2.48 Hz, 1H), 7.64-7.66 (m, 1H), 7.98 (s, 1H), 8.16 (d, J = 2.36 Hz, 1H), 8.96 (s, 1H), 10.45 (s, 1H), 12.98 (s, 1H).	**Example 739** methyl 5-{2-[(3-chlorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 744	 5-{2-[(3-chlorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS (ES): 475 (M+1) for $C_{21}H_{14}ClF_3N_6O_2$. 400 MHz, DMSO-d_6: δ 2.44 (s, 3H), 6.77 (s, 1H), 7.09 (dd, J = 1.40, 7.94 Hz, 1H), 7.38 (t, J = 8.12 Hz, 1H), 7.65 (dd, J = 1.40, 8.16 Hz, 1H), 7.82 (t, J = 2.12 Hz, 1H), 7.98 (s, 1H), 8.54 (d, J = 2.24 Hz, 1H), 8.96 (d, J = 1.92 Hz, 1H), 9.00 (s, 1H), 10.50 (s, 1H), 13.46 (br s, 1H).	**Example 741** ethyl 5-{2-[(3-chlorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

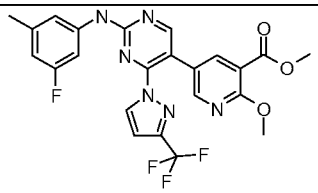
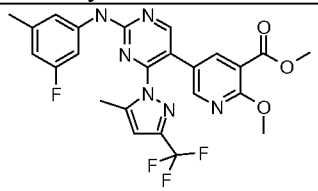
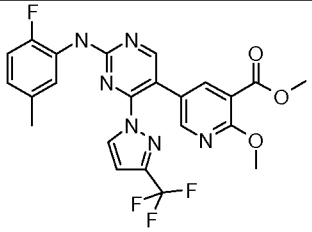
Ester derivative (100 mg, 1eq) was dissolved in tetrahydrofuran (3 mL) and treated with potassium trimethyl silanolate (10 eq) and allowed to stir at room temperature for 1 h. The solvent was concentrated *in vacuo* and the resultant crude mass was carefully acidified with 1 N HCl, then diluted with ethyl acetate (50 mL), washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using chloroform: methanol (9:1) as an eluent to yield the product. The compound in the below table was prepared using this method and the specified starting material.

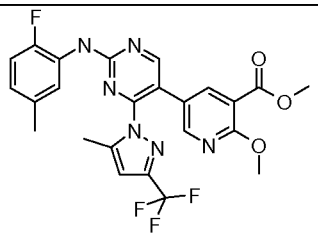
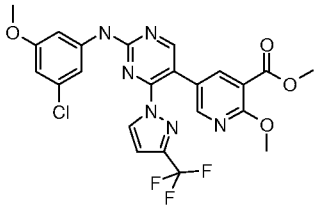
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 745	 5-{2-[(3-chlorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS (ES): 461 (M+1) for $C_{20}H_{12}ClF_3N_6O_2$. 400 MHz, DMSO-d_6: δ 7.03 (d, J = 1.72 Hz, 1H), 7.08 (d, J = 7.52 Hz, 1H), 7.38 (t, J = 8.12 Hz, 1H), 7.73 (d, J = 8.44 Hz, 1H), 8.00 (d, J = 8.60 Hz, 2H), 8.51 (m, 2H), 8.82 (s, 1H), 8.99 (s, 1H), 10.46 (s, 1H), 12.89 (s, 1H).	**Example 740** ethyl 5-{2-[(3-chlorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

General method for the synthesis of methyl 5-(2-{arylamino}-4-[1*H*-azol-1-yl]pyrimidin-5-yl)-2-methoxypyridine-3-carboxylate

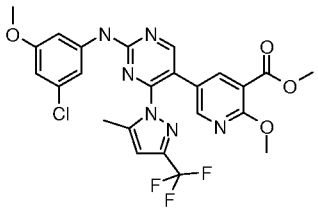
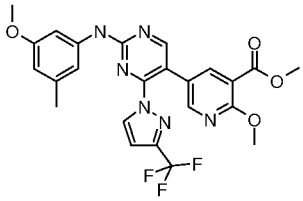
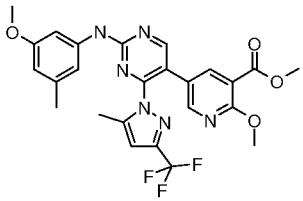


A suspension of 5-bromopyrimidine derivative (1 eq), methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (1.1–1.2 eq), [1,1′-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (10-20 mol%) and sodium carbonate (1-2 eq) in acetonitrile/water (4:1) was degassed and heated to 90 °C for 15-30 minutes under inert atmosphere. The solvent was removed *in vacuo* and the crude mixture taken in $CHCl_3$ was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using 50 % ethyl acetate / hexanes as eluent. The compounds in the below table were prepared using this procedure and the specified starting material.

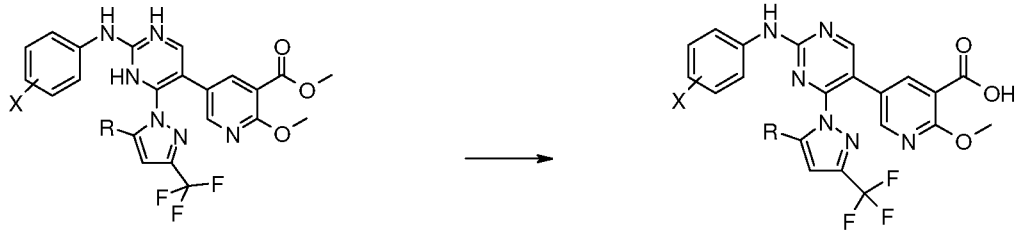
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 746	 methyl 5-{2-[(3-fluoro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 503 (M+1) for $C_{23}H_{18}F_4N_6O_3$. 400 MHz, DMSO-d_6: δ 2.32 (s, 3H), 3.77 (s, 3H), 3.95 (s, 3H), 6.70 (d, J = 9.48 Hz, 1H), 7.05 (d, J = 2.64 Hz, 1H), 7.37 (s, 1H), 7.60 (d, J = 11.80 Hz, 1H), 7.86 (d, J = 2.52 Hz, 1H), 8.29 (d, J = 2.48 Hz, 1H), 8.51 (t, J = 1.68 Hz, 1H), 8.80 (s, 1H), 10.37 (s, 1H).	**Intermediate 287** 5-bromo-*N*-(3-fluoro-5-methylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 747	 methyl 5-{2-[(3-fluoro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 517 (M+1) for $C_{24}H_{20}F_4N_6O_3$. 400 MHz, DMSO-d_6: δ 2.31 (s, 3H), 2.33 (s, 3H), 3.75 (s, 3H), 3.92 (s, 3H), 6.70 (d, J = 9.80 Hz, 1H), 6.77 (s, 1H), 7.33 (s, 1H), 7.58 (d, J = 11.60 Hz, 1H), 7.61 (d, J = 2.52 Hz, 1H), 8.24 (d, J = 2.48 Hz, 1H), 8.97 (s, 1H), 10.41 (s, 1H).	**Intermediate 288** 5-bromo-*N*-(3-fluoro-5-methylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 748	 methyl 5-{2-[(2-fluoro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 503 (M+1) for $C_{23}H_{18}F_4N_6O_3$. 400 MHz, DMSO-d_6: δ 2.32 (s, 3H), 3.77 (s, 3H), 3.94 (s, 3H), 7.00 (d, J = 2.60 Hz, 1H), 7.03-7.05 (m, 1H), 7.18 (dd, J = 8.32, 10.68 Hz, 1H), 7.51 (dd, J = 5.92, 6.48 Hz, 1H), 7.86 (d, J = 2.48 Hz, 1H), 8.27 (d, J = 2.48 Hz, 1H), 8.41 (s, 1H), 8.68 (s, 1H), 9.77 (s, 1H).	**Intermediate 289** 5-bromo-*N*-(2-fluoro-5-methylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 749	 methyl 5-{2-[(2-fluoro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	Taken to the next step based on LCMS. MS(ES): 517 (M+1) for $C_{24}H_{20}F_4N_6O_3$.	**Intermediate 290** 5-bromo-*N*-(2-fluoro-5-methylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 750	 methyl 5-{2-[(3-chloro-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 535 (M+1) for $C_{23}H_{18}ClF_3N_6O_4$. 300 MHz, DMSO-d_6: δ 3.76 (s, 3H), 3.77 (s, 3H), 3.93 (s, 3H), 6.68 (s, 1H), 7.04 (d, J = 2.55 Hz, 1H), 7.45 (s, 1H), 7.51 (s, 1H), 7.85 (d, J = 2.46 Hz, 1H), 8.27 (d, J = 2.46 Hz, 1H), 8.46 (s, 1H), 8.81 (s, 1H), 10.38 (s, 1H) .	**Intermediate 291** 5-bromo-*N*-(3-chloro-5-methoxyphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

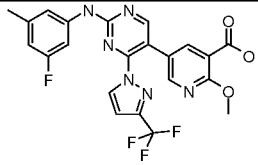
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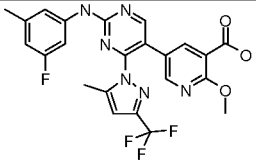
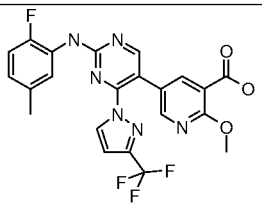
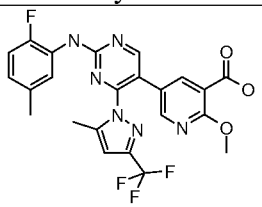
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 751	 methyl 5-{2-[(3-chloro-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 549 (M+1) for $C_{24}H_{20}ClF_3N_6O_4$. 400 MHz, DMSO-d_6: δ 3.32 (s, 3H), 3.74 (s, 3H), 3.75 (s, 3H), 3.91 (s, 3H), 6.70 (s, 1H), 6.76 (s, 1H), 7.37 (s, 1H), 7.52 (s, 1H), 7.61 (d, J = 2.32 Hz, 1H), 8.23 (d, J = 2.36 Hz, 1H), 8.98 (s, 1H), 10.42 (s, 1H) .	**Intermediate 292** 5-bromo-*N*-(3-chloro-5-methoxyphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 752	 methyl 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 515 (M+1) for $C_{24}H_{21}F_3N_6O_4$. 400 MHz, DMSO-d_6: δ 2.28 (s, 3H), 3.74 (s, 3H), 3.77 (s, 3H), 3.95 (s, 3H), 6.46 (s, 1H), 7.04 (d, J = 2.64 Hz, 1H), 7.16 (s, 1H), 7.36 (s, 1H), 7.86 (d, J = 2.36 Hz, 1H), 8.28 (d, J = 2.40 Hz, 1H), 8.49 (d, J = 1.88 Hz, 1H), 8.77 (s, 1H), 10.15 (s, 1H).	**Intermediate 293** 5-bromo-*N*-(3-methoxy-5-methylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 753	 methyl 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 529 (M+1) for $C_{25}H_{23}F_3N_6O_4$. 300 MHz, DMSO-d_6: δ 2.25 (s, 3H), 2.31 (s, 3H), 3.70 (s, 3H), 3.74 (s, 3H), 3.90 (s, 3H), 6.45 (s, 1H), 6.74 (s, 1H), 7.11 (s, 1H), 7.27 (s, 1H), 7.59 (d, J = 2.49 Hz, 1H), 8.21 (d, J = 2.52 Hz, 1H), 8.91 (s, 1H), 10.15 (s, 1H).	**Intermediate 294** 5-bromo-*N*-(3-methoxy-5-methylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

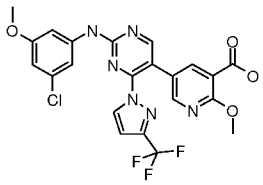
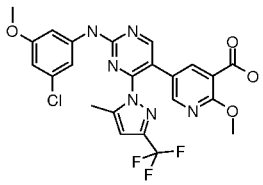
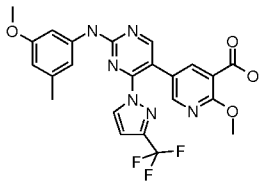
General procedure for the synthesis of 5-{2-(arylamino)-4-[1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

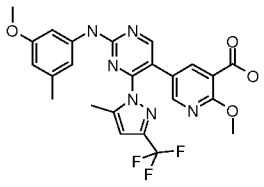


To 1 eq of methyl 5-(2-{arylamino}-4-[1*H*-azol-1-yl]pyrimidin-5-yl)-2-methoxypyridine-3-carboxylate taken in dioxane (5 mL), was added 1 N aq. Barium hydroxide (2 eq) and stirred for the amount of time indicated in the below table. The reaction mixture was carefully acidified with 1 N HCl and the solid that precipitated was filtered, washed with water and dried *in vacuo* to yield the carboxylic acid product. The compounds in the below table were prepared using this procedure and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 754[b)]	 5-{2-[(3-fluoro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 489 (M+1) for $C_{22}H_{16}F_4N_6O_3$. 400 MHz, DMSO-d_6: δ 2.32 (s, 3H), 3.93 (s, 3H), 6.70 (d, J = 8.96 Hz, 1H), 7.04 (d, J = 2.52 Hz, 1H), 7.38 (s, 1H), 7.61 (d, J = 11.72 Hz, 1H), 7.82 (d, J = 2.36 Hz, 1H), 8.24 (d, J = 2.20 Hz, 1H), 8.49 (s, 1H), 8.80 (s, 1H), 10.37 (s, 1H), 12.96 (s, 1H).	**Example 746** methyl 5-{2-[(3-fluoro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

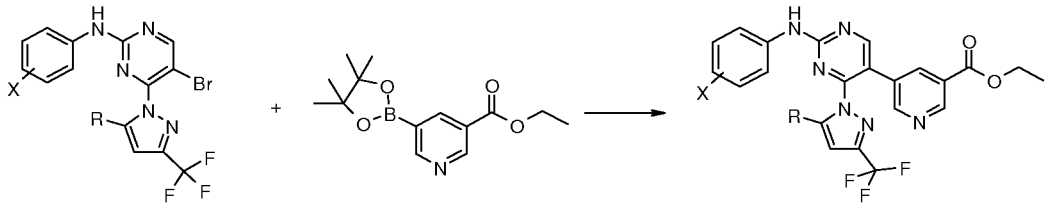
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 755[b)]	 5-{2-[(3-fluoro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 503 (M+1) for $C_{23}H_{18}F_4N_6O_3$. 400 MHz, DMSO-d_6: δ 2.30 (s, 3H), 2.34 (s, 3H), 3.90 (s, 3H), 6.69 (d, J = 9.52 Hz, 1H), 6.75 (s, 1H), 7.32 (s, 1H), 7.57 (d, J = 11.76 Hz, 1H), 7.62 (d, J = 2.52 Hz, 1H), 8.16 (d, J = 2.52 Hz, 1H), 8.95 (s, 1H), 10.38 (s, 1H), 12.95 (s, 1H).	**Example 747** methyl 5-{2-[(3-fluoro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate
Example 756[c)]	 5-{2-[(2-fluoro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 489 (M+1) for $C_{22}H_{16}F_4N_6O_3$. 400 MHz, DMSO-d_6: δ 2.31 (s, 3H), 3.93 (s, 3H), 7.01 (d, 1H), 7.03-7.04 (m, 1H), 7.17 (dd, J = 8.4, 10.32 Hz, 1H), 7.50 (dd, J = 1.72, 7.56 Hz, 1H), 7.83 (d, J = 2.48 Hz, 1H), 8.23 (d, J = 2.52 Hz, 1H), 8.40 (s, 1H), 8.68 (s, 1H), 9.75 (s, 1H), 12.93 (br s, 1 H).	**Example 748** methyl 5-{2-[(2-fluoro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate
Example 757[c, e)]	 5-{2-[(2-fluoro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 503 (M+1) for $C_{23}H_{18}F_4N_6O_3$. 400 MHz, DMSO-d_6: δ 2.28 (s, 3H), 2.29 (s, 3H), 3.88 (s, 3H), 6.69 (s, 1H), 7.02 (m, 1H), 7.15 (t, J = 10.44 Hz, 1H), 7.41 (d, J = 6.92 Hz, 1H), 7.60 (d, J = 2.44 Hz, 1H), 8.13 (d, J = 2.40 Hz, 1H), 8.81 (s, 1H), 9.78 (s, 1H), 12.92 (s, 1H).	**Example 749** methyl 5-{2-[(2-fluoro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 758[d]	 5-{2-[(3-chloro-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 521 (M+1) for $C_{22}H_{16}ClF_3N_6O_4$. 400 MHz, DMSO-d_6: δ 3.79 (s, 3H), 3.94 (s, 3H), 6.70 (t, J = 1.96 Hz, 1H), 7.05 (d, J = 2.60 Hz, 1H), 7.48 (d, J = 1.92 Hz, 1H), 7.53 (s, 1H), 7.84 (d, J = 2.36 Hz, 1H), 8.25 (d, J = 2.36 Hz, 1H), 8.47 (d, J = 1.64 Hz, 1H), 8.82 (s, 1H), 10.39 (s, 1H), 12.95 (s, 1H).	**Example 750** methyl 5-{2-[(3-chloro-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate
Example 759[d]	 5-{2-[(3-chloro-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 535 (M+1) for $C_{23}H_{18}ClF_3N_6O_4$. 400 MHz, DMSO-d_6: δ 2.34 (s, 3H), 3.76 (s, 3H), 3.90 (s, 3H), 6.70 (s, 1H), 6.76 (s, 1H), 7.38 (s, 1H), 7.53 (s, 1H), 7.62 (d, J = 2.48 Hz, 1H), 8.17 (d, J = 2.48 Hz, 1H), 8.97 (s, 1H), 10.41 (s, 1H), 12.97 (s, 1H).	**Example 751** methyl 5-{2-[(3-chloro-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate
Example 760[c]	 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 501 (M+1) for $C_{23}H_{19}F_3N_6O_4$. 400 MHz, DMSO-d_6: δ 2.28 (s, 3H), 3.74 (s, 3H), 3.92 (s, 3H), 6.45 (s, 1H), 7.02 (d, J = 2.60 Hz, 1H), 7.15 (s, 1H), 7.36 (s, 1H), 7.80 (d, J = 2.48 Hz, 1H), 8.20 (d, J = 2.44 Hz, 1H), 8.46 (d, J = 1.68 Hz, 1H), 8.75 (s, 1H), 10.12 (s, 1H), 12.98 (s, 1H).	**Example 752** methyl 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

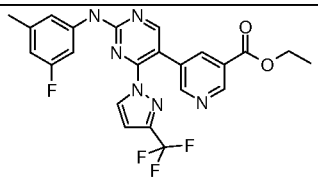
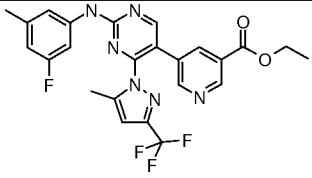
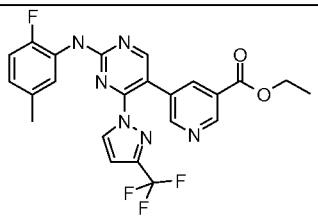
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 761[c)]	 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 515 (M+1) for $C_{24}H_{21}F_3N_6O_4$. 400 MHz, DMSO-d_6: δ 2.26 (s, 3H), 2.32 (s, 3H), 3.71 (s, 3H), 3.89 (s, 3H), 6.45 (s, 1H), 6.74 (s, 1H), 7.12 (s, 1H), 7.28 (s, 1H), 7.61 (d, J = 2.40 Hz, 1H), 8.15 (d, J = 2.36 Hz, 1H), 8.90 (s, 1H), 10.15 (s, 1H), 12.96 (s, 1H).	**Example 753** methyl 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

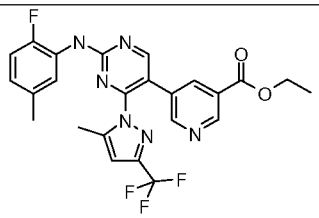
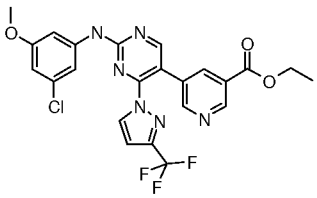
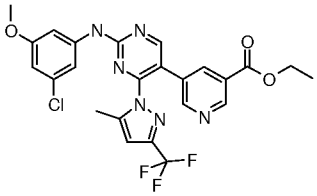
[b)] 45 °C 2 h, [c)] 40 °C, 2 h, [d)] 50 °C, 45 min [e)] Purified by preparative HPLC

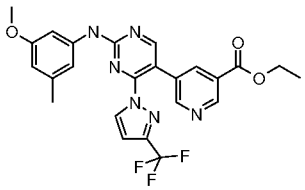
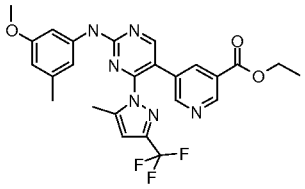
General procedure for the synthesis of ethyl 5-(2-{arylamino}-4-[1*H*-azol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylate



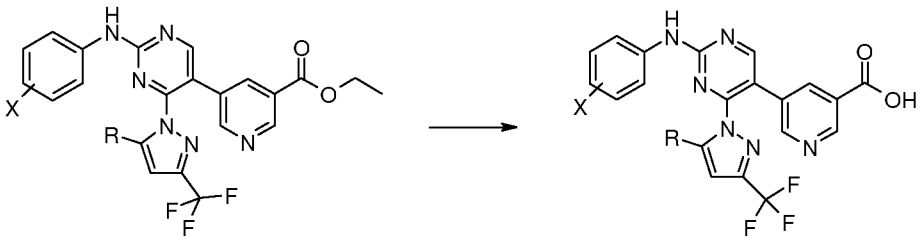
A suspension of 5-bromo-*N*-(aryl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine or 5-bromo-*N*-(aryl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (1 eq), ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (1.1–1.2 eq), [1,1′-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (10-20 mol%) and sodium carbonate (1-2 eq) in acetonitrile/water (4:1) was degassed and heated to 90 °C for 15-30 min under inert atmosphere. The solvent was removed *in vacuo* and the crude mixture taken in $CHCl_3$ was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using 30 % ethyl acetate / hexanes as eluent to give the product. The compounds in the below table were prepared using this procedure and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 762	 ethyl 5-{2-[(3-fluoro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 487 (M+1) for $C_{23}H_{18}F_4N_6O_2$. 300 MHz, DMSO-d_6: δ 1.29 (t, J = 7.05 Hz, 3H), 2.31 (s, 3H), 4.32 (q, J = 7.02 Hz, 2H), 6.70 (d, J = 9.81 Hz, 1H), 7.05 (s, 1H), 7.36 (s, 1H), 7.59 (d, J = 11.94 Hz, 1H), 8.03 (s, 1H), 8.54 (s, 1H), 8.70 (s, 1H), 8.84 (s, 1H), 9.00 (s, 1H), 10.42 (s, 1H).	**Intermediate 287** 5-bromo-*N*-(3-fluoro-5-methylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 763	 ethyl 5-{2-[(3-fluoro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 501 (M+1) for $C_{24}H_{20}F_4N_6O_2$. 400 MHz, DMSO-d_6: δ 1.31 (t, J = 7.04 Hz, 3H), 2.31 (s, 3H), 2.43 (s, 3H), 4.32 (q, J = 7.08 Hz, 2H), 6.72 (d, J = 9.24 Hz, 1H), 6.79 (s, 1H), 7.34 (s, 1H), 7.58 (d, J = 11.72 Hz, 1H), 7.81 (t, J = 2.08 Hz, 1H), 8.62 (d, J = 2.20 Hz, 1H), 8.99 (d, J = 1.92 Hz, 1H), 9.00 (s, 1H), 10.46 (s, 1H).	**Intermediate 288** 5-bromo-*N*-(3-fluoro-5-methylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 764	 ethyl 5-{2-[(2-fluoro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 487 (M+1) for $C_{23}H_{18}F_4N_6O_2$. 400 MHz, DMSO-d_6: δ 1.29 (t, J = 7.08 Hz, 3H), 2.31 (s, 3H), 4.32 (q, J = 7.16 Hz, 2H), 6.99 (d, J = 2.64 Hz, 1H), 7.03-7.07 (m, 1H), 7.17 (dd, J = 8.52, 10.66 Hz, 1H), 7.49 (d, J = 6.40 Hz, 1H), 8.02 (t, J = 2.04 Hz, 1H), 8.43 (s, 1H), 8.67 (d, J = 2.16 Hz, 1H), 8.71 (s, 1H), 9.01 (d, J = 1.96 Hz, 1H), 9.82 (s, 1H).	**Intermediate 289** 5-bromo-*N*-(2-fluoro-5-methylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 765	 ethyl 5-{2-[(2-fluoro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 501 (M+1) $C_{24}H_{20}F_4N_6O_2$. Taken to the next step based on LCMS without further purification.	**Intermediate 290** 5-bromo-*N*-(2-fluoro-5-methylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 766	 ethyl 5-{2-[(3-chloro-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 519 (M+1) for $C_{23}H_{18}ClF_3N_6O_3$ 300 MHz, DMSO-d_6: δ 1.29 (t, *J* = 7.08 Hz, 3H), 3.77 (s, 3H), 4.32 (q, *J* = 7.08 Hz, 2H), 6.70 (d, *J* = 1.98 Hz, 1H), 7.05 (d, *J* = 2.55 Hz, 1H), 7.46 (s, 1H), 7.52 (s, 1H), 8.03 (t, *J* = 2.07 Hz, 1H), 8.51 (s, 1H), 8.68 (d, *J* = 2.19 Hz, 1H), 8.86 (s, 1H), 9.02 (d, *J* = 1.98 Hz, 1H), 10.44 (s, 1H).	**Intermediate 291** 5-bromo-*N*-(3-chloro-5-methoxyphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 767	 ethyl 5-{2-[(3-chloro-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 533 (M+1) for $C_{24}H_{20}ClF_3N_6O_3$ 400 MHz, DMSO-d_6: δ 1.31 (t, *J* = 7.08 Hz, 3H), 2.43 (s, 3H), 3.77 (s, 3H), 4.32 (q, *J* = 7.08 Hz, 2H), 6.73 (d, *J* = 1.68 Hz, 1H), 6.80 (s, 1H), 7.38 (s, 1H), 7.55 (s, 1H), 7.82 (t, *J* = 1.88 Hz, 1H), 8.62 (d, *J* = 2.00 Hz, 1H), 8.99 (d, *J* = 1.76 Hz, 1H), 9.04 (s, 1H), 10.48 (s, 1H) .	**Intermediate 292** 5-bromo-*N*-(3-chloro-5-methoxyphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

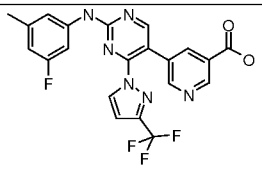
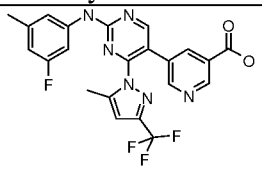
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 768	 ethyl 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 499 (M+1) for $C_{24}H_{21}F_3N_6O_3$. 400 MHz, DMSO-d_6: δ 1.31 (t, J = 7.04 Hz, 3H), 2.29 (s, 3H), 3.75 (s, 3H), 4.35 (q, J = 7.08 Hz, 2H), 6.48 (s, 1H), 7.06 (d, J = 2.52 Hz, 1H), 7.17 (s, 1H), 7.36 (s, 1H), 8.04 (t, J = 2.08 Hz, 1H), 8.54 (s, 1H), 8.69 (d, J = 2.20 Hz, 1H), 8.82 (s, 1H), 9.03 (d, J = 1.92 Hz, 1H), 10.21 (s, 1H).	**Intermediate 293** 5-bromo-*N*-(3-methoxy-5-methylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine
Example 769	 ethyl 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 513 (M+1) for $C_{25}H_{23}F_3N_6O_3$. 400 MHz, DMSO-d_6: δ 1.31 (t, J = 7.08 Hz, 3H), 2.28 (s, 3H), 2.42 (s, 3H), 3.73 (s, 3H), 4.32 (q, J = 7.12 Hz, 2H), 6.49 (s, 1H), 6.78 (s, 1H), 7.15 (s, 1H), 7.29 (s, 1H), 7.80 (t, J = 2.12 Hz, 1H), 8.61 (d, J = 2.20 Hz, 1H), 8.98 (m, 2H), 10.23 (s, 1H).	**Intermediate 294** 5-bromo-*N*-(3-methoxy-5-methylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

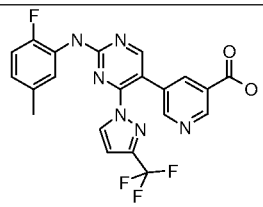
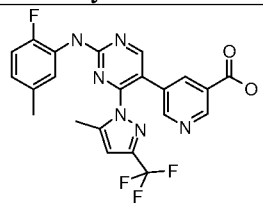
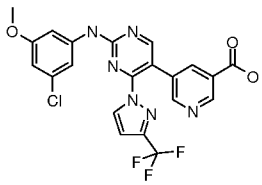
General procedure for the synthesis of 5-{2-(arylamino)-4-[1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

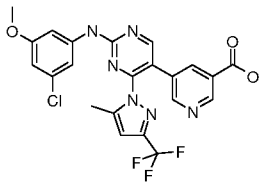
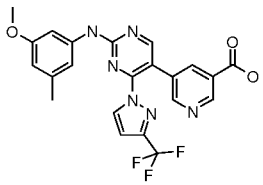
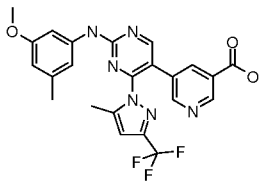


To 1 eq of ethyl 5-(2-{arylamino}-4-[1*H*-azol-1-yl]pyrimidin-5-yl)pyridine-3-carboxylate taken in dioxane (5 mL), was added 1 N aq. Barium hydroxide (2 eq) and stirred for the time indicated in the below table. The reaction mixture was carefully acidified with 1 N HCl and the solid that

precipitated was filtered, washed with water and dried *in vacuo* to yield the carboxylic acid product. The compounds in the below table were prepared using this procedure and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 770[f]	 5-{2-[(3-fluoro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 459 (M+1) for $C_{21}H_{14}F_4N_6O_2$. 400 MHz, DMSO-d_6: δ 2.32 (s, 3H), 6.70 (d, J = 9.52 Hz, 1H), 7.05 (d, J = 2.64 Hz, 1H), 7.38 (s, 1H), 7.60 (d, J = 11.72 Hz, 1H), 8.02 (t, J = 2.08 Hz, 1H), 8.54 (d, J = 1.64 Hz, 1H), 8.65 (d, J = 2.20 Hz, 1H), 8.84 (s, 1H), 9.01 (d, J = 1.96 Hz, 1H), 10.41 (s, 1H), 13.42 (br s, 1H).	**Example 762** ethyl 5-{2-[(3-fluoro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 771[g]	 5-{2-[(3-fluoro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 473 (M+1) for $C_{22}H_{16}F_4N_6O_2$. 400 MHz, DMSO-d_6: δ 2.31 (s, 3H), 2.43 (s, 3H), 6.71 (d, J = 9.28 Hz, 1H), 6.77 (s, 1H), 7.33 (s, 1H), 7.57 (d, J = 11.56 Hz, 1H), 7.83 (t, J = 2.00 Hz, 1H), 8.54 (d, J = 2.16 Hz, 1H), 8.96 (d, J = 1.88 Hz, 1H), 9.00 (s, 1H), 10.43 (s, 1H), 13.43 (s, 1H).	**Example 763** ethyl 5-{2-[(3-fluoro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

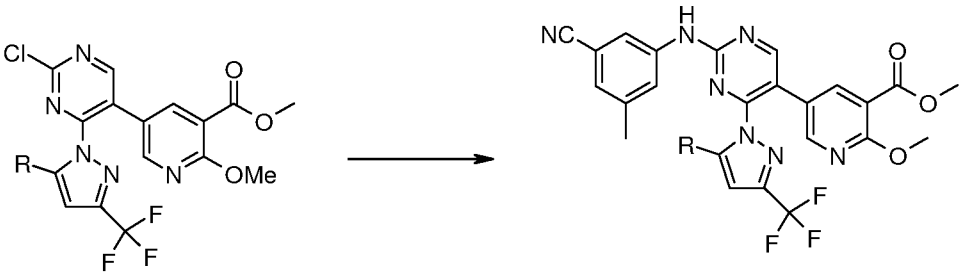
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 772[h)]	 5-{2-[(2-fluoro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 459 (M+1) for $C_{21}H_{14}F_4N_6O_2$. 400 MHz, DMSO-d_6: δ 2.32 (s, 3H), 7.00 (d, J = 2.68 Hz, 1H), 7.02-7.06 (m, 1H), 7.19 (dd, J = 8.36, 10.68 Hz, 1H), 7.51 (dd, J = 1.80, 7.68 Hz, 1H), 8.02 (t, J = 2.08 Hz, 1H), 8.41 (s, 1H), 8.64 (d, J = 2.24 Hz, 1H), 8.72 (s, 1H), 9.00 (d, J = 1.96 Hz, 1H), 9.82 (s, 1H), 13.41 (br s, 1H).	**Example 764** ethyl 5-{2-[(2-fluoro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 773[h)]	 5-{2-[(2-fluoro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 473 (M+1) for $C_{22}H_{16}F_4N_6O_2$. 400 MHz, DMSO-d_6: δ 2.30 (s, 3H), 2.38 (s, 3H), 6.72 (s, 1H), 7.06-7.07 (m, 1H), 7.18 (dd, J = 8.40, 10.80 Hz, 1H), 7.42 (d, J = 6.40 Hz, 1H), 7.83 (t, J = 2.00 Hz, 1H), 8.53 (d, J = 2.00 Hz, 1H), 8.87 (s, 1H), 8.95 (d, J = 2.00 Hz, 1H), 9.87 (s, 1H), 13.43 (s, 1H).	**Example 765** ethyl 5-{2-[(2-fluoro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 774[i)]	 5-{2-[(3-chloro-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 491 (M+1) for $C_{21}H_{14}ClF_3N_6O_3$. 400 MHz, DMSO-d_6: δ 3.78 (s, 3H), 6.70 (s, 1H), 7.05 (s, 1H), 7.47 (s, 1H), 7.52 (s, 1H), 8.02 (s, 1H), 8.50 (s, 1H), 8.62 (s, 1H), 8.85 (s, 1H), 9.00 (s, 1H), 10.43 (s, 1H), 13.55 (s, 1H).	**Example 766** ethyl 5-{2-[(3-chloro-5-methoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 775[i)]	 5-{2-[(3-chloro-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 505 (M+1) for $C_{22}H_{16}ClF_3N_6O_3$. 400 MHz, DMSO-d_6: δ 2.42 (s, 3H), 3.76 (s, 3H), 6.71 (d, J = 1.80 Hz, 1H), 6.77 (s, 1H), 7.37 (s, 1H), 7.53 (s, 1H), 7.83 (t, J = 2.00 Hz, 1H), 8.55 (d, J = 2.12 Hz, 1H), 8.96 (d, J = 1.84 Hz, 1H), 9.01 (s, 1H), 10.45 (s, 1H), 13.44 (s, 1H).	**Example 767** ethyl 5-{2-[(3-chloro-5-methoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 776[h)]	 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 471 (M+1) for $C_{22}H_{17}F_3N_6O_3$. 400 MHz, DMSO-d_6: δ 2.28 (s, 3H), 3.74 (s, 3H), 6.47 (s, 1H), 7.03 (d, J = 2.60 Hz, 1H), 7.16 (s, 1H), 7.35 (s, 1H), 8.01 (t, J = 1.92 Hz, 1H), 8.52 (d, J = 1.52 Hz, 1H), 8.62 (s, 1H), 8.79 (s, 1H), 8.99 (d, J = 1.44 Hz, 1H), 10.18 (s, 1H), 13.41 (s, 1H).	**Example 768** ethyl 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 777[h)]	 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 485 (M+1) for $C_{23}H_{19}F_3N_6O_3$. 400 MHz, DMSO-d_6: δ 2.27 (s, 3H), 2.42 (s, 3H), 3.72 (s, 3H), 6.47 (s, 1H), 6.76 (s, 1H), 7.13 (s, 1H), 7.27 (s, 1H), 7.81 (d, J = 1.84 Hz, 1H), 8.53 (d, J = 1.92 Hz, 1H), 8.95 (m, 2H), 10.21 (s, 1H), 13.45 (s, 1H).	**Example 769** ethyl 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

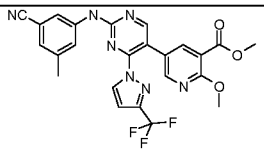
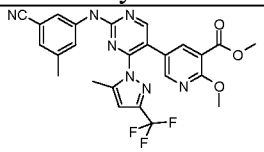
[f)] overnight, RT, [g)] 6 h, RT, [h)] 40 °C, 2 h, [i)] 50 °C, 45 min

Example 778: methyl 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

Example 779: methyl 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

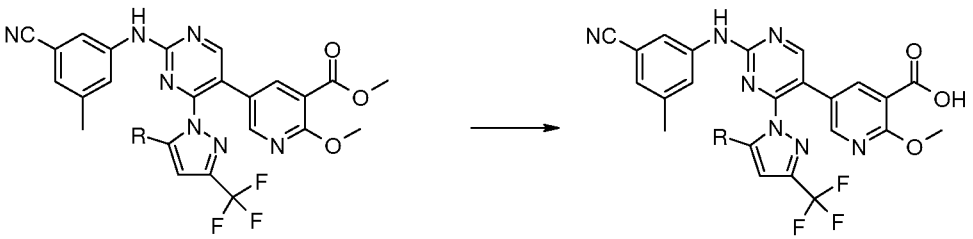


A suspension of methyl 5-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate (**Intermediate 325**, 1 eq) or methyl 5-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate (**Intermediate 273**, 1 eq), 3-amino-5-methylbenzonitrile (1.0 eq), tris(dibenzylideneacetone)dipalladium(0) (10 mol%), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (20 mol%) and sodium carbonate (1 eq) in acetonitrile/water (5:1) was heated to 90 °C for 30 min. The reaction mixture was concentrated. The residue was taken in ethyl acetate, washed with water and brine. The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using ethyl acetate/hexanes as an eluent to give the product. The compounds in the below table were prepared using this procedure and the specified starting material.

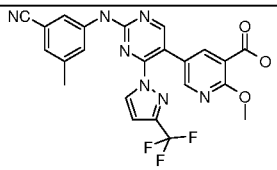
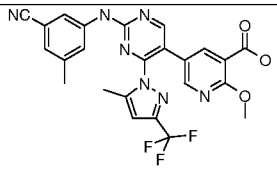
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 778	 methyl 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 510 (M+1) for $C_{24}H_{18}F_3N_7O_3$. 400 MHz, DMSO-d_6: δ 2.34 (s, 3H), 3.77 (s, 3H), 3.92 (s, 3H), 7.04 (s, 1H), 7.33 (s, 1H), 7.77 (m, 2H), 8.11 (s, 1H), 8.30 (d, *J* = 2.24 Hz, 1H), 8.51 (s, 1H), 8.84 (s, 1H), 9.16 (s, 1H).	**Intermediate 325** methyl 5-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate
Example 779	 methyl 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 524 (M+1) for $C_{25}H_{20}F_3N_7O_3$. 400 MHz, DMSO-d_6: δ 2.35 (s, 3H), 2.35 (s, 3H), 3.76 (s, 3H), 3.93 (s, 3H), 6.79 (s, 1H), 7.34 (s, 1H), 7.62 (d, *J* = 2.56 Hz, 1H), 7.81 (s, 1H), 8.10 (s, 1H), 8.25 (d, *J* = 2.56 Hz, 1H), 9.01 (s, 1H), 10.55 (s, 1H).	**Intermediate 273** methyl 5-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

Example 780: 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol- 1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

Example 781: 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid



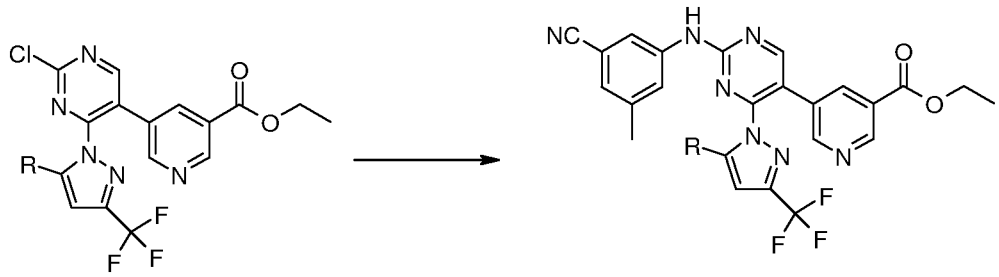
To 1 eq of methyl 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[1*H*-azol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate taken in dioxane (5 mL), was added 1 N aq. sodium hydroxide (1 - 3 eqs) and stirred at RT for 1 h. The reaction mixture was carefully acidified with 1 N HCl and the solid that precipitated was filtered, washed with water and dried *in vacuo* to yield the carboxylic acid product. The compounds in the below table were prepared using this procedure and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 780[j]	 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 496 (M+1) for $C_{23}H_{16}F_3N_7O_3$. 400 MHz, DMSO-d_6: δ 2.35 (s, 3H), 3.91 (s, 3H), 7.03 (d, J = 2.56 Hz, 1H), 7.31 (s, 1H), 7.79 (d, J = 2.20 Hz, 1H), 7.87 (s, 1H), 8.10 (s, 1H), 8.18 (s, 1H), 8.46 (s, 1H), 8.81 (s, 1H), 10.50 (s, 1H).	**Example 778** methyl 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate
Example 781[k]	 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 510 (M+1) for $C_{24}H_{18}F_3N_7O_3$. 400 MHz, DMSO-d_6: δ 2.35 (s, 6H), 3.89 (s, 3H), 6.77 (s, 1H), 7.33 (s, 1H), 7.61 (d, J = 2.36 Hz, 1H), 7.81 (s, 1H), 8.10 (m, 2H), 8.99 (s, 1H), 10.54 (s, 1H), 12.99 (s, 1H).	**Example 779** methyl 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

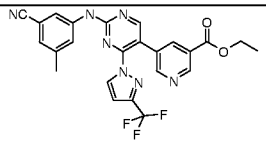
[j] (2 eq NaOH), [k] (3 eq NaOH).

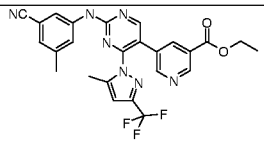
Example 782: ethyl 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

Example 783: ethyl 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate



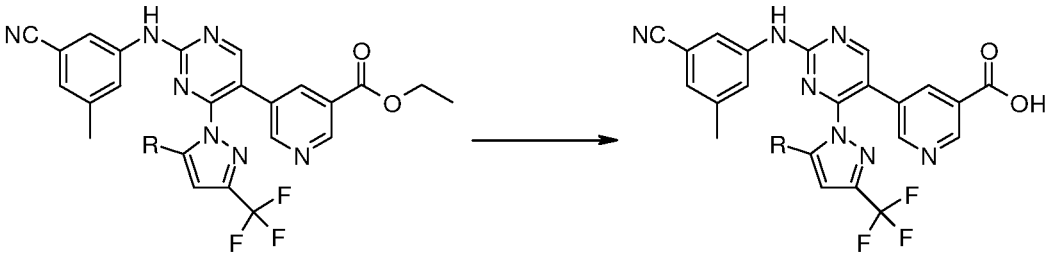
A suspension of ethyl 5-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate (**Intermediate 270**, 1 eq) or ethyl 5-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate (**Intermediate 271**, 1 eq), 3-amino-5-methylbenzonitrile (1.2 eq), tris(dibenzylideneacetone)dipalladium(0) (10 mol%), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (20 mol%) and sodium carbonate (1 eq) in acetonitrile/water (5:1) was heated to 90 °C for 30 min. The reaction mixture was concentrated. The residue taken in ethyl acetate was washed with water and brine. The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using ethyl acetate/hexanes as an eluent to give the product. The compounds in the below table were prepared using this procedure and the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 782	 ethyl 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 494 (M+1) for $C_{24}H_{18}F_3N_7O_2$. 400 MHz, DMSO-d_6: δ 1.27 (t, J = 7.12 Hz, 3H), 2.36 (s, 3H), 4.33 (q, J = 7.16 Hz, 2H), 7.06 (d, J = 2.64 Hz, 1H), 7.33 (s, 1H), 7.87 (s, 1H), 8.04 (s, 1H), 8.10 (s, 1H), 8.55 (d, J = 1.88 Hz, 1H), 8.69 (d, J = 2.00 Hz, 1H), 8.87 (s, 1H), 9.03 (s, 1H), 10.56 (s, 1H).	**Intermediate 270** ethyl 5-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

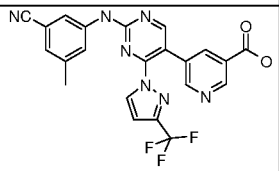
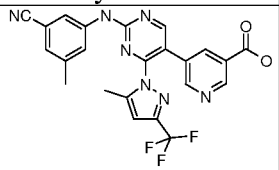
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 783	 ethyl 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate	MS(ES): 508 (M+1) for $C_{25}H_{20}F_3N_7O_2$. 300 MHz, DMSO-d_6: δ 1.29 (t, J = 7.08 Hz, 3H), 2.34 (s, 3H), 2.39 (s, 3H), 4.30 (q, J = 6.00 Hz, 2H), 6.66 (m, 1H), 6.78 (s, 1H), 7.33 (s, 1H), 7.80 (m, 2H), 8.09 (s, 1H), 8.60 (s, 1H), 8.98 (s, 1H), 9.03 (s, 1H).	**Intermediate 271** ethyl 5-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

Example 784: 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

Example 785: 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

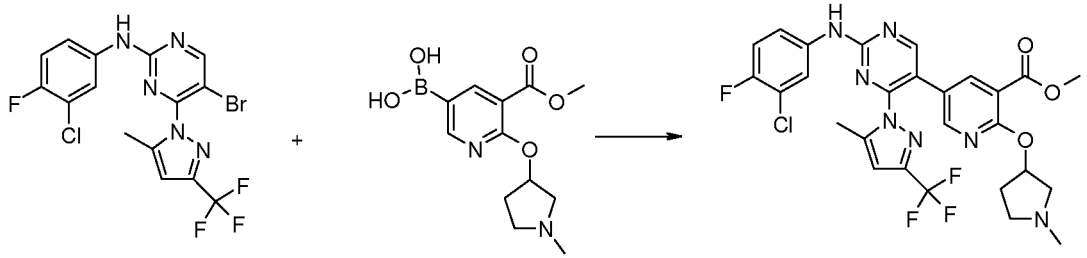


To 1 eq of ethyl 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[1*H*-azol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate taken in dioxane (5 mL), was added 1 N aq. sodium hydroxide (1 - 3 eq) and stirred at RT for 1 h. After completion of reaction, reaction mixture was carefully acidified with 1 N HCl and the solid that precipitated was filtered, washed with water and dried *in vacuo* to yield the carboxylic acid product. The compounds in the below table were prepared using this procedure and the specified starting material.

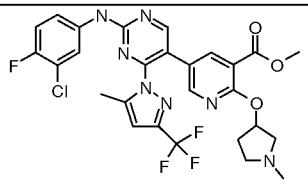
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 784[l]	 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 466 (M+1) for $C_{22}H_{14}F_3N_7O_2$. 400 MHz, DMSO-d_6: δ 2.36 (s, 3H), 7.04 (s, 1H), 7.32 (s, 1H), 7.88 (s, 1H), 8.02 (s, 1H), 8.10 (s, 1H), 8.51 (s, 2H), 8.84 (s, 1H), 8.99 (s, 1H), 10.55 (s, 1H).	**Example 782** ethyl 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate
Example 785[m]	 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid	MS(ES): 480 (M+1) for $C_{23}H_{16}F_3N_7O_2$. 400 MHz, DMSO-d_6: δ 2.36 (s, 3H), 2.40 (s, 3H), 6.76 (s, 1H), 7.33 (s, 1H), 7.82 (s, 1H), 7.92 (s, 1H), 8.10 (s, 1H), 8.30 (s, 1H), 8.95 (s, 1H), 8.99 (s, 1H), 10.56 (s, 1H).	**Example 783** ethyl 5-{2-[(3-cyano-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylate

[l] (1 eq NaOH), [m] (3 eq NaOH).

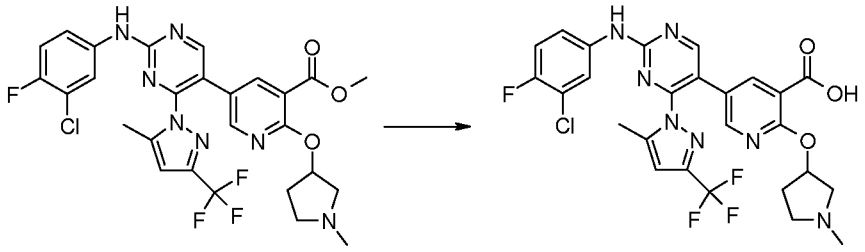
Example 786: methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[(1-methylpyrrolidin-3-yl)oxy]pyridine-3-carboxylate



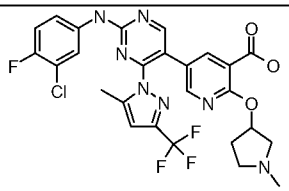
A suspension of 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 113**, 0.75 mmol, 0.340 g), a mixture of {5-(methoxycarbonyl)-6-[(1-methylpyrrolidin-3-yl)oxy]pyridin-3-yl}boronic acid and methyl 2-[(1-methylpyrrolidin-3-yl)oxy]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (**Intermediate 297**, 1.5 mmol based on the boronic acid, 0.423 g), [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (0.15 mmol, 0.109 g) and sodium carbonate (0.75 mmol, 0.074 g) in acetonitrile/water (5 : 1) was degassed and heated to 90 °C for 15 min under an inert atmosphere. The reaction mass was passed through a celite bed and solvent was concentrated *in vacuo*. The resultant residue taken in EtOAc (50 mL) was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude mass was further purified by silica gel column chromatography (eluted with 3 % Et_3N in EtOAc) to yield 0.210 g of the product.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 786	 methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[(1-methylpyrrolidin-3-yl)oxy]pyridine-3-carboxylate	MS(ES): 606 (M+1) for $C_{27}H_{24}ClF_4N_7O_3$. 400 MHz, DMSO-d_6: δ 1.78 (br s, 1H), 2.24 (s, 3H), 2.27 (d, *J* = 5.48 Hz, 1H), 2.32 (s, 3H), 2.55 (dd, *J* = 2.08, 10.80 Hz, 1H), 2.65 (t, *J* = 6.52 Hz, 1H), 2.79 (dd, *J* = 6.20, 10.50 Hz, 1H), 3.74 (s, 3H), 5.36 (br s, 1H), 6.77 (s, 1H), 7.42 (t, *J* = 9.12 Hz, 1H), 7.61-7.66 (m, 2H), 8.05 (d, *J* = 4.40 Hz, 1H), 8.14 (d, *J* = 2.48 Hz, 1H), 8.95 (s, 1H), 10.44 (s, 1H).	**Intermediate 297** {5-(methoxycarbonyl)-6-[(1-methylpyrrolidin-3-yl)oxy]pyridin-3-yl}boronic acid

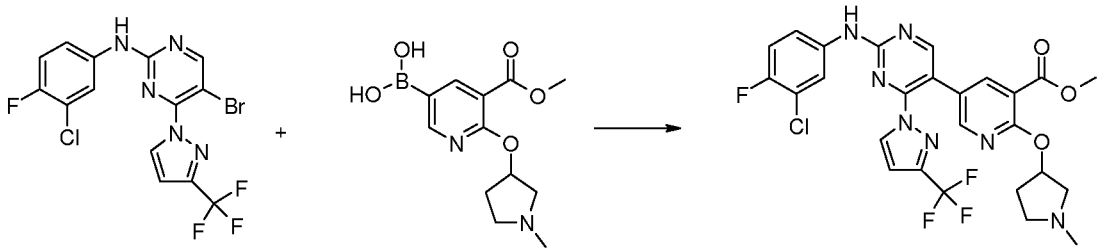
Example 787: 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[(1-methylpyrrolidin-3-yl)oxy]pyridine-3-carboxylic acid



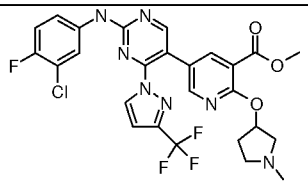
To 130 mg of methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[(1-methylpyrrolidin-3-yl)oxy]pyridine-3-carboxylate (**Example 786**, 0.2 mmol) taken in a mixture of THF (5 mL) and water (5 mL), was added Barium hydroxide monohydrate (0.162 g, 0.8 mmol) and stirred at room temperature for 7 h. The mixture was carefully acidified with 1 N HCl. It was extracted with ethyl acetate (50 mL) and the organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated to yield 85 mg of **Example 787**.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 787	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[(1-methylpyrrolidin-3-yl)oxy]pyridine-3-carboxylic acid	MS(ES): 592 (M+1) for $C_{26}H_{22}ClF_4N_7O_3$. 400 MHz, DMSO-d_6: δ 1.92-1.95 (m, 1H), 2.28-2.29 (m, 1H), 2.35 (s, 3H), 2.43 (s, 3H), 2.64 (d, J = 7.00 Hz, 1H), 2.76-2.79 (m, 1H), 2.92-2.95 (m, 1H), 3.00-3.01 (m, 1H), 5.41 (s, 1H), 6.75 (s, 1H), 7.41 (t, J = 9.08 Hz, 1H), 7.55 (s, 1H), 7.59-7.65 (m, 1H), 7.94 (s, 1H), 8.05 (d, J = 4.60 Hz, 1H), 8.91 (s, 1H), 10.42 (s, 1H).	**Example 786** methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[(1-methylpyrrolidin-3-yl)oxy]pyridine-3-carboxylate

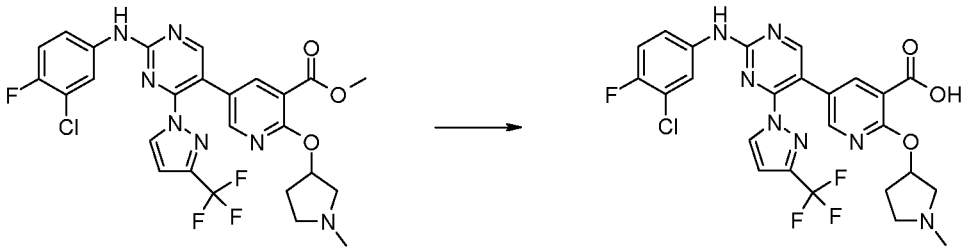
Example 788: methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[(1-methylpyrrolidin-3-yl)oxy]pyridine-3-carboxylate



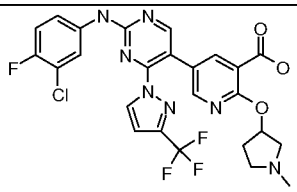
A suspension of 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 115**, 1.1 mmol, 0.5 g), a mixture of {5-(methoxycarbonyl)-6-[(1-methylpyrrolidin-3-yl)oxy]pyridin-3-yl}boronic acid and methyl 2-[(1-methylpyrrolidin-3-yl)oxy]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (**Intermediate 297**, 2.3 mmol based on the boronic acid, 0.644 g), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.22 mmol, 0.160 g) and sodium carbonate (1.1 mmol, 0.116 g) in acetonitrile/water (20 : 5, v/v) was degassed and heated to 90 °C for 15 min under an inert atmosphere. The reaction mass was passed through a celite bed. The solvent was concentrated *in vacuo* and the resultant crude mass was taken in EtOAc (50 mL), washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude mass was further purified by silica gel column chromatography (eluted with 4 % Et_3N in EtOAc) to yield 0.240 g of the product.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 788	 methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[(1-methylpyrrolidin-3-yl)oxy]pyridine-3-carboxylate	MS(ES): 592 (M+1) for $C_{26}H_{22}ClF_4N_7O_3$. 400 MHz, DMSO-d_6: δ 1.81-1.86 (m, 1H), 2.26 (s, 3H), 2.28-2.40 (m, 2H), 2.59 (dd, *J* = 2.76, 10.58 Hz, 1H), 2.64-2.67 (m, 1H), 2.82 (dd, *J* = 6.24, 10.62 Hz, 1H), 3.81 (s, 3H), 5.40-5.44 (m, 1H), 7.05 (d, *J* = 2.60 Hz, 1H), 7.43 (t, *J* = 9.12 Hz, 1H), 7.71-7.75 (m, 1H), 7.87 (d, *J* = 2.44 Hz, 1H), 8.07 (dd, *J* = 2.56, 6.72 Hz, 1H), 8.21 (d, *J* = 2.48 Hz, 1H), 8.52 (d, *J* = 1.60 Hz, 1H), 8.80 (s, 1H), 10.42 (s, 1H).	**Intermediate 297** {5-(methoxycarbonyl)-6-[(1-methylpyrrolidin-3-yl)oxy]pyridin-3-yl}boronic acid

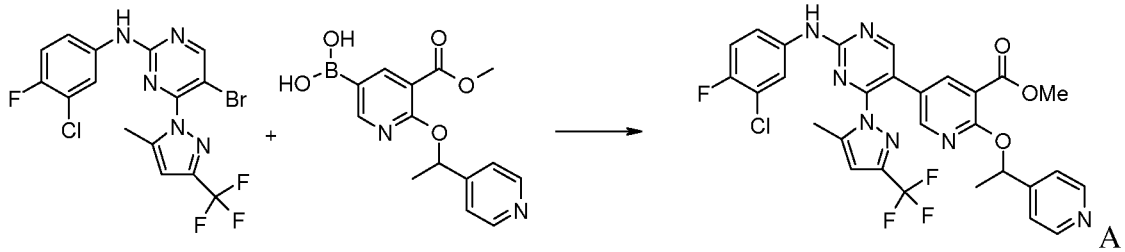
Example 789: 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[(1-methylpyrrolidin-3-yl)oxy]pyridine-3-carboxylic acid



To 180 mg of methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[(1-methylpyrrolidin-3-yl)oxy]pyridine-3-carboxylate (**Example 788**, 0.3 mmol, 1 eq) taken in a mixture of THF (5 mL) and water (5 mL), was added Barium hydroxide monohydrate (0.231 g, 1.2 mmol, 4 eq) and stirred at room temperature for 7 h. The mixture was carefully acidified with 1 N HCl. It was extracted with ethyl acetate (50 mL) and the organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated to yield 120 mg of the product.

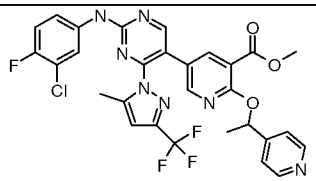
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 789	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[(1-methylpyrrolidin-3-yl)oxy]pyridine-3-carboxylic acid	MS(ES): 578 (M+1) for $C_{25}H_{20}ClF_4N_7O_3$. 400 MHz, DMSO-d_6: δ 1.95 (br s, 1H), 2.31 (br s, 1H), 2.43 (s, 3H), 2.65 (br s, 1H), 2.80 (d, J = 10.36 Hz, 1H), 2.96 (m, 2H), 5.44 (br s, 1H), 7.02 (s, 1H), 7.40 (t, J = 9.00 Hz, 1H), 7.7-7.73 (m, 2H), 8.05-8.07 (m, 2H), 8.47 (s, 1H), 8.76 (s, 1H), 10.40 (s, 1H).	**Example 788** methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[(1-methylpyrrolidin-3-yl)oxy]pyridine-3-carboxylate

Example 790: methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[1-(pyridin-4-yl)ethoxy]pyridine-3-carboxylate

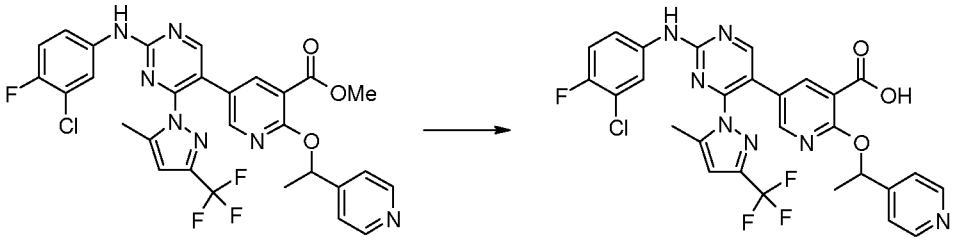


A suspension of 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 113**, 0.97 mmol, 0.440 g), a mixture of methyl 2-[1-(pyridin-4-yl)ethoxy]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate and {5-(methoxycarbonyl)-6-[1-(pyridin-4-yl)ethoxy]pyridin-3-yl}boronic acid (**Intermediate 300,** 1.46 mmol based on the boronic acid, 0.442 g), [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with CH_2Cl_2 (0.2 mmol, 0.159 g) and sodium carbonate (0.97

mmol, 0.103 g) in acetonitrile/water (4 : 1) was degassed and heated to 90 °C for 30 min under an inert atmosphere. The reaction mixture was diluted with EtOAc (50 mL), washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography (product eluted with 45 % ethyl acetate/hexanes) to yield 0.440 g of product.

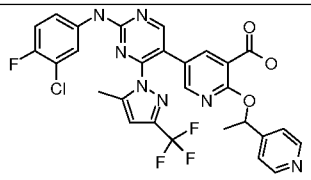
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 790	 methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[1-(pyridin-4-yl)ethoxy]pyridine-3-carboxylate	MS(ES): 628 (M+1) for $C_{29}H_{22}ClF_4N_7O_3$. 400 MHz, DMSO-d_6: δ 1.54 (d, J = 8.72 Hz, 3H), 2.33 (s, 3H), 3.82 (s, 3H), 6.27 (q, J = 8.60 Hz, 1H), 6.74 (s, 1H), 7.37-7.40 (m, 3H), 7.61-7.62 (m, 1H), 7.68 (d, J = 3.32 Hz, 1H), 8.03 (dd, J = 3.12, 8.82 Hz, 1H), 8.09 (d, J = 3.36 Hz, 1H), 8.53 (s, 2H), 8.93 (s, 1H), 10.43 (s, 1H).	**Intermediate 300** {5-(methoxycarbonyl)-6-[1-(pyridin-4-yl)ethoxy]pyridin-3-yl}boronic acid

Example 791: 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[1-(pyridin-4-yl)ethoxy]pyridine-3-carboxylic acid

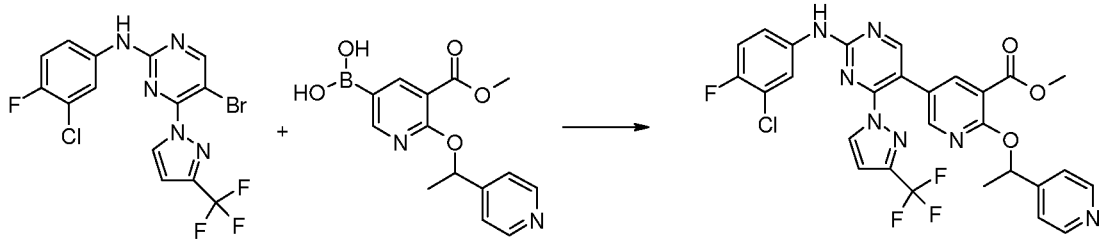


To 162 mg of methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[1-(pyridin-4-yl)ethoxy]pyridine-3-carboxylate (**Example 790**, 0.25 mmol, 0.162 g) taken in a mixture of dioxane (4 mL) and water (4 mL) was added Barium hydroxide monohydrate (0.51 mmol, 0.098 g) and stirred at 50 °C for 1 h. After completion of the reaction, the mixture was then carefully acidified with 1 N HCl. It

was then extracted with ethyl acetate (50 mL), and the organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated to yield 120 mg of the title compound.

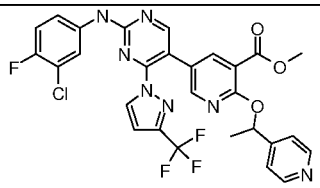
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 791	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[1-(pyridin-4-yl)ethoxy]pyridine-3-carboxylic acid	MS(ES): 614 (M+1) for $C_{28}H_{20}ClF_4N_7O_3$. 400 MHz, DMSO-d_6: δ 1.50 (d, J = 6.48 Hz, 3H), 2.25 (s, 3H), 6.20 (q, J = 6.48 Hz, 1H), 6.69 (s, 1H), 7.39 (t, J = 9.08 Hz, 1H), 7.51 (m, 3H), 7.59-7.62 (m, 2H), 8.03 (dd, J = 2.32, 6.62 Hz, 1H), 8.46 (d, J = 4.60 Hz, 2H), 8.85 (s, 1H), 10.41 (s, 1H).	**Example 790** methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[1-(pyridin-4-yl)ethoxy]pyridine-3-carboxylate

Example 792: methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[1-(pyridin-4-yl)ethoxy]pyridine-3-carboxylate

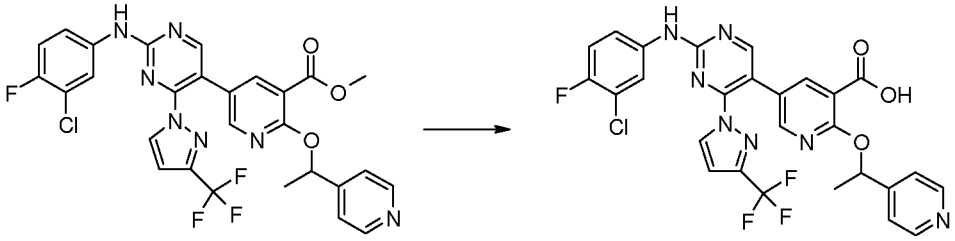


A suspension of 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 115**, 0.95 mmol, 0.415 g), a mixture of methyl 2-[1-(pyridin-4-yl)ethoxy]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate and {5-(methoxycarbonyl)-6-[1-(pyridin-4-yl)ethoxy]pyridin-3-yl}boronic acid (**Intermediate 300**, 1.42 mmol based on the boronic acid, 0.431 g), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (0.19 mmol, 0.155

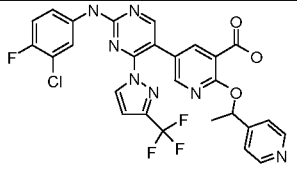
g) and sodium carbonate (0.95 mmol, 0.101 g) in acetonitrile/water (5 : 1) was degassed and heated to 90 °C for 30 min under an inert atmosphere. The solvent was concentrated *in vacuo* and the resultant crude mass was taken in EtOAc (50 mL), washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude mass was purified by silica gel column chromatography (product eluted with 45 % ethyl acetate/hexanes) to yield 0.415 g of the product.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 792	 methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[1-(pyridin-4-yl)ethoxy]pyridine-3-carboxylate	MS(ES): 614 (M+1) for $C_{28}H_{20}ClF_4N_7O_3$. 400 MHz, DMSO-d_6: δ 1.58 (d, *J* = 6.56 Hz, 3H), 3.85 (s, 3H), 6.33 (q, *J* = 6.52 Hz, 1H), 7.04 (d, *J* = 2.64 Hz, 1H), 7.43 (t, *J* = 9.12 Hz, 1H), 7.49 (d, *J* = 5.92 Hz, 2H), 7.70-7.71 (m, 1H), 7.94 (d, *J* = 2.44 Hz, 1H), 8.06 (dd, *J* = 2.56, 6.66 Hz, 1H), 8.18 (d, *J* = 2.44 Hz, 1H), 8.52 (s, 1H), 8.56 (m, 2H), 8.79 (s, 1H), 10.42 (s, 1H).	**Intermediate 300** {5-(methoxycarbonyl)-6-[1-(pyridin-4-yl)ethoxy]pyridin-3-yl}boronic acid

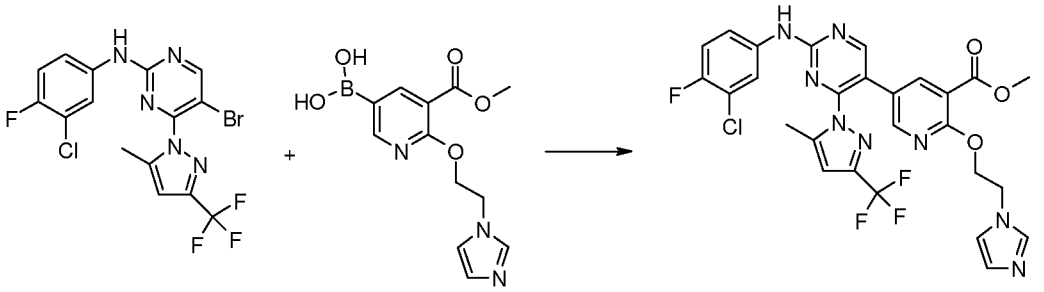
Example 793: 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[1-(pyridin-4-yl)ethoxy]pyridine-3-carboxylic acid



To 100 mg of methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[1-(pyridin-4-yl)ethoxy]pyridine-3-carboxylate (**Example 792**, 0.16 mmol) taken in a mixture of dioxane (4 mL) and water (4 mL), was added Barium hydroxide monohydrate (0.32 mmol, 0.062 g) and allowed to stir overnight at room temperature. The mixture was then carefully acidified with 1 N HCl and then diluted with ethyl acetate (50 mL), washed with water and brine, dried over Na_2SO_4 and concentrated. It was further purified by column chromatography using 1 % MeOH in $CHCl_3$ to yield 0.080 g of the product.

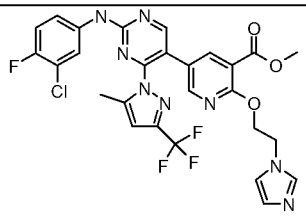
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 793	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[1-(pyridin-4-yl)ethoxy]pyridine-3-carboxylic acid	MS(ES): 600 (M+1) for $C_{27}H_{18}ClF_4N_7O_3$. 400 MHz, DMSO-d_6: δ 1.57 (d, J = 6.56 Hz, 3H), 6.31 (q, J = 6.48 Hz, 1H), 7.01 (d, J = 2.60 Hz, 1H), 7.41 (t, J = 9.08 Hz, 1H), 7.47 (d, J = 5.72 Hz, 2H), 7.68-7.72 (m, 1H), 7.87 (d, J = 2.40 Hz, 1H), 8.05 (dd, J = 2.48, 6.70 Hz, 1H), 8.11 (d, J = 2.28 Hz, 1H), 8.49 (s, 1H), 8.52 (d, J = 5.76 Hz, 2H), 8.76 (s, 1H), 10.40 (s, 1H), 13.09 (s, 1H).	**Example 792** methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[1-(pyridin-4-yl)ethoxy]pyridine-3-carboxylate

Example 794: methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[2-(1*H*-imidazol-1-yl)ethoxy]pyridine-3-carboxylate

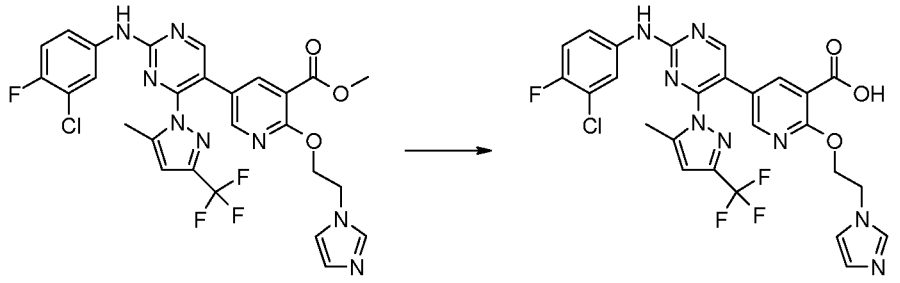


A suspension of 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 113**, 1.11 mmol, 0.5 g), a mixture of {6-[2-(1*H*-imidazol-1-yl)ethoxy]-5-(methoxycarbonyl)pyridin-3-yl}boronic acid and methyl 2-[2-(1*H*-imidazol-1-yl)ethoxy]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate (**Intermediate 303**, 1.66 mmol based on the boronic acid, 0.486 g), [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (0.22 mmol, 0.162 g) and sodium carbonate (1.1 mmol, 0.117 g) in acetonitrile/water (5 : 1) was degassed and heated to 90 °C for 1

h under an inert atmosphere. The solvent was concentrated *in vacuo* and the resultant crude mass taken in EtOAc (50 mL), was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was further purified by silica gel column chromatography (product eluted with 0.5 % Et_3N in EtOAc) to yield 0.31 g of the product.

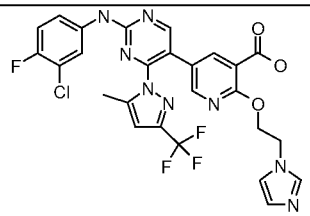
Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 794	 methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[2-(1*H*-imidazol-1-yl)ethoxy]pyridine-3-carboxylate	MS(ES): 617 (M+1) for $C_{27}H_{21}ClF_4N_8O_3$. 400 MHz, DMSO-d_6: δ 2.32 (s, 3H), 3.78 (s, 3H), 4.38 (t, *J* = 4.52 Hz, 2H), 4.55 (t, *J* = 5.00 Hz, 2H), 6.77 (s, 1H), 6.88 (s, 1H), 7.29 (s, 1H), 7.43 (t, *J* = 9.08 Hz, 1H), 7.63-7.68 (m, 2H), 7.69 (s, 1H), 8.07 (d, *J* = 4.60 Hz, 1H), 8.22 (d, *J* = 2.40 Hz, 1H), 8.96 (s, 1H), 10.47 (s, 1H).	**Intermediate 303** {6-[2-(1*H*-imidazol-1-yl)ethoxy]-5-(methoxycarbonyl)pyridin-3-yl}boronic acid

Example 795: 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[2-(1*H*-imidazol-1-yl)ethoxy]pyridine-3-carboxylic acid

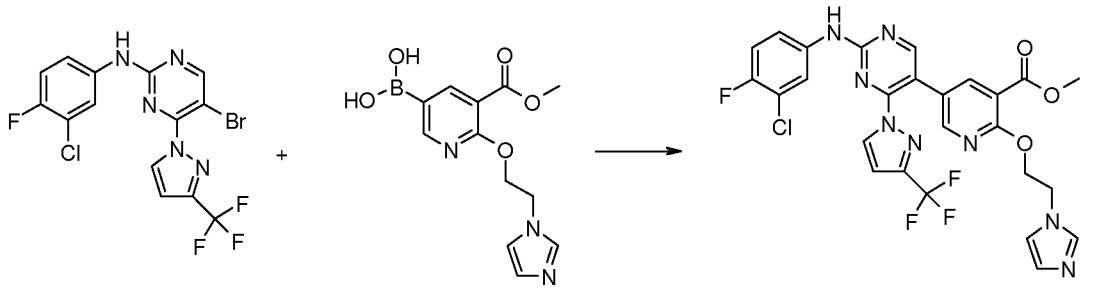


To 170 mg of methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[2-(1*H*-imidazol-1-yl)ethoxy]pyridine-3-carboxylate (**Example 794**, 0.27 mmol) taken in a mixture of dioxane (20 mL) and water (20 mL), was added Barium hydroxide monohydrate (0.27 mmol, 0.052 g) and the reaction mixture warmed to 50 °C for 24 h. Another equivalent of Barium hydroxide monohydrate (0.27 mmol,

0.052 g) was added and the reaction continued at 50 °C for 3 h more. The mixture was then carefully acidified with 1 N HCl. It was extracted with ethyl acetate (50 mL) and the organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated to yield 0.112 g of **Example 795.**

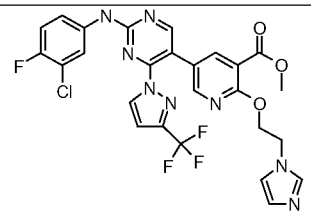
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 795	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[2-(1*H*-imidazol-1-yl)ethoxy]pyridine-3-carboxylic acid	MS(ES): 603 (M+1) for $C_{26}H_{19}ClF_4N_8O_3$. 400 MHz, DMSO-d_6: δ 2.30 (s, 3H), 4.35 (s, 2H), 4.49 (s, 2H), 6.74 (s, 1H), 6.85 (s, 1H), 7.35 (s, 1H), 7.41 (t, J = 9.16 Hz, 1H), 7.63 (br s, 2H), 7.73 (s, 1H), 8.00 (s, 1H), 8.05 (d, J = 4.52 Hz, 1H), 8.92 (s, 1H), 10.43 (s, 1H).	**Example 794** methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[2-(1*H*-imidazol-1-yl)ethoxy]pyridine-3-carboxylate

<u>Example 796: methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[2-(1*H*-imidazol-1-yl)ethoxy]pyridine-3-carboxylate</u>

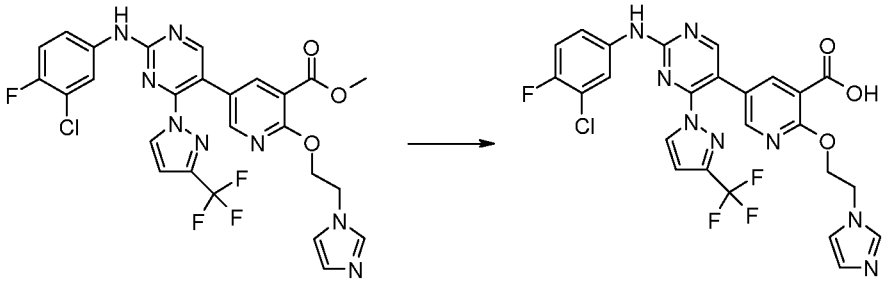


A suspension of 5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 115**, 1.14 mmol, 0.5 g), a mixture of {6-[2-(1*H*-imidazol-1-yl)ethoxy]-5-(methoxycarbonyl)pyridin-3-yl}boronic acid and methyl 2-[2-(1*H*-imidazol-1-yl)ethoxy]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate

(**Intermediate 303**, 1.72 mmol based on the boronic acid, 0.502 g), [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium (II) (0.22 mmol, 0.167 g) and sodium carbonate (1.14 mmol, 0.121 g) in acetonitrile/water (3 : 1) was degassed and heated to 90 °C for 1 h under an inert atmosphere. The solvent was concentrated *in vacuo* and the resultant crude mass was taken in EtOAc (50 mL), washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude material was further purified by silica gel column chromatography (product eluted with 0.5 % Et_3N in EtOAc) to yield 0.24 g of the product.

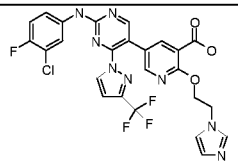
Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 796	 methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[2-(1*H*-imidazol-1-yl)ethoxy]pyridine-3-carboxylate	MS(ES): 603 (M+1) for $C_{26}H_{19}ClF_4N_8O_3$. 400 MHz, DMSO-d_6: δ 3.79 (s, 3H), 4.40-4.41 (m, 2H), 4.57-4.58 (m, 2H), 6.89 (s, 1H), 7.05 (d, *J* = 2.48 Hz, 1H), 7.30 (s, 1H), 7.52 (t, *J* = 9.04 Hz, 1H), 7.71-7.74 (m, 2H), 7.90 (d, *J* = 2.36 Hz, 1H), 8.08 (dd, *J* = 2.48, 6.58 Hz, 1H), 8.27 (d, *J* = 2.40 Hz, 1H), 8.51 (s, 1H), 8.79 (s, 1H), 10.43 (s, 1H).	**Intermediate 303** {6-[2-(1*H*-imidazol-1-yl)ethoxy]-5-(methoxycarbonyl)pyridin-3-yl}boronic acid

Example 797: 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[2-(1*H*-imidazol-1-yl)ethoxy]pyridine-3-carboxylic acid

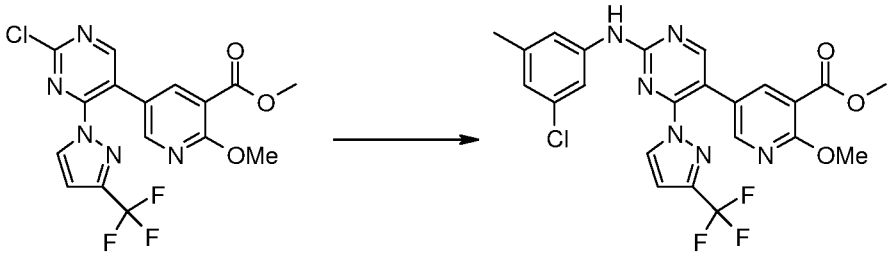


To 75 mg of methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[2-(1*H*-imidazol-1-yl)ethoxy]pyridine-3-carboxylate (**Example 796**, 0.12 mmol) taken in a mixture of dioxane (20 mL) and water (20 mL), was added Barium

hydroxide monohydrate (0.48 mmol, 0.094 g) and warmed to 50 °C for 3 h. The mixture was then carefully acidified with 1 N HCl. It was extracted with ethyl acetate (50 mL) and the organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated to yield 0.05 g of the title compound.

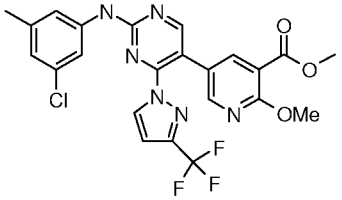
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 797	 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[2-(1*H*-imidazol-1-yl)ethoxy]pyridine-3-carboxylic acid	MS(ES): 589 (M+1) for $C_{25}H_{17}ClF_4N_8O_3$. 400 MHz, DMSO-d_6: δ 4.38-4.39 (m, 2H), 4.54 (s, 2H), 6.87 (s, 1H), 7.03 (s, 1H), 7.33 (s, 1H), 7.42 (t, J = 9.00 Hz, 1H), 7.70-7.72 (m, 2H), 7.86 (s, 1H), 8.08 (dd, J = 3.92 Hz, 1H), 8.21 (s, 1H), 8.48 (s, 1H), 8.78 (s, 1H), 10.40 (s, 1H).	**Example 796** methyl 5-{2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-[2-(1*H*-imidazol-1-yl)ethoxy]pyridine-3-carboxylate

Example 798: methyl 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

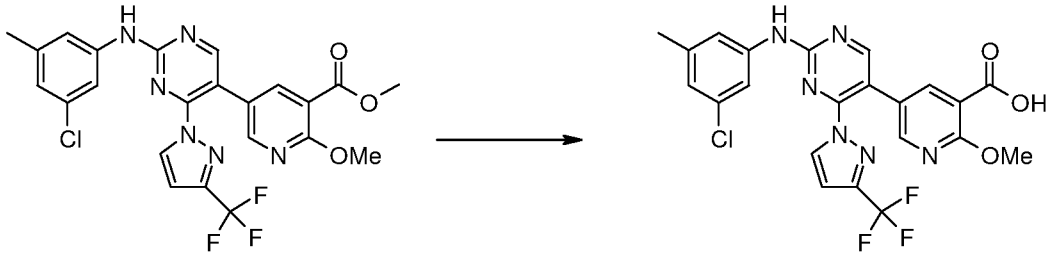


A suspension of methyl 5-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate (**Intermediate 325**, 0.73 mmol, 0.30 g), 3-chloro-5-methylaniline (0.87 mmol, 0.12 g), tris(dibenzylideneacetone)dipalladium(0) (0.073 mmol, 0.07 g), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (0.15 mmol, 0.07 g) and sodium carbonate (0.73 mmol, 0.08 g) in acetonitrile/water (25 mL:6 mL) was heated to 90 °C for 30

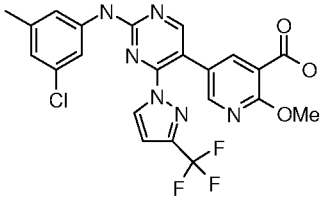
min. The reaction mixture was concentrated. The residue was taken in ethyl acetate, washed with water and brine. The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using 25% ethyl acetate/hexanes as an eluent to yield 0.200 g of **Example 798**.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 798	 methyl 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 519 (M+1) for $C_{23}H_{18}ClF_3N_6O_3$. 300 MHz, DMSO-d_6: δ 2.42 (s, 3H), 3.75 (s, 3H), 3.93 (s, 3H), 6.91 (s, 1H), 7.04 (d, J = 2.67 Hz, 1H), 7.62 (s, 1H), 7.79 (s, 1H), 7.85 (d, J = 2.46 Hz, 1H), 8.27 (d, J = 2.49 Hz, 1H), 8.46 (s, 1H), 8.80 (s, 1H), 10.34 (s, 1H).	**Intermediate 325** methyl 5-{2-chloro-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

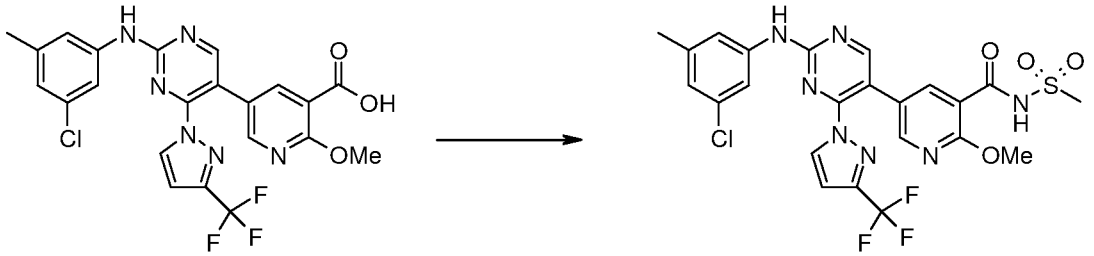
Example 799: 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid



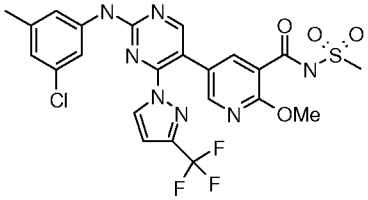
To 185 mg of methyl 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate (**Example 798**, 0.36 mmol) taken in a mixture of dioxane (5 mL) and water (5 mL), was added sodium hydroxide (0.9 mmol, 36 mg) and stirred at room temperature for 3 h. The reaction mixture was carefully acidified with 1 N HCl and further extracted with ethyl acetate (50 mL). The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was dissolved in a minimum amount of CH_2Cl_2, then hexanes was added and the solid that precipitated was filtered, washed and dried *in vacuo* to yield 85 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 799	 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 505 (M+1) for $C_{22}H_{16}ClF_3N_6O_3$. 400 MHz, DMSO-d_6: δ 2.31 (s, 3H), 3.92 (s, 3H), 6.92 (s, 1H), 7.03 (d, J = 2.56 Hz, 1H), 7.54 (s, 1H), 7.79 (s, 1H), 7.80 (m, 1H), 8.19 (s, 1H), 8.44 (s, 1H), 8.79 (s, 1H), 10.34 (s, 1H).	**Example 798** methyl 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

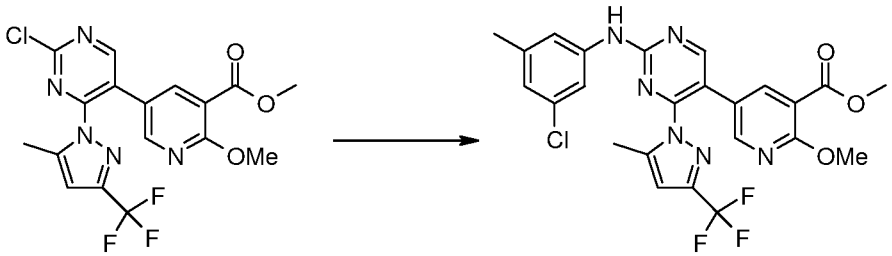
Example 800: 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(methylsulfonyl)pyridine-3-carboxamide



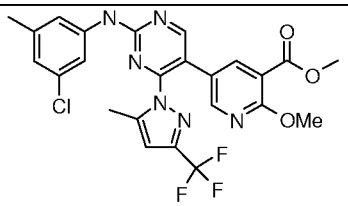
To a solution of 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 799**, 0.089 mmol, 45 mg) in CH_2Cl_2 (5mL), were added methanesulfonamide (0.22 mmol, 21 mg), 2-chloro-1-methylpyridinium iodide (0.11 mmol, 28 mg), 4-(Dimethylamino)pyridine (0.018 mmol, 2.1 mg) and triethylamine (0.27 mmol, 30 mg), and the solution stirred for 90 min at RT. The reaction mixture was diluted with dichloromethane and further washed with 25% citric acid solution, water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 1% MeOH in $CHCl_3$) to afford 30 mg of **Example 800** as an off-white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 800	 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(methylsulfonyl)pyridine-3-carboxamide	MS(ES): 582 (M+1) for $C_{23}H_{19}ClF_3N_7O_4S$. 400 MHz, DMSO-d_6: δ 2.32 (s, 3H), 3.33 (s, 3H), 3.97 (s, 3H), 6.94 (s, 1H), 7.06 (d, J = 2.60 Hz, 1H), 7.55 (s, 1H), 7.82 (s, 1H), 7.87 (d, J = 2.40 Hz, 1H), 8.19 (d, J = 2.40 Hz, 1H), 8.46 (d, J = 1.68 Hz, 1H), 8.81 (s, 1H), 10.39 (s, 1H), 11.75 (br s, 1H).	**Example 799** 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

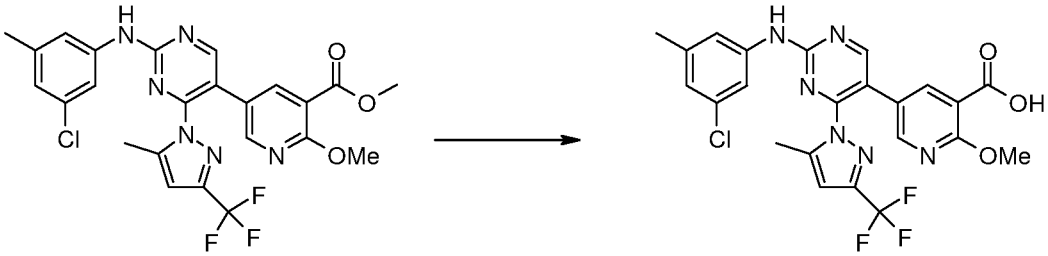
Example 801: methyl 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate



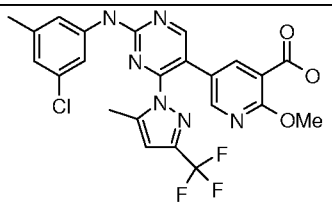
A suspension of methyl 5-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate (**Intermediate 327**, 0.82 mmol, 0.35 g), 3-chloro-5-methylaniline (0.98 mmol, 0.14 g), tris(dibenzylideneacetone)dipalladium(0) (0.08 mmol, 0.075 g), 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (0.16 mmol, 0.08 g) and sodium carbonate (0.8 mmol, 0.09 g) in acetonitrile/water (25 mL:6 mL) was heated to 90 °C for 30 min. The reaction mixture was concentrated. The residue was taken in ethyl acetate, washed with water and brine. The organic layer was separated, dried over sodium sulfate, filtered and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using 20-25% ethyl acetate/hexanes as an eluent to yield 0.230 g of **Example 801**.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 801	 methyl 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate	MS(ES): 533 (M+1) for $C_{24}H_{20}ClF_3N_6O_3$. 400 MHz, DMSO-d_6: δ 2.29 (s, 3H), 2.34 (s, 3H), 3.74 (s, 3H), 3.91 (s, 3H), 6.76 (s, 1H), 6.92 (s, 1H), 7.45 (s, 1H), 7.60 (d, J = 2.36 Hz, 1H), 7.79 (s, 1H), 8.22 (d, J = 2.40 Hz, 1H), 8.96 (s, 1H), 10.38 (s, 1H).	3-chloro-5-methylaniline and **Intermediate 327** methyl 5-{2-chloro-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

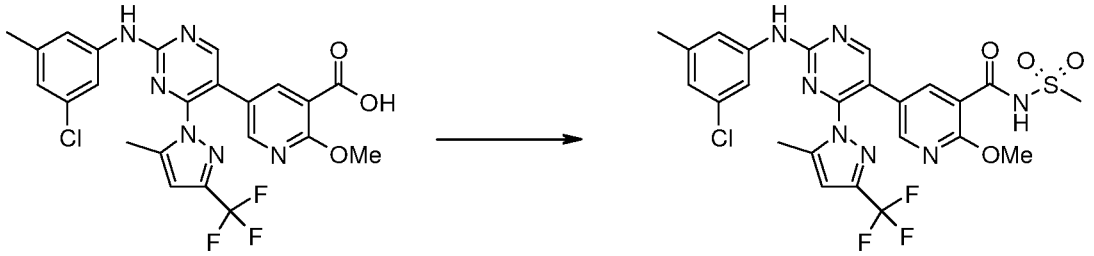
Example 802: 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid



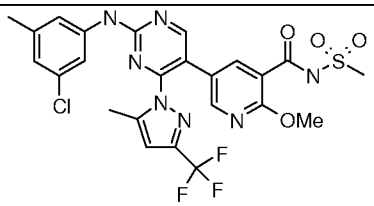
To 230 mg of methyl 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate (**Example 801**, 0.43 mmol) taken in a mixture of dioxane (10 mL) and water (5 mL), was added 1 N aq.sodium hydroxide (1.08 mmol) and stirred overnight at room temperature. The reaction mixture was carefully acidified with 1 N HCl and further extracted with ethyl acetate (50 mL). The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The oily compound that was obtained was further stirred with hexanes and the solid that precipitated was filtered, and dried *in vacuo* to yield 150 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 802	 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid	MS(ES): 519 (M+1) for $C_{23}H_{18}ClF_3N_6O_3$. 400 MHz, DMSO-d_6: δ 2.30 (s, 3H), 2.37 (s, 3H), 3.91 (s, 3H), 6.77 (s, 1H), 6.93 (s, 1H), 7.46 (s, 1H), 7.62 (d, J = 2.52 Hz, 1H), 7.80 (s, 1H), 8.17 (d, J = 2.48 Hz, 1H), 8.97 (s, 1H), 10.38 (s, 1H), 12.99 (br s, 1H).	**Example 801** methyl 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylate

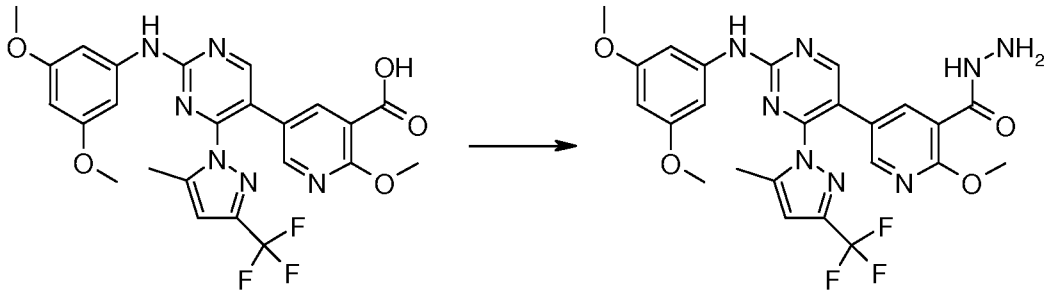
Example 803: 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(methylsulfonyl)pyridine-3-carboxamide



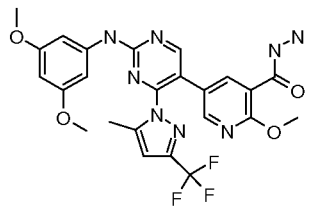
To a solution of 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 802**, 0.22 mmol, 0.115 g) in CH_2Cl_2 (10 mL), were added methanesulfonamide (0.55 mmol, 52 mg), 2-chloro-1-methylpyridinium iodide (0.27 mmol, 70 mg), 4-(Dimethylamino)pyridine (0.044 mmol, 5.4 mg) and triethylamine (0.06 mmol, 0.1 mL), and the solution stirred for 90 min at RT. The reaction mixture was diluted with dichloromethane and further washed with 25% citric acid solution, water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 1% MeOH in $CHCl_3$) to afford 90 mg of **Example 803**.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 803	 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(methylsulfonyl)pyridine-3-carboxamide	MS(ES): 596 (M+1) for $C_{24}H_{21}ClF_3N_7O_4S$. 400 MHz, DMSO-d_6: δ 2.30 (s, 3H), 2.36 (s, 3H), 3.33 (s, 3H), 3.93 (s, 3H), 6.79 (s, 1H), 6.94 (s, 1H), 7.47 (s, 1H), 7.70 (d, J = 2.40 Hz, 1H), 7.80 (s, 1H), 8.01 (d, J = 2.40 Hz, 1H), 8.98 (s, 1H), 10.41 (s, 1H), 11.78 (s, 1H).	**Example 802** 5-{2-[(3-chloro-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

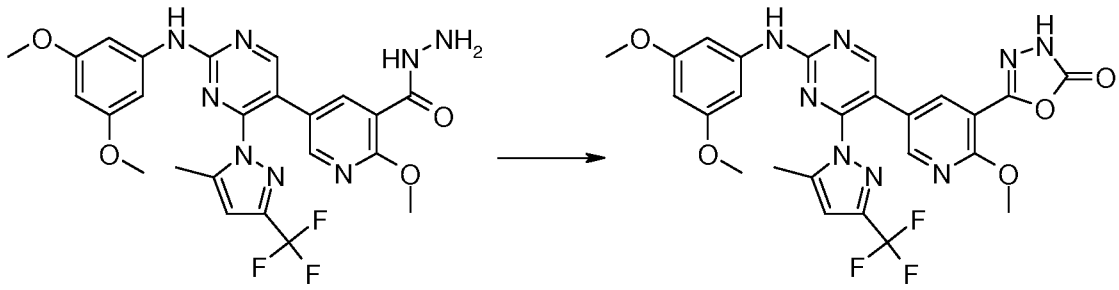
Example 804: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carbohydrazide



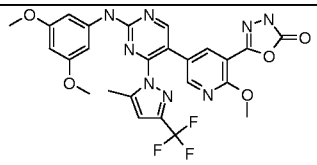
To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 677**, 0.37 mmol, 200 mg) and 4-(Dimethylamino)pyridine (0.075 mmol, 9 mg) in CH_2Cl_2 (25 mL) were added Hydrazine monohydrochloride (0.94 mmol, 64 mg), triethylamine (1.89 mmol, 0.255 mL), 2-chloro-1-methylpyridinium iodide (0.47 mmol, 120 mg) and stirred for 2 h at RT. The reaction mixture was diluted with dichloromethane (50 mL) and further washed with water (100 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 230-400 mesh silica (product eluted with 3-4% methanol/ dichloromethane) to afford 100 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 804	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carbohydrazide	Taken to the next step based on LCMS without further purification. MS(ES): 545 (M+1) for $C_{24}H_{23}F_3N_8O_4$. (70 % pure by UPLC)	**Example 677** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

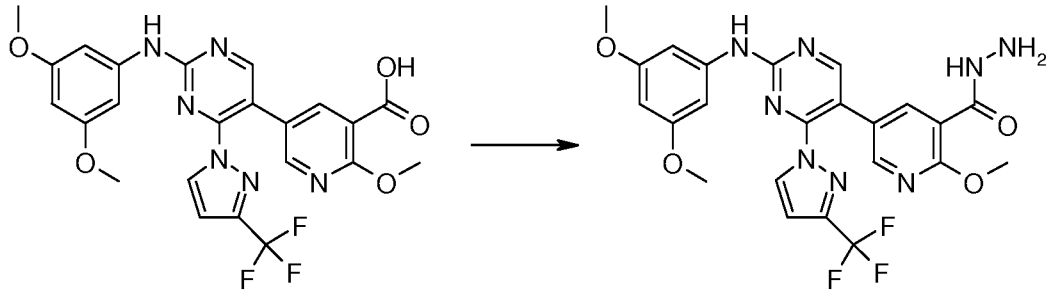
Example 805: 5-(5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridin-3-yl)-1,3,4-oxadiazol-2(3*H*)-one



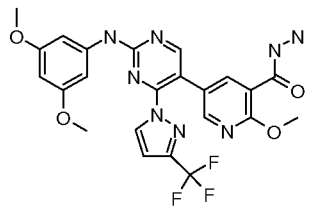
5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carbohydrazide (**Example 804**, 0.18 mmol,100 mg), 1,1′-carbonyldiimidazole (0.28 mmol, 44 mg), and *N*,*N*-diisopropylethylamine (0.28 mmol, 36 mg) in DMF (2 mL) were combined to give a white suspension. The reaction mixture was stirred at room temperature over 1 h, and then stirred at 50 °C for 1 h. The reaction mixture was poured onto ice-water, then extracted with ethyl acetate(50 mL x 2) and further washed with water (75 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 230-400 mesh silica (product eluted with 1% methanol/ dichloromethane) to afford **Example 805** as off-white solid (46 mg).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 805	 5-(5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridin-3-yl)-1,3,4-oxadiazol-2(3*H*)-one	MS(ES): 571 (M+1) for $C_{25}H_{21}F_3N_8O_5$. 400 MHz, DMSO-d_6: δ 2.34 (s, 3H), 3.71 (s, 6H), 3.95 (s, 3H), 6.20 (t, J = 2.16 Hz, 1H), 6.74 (s, 1H), 7.03 (s, 1H), 7.04 (s, 1H), 7.61 (d, J = 2.40 Hz, 1H), 8.14 (d, J = 2.36 Hz, 1H), 8.93 (s, 1H), 10.20 (s, 1H), 12.64 (s, 1H).	**Example 804** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carbohydrazide

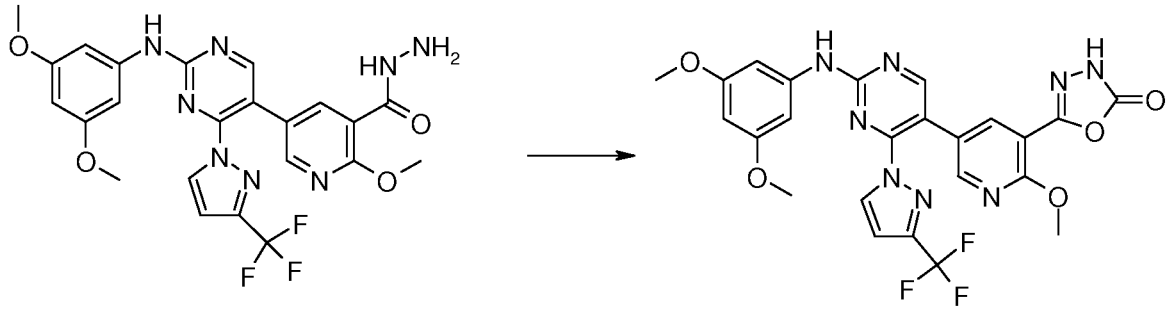
Example 806: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carbohydrazide



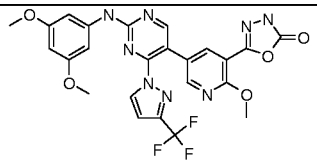
To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.38 mmol, 200 mg) and 4-(Dimethylamino)pyridine (0.077 mmol, 9 mg) in CH_2Cl_2 (25 mL) were added Hydrazine monohydrochloride (0.97 mmol, 66 mg), triethylamine (1.94 mmol, 2.62 mL), 2-chloro-1-methylpyridinium iodide (0.48 mmol, 124 mg) and stirred 8 h at RT. The reaction mixture was diluted with dichloromethane (50 mL) and further washed with water (100 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 230-400 mesh silica (product eluted with 3-4% methanol/ dichloromethane) to afford 120 mg of **Example 806.**

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 806	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carbohydrazide	Taken to the next step based on LCMS without further purification. MS(ES): 531 (M+1) for $C_{23}H_{21}F_3N_8O_4$. (40 % pure by UPLC)	**Example 675** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

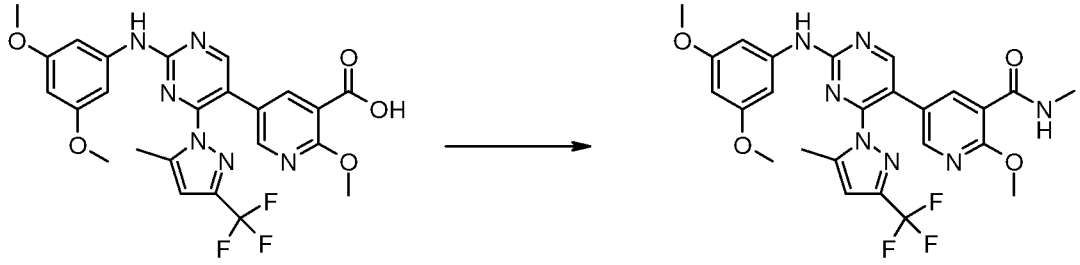
Example 807: 5-(5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridin-3-yl)-1,3,4-oxadiazol-2(3*H*)-one



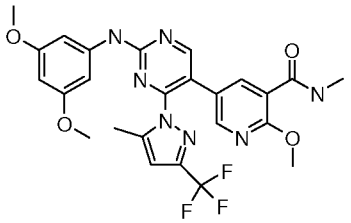
5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carbohydrazide (**Example 806**, 0.36 mmol, 190 mg), 1,1′-carbonyldiimidazole (0.54 mmol, 87 mg), and *N*,*N*-diisopropylethylamine (0.54 mmol, 70 mg) in DMF (2 mL) were combined to give a white suspension. The reaction mixture was stirred at room temperature over 1 h, and then stirred at 50 °C for 1 h. The reaction mixture was poured on to ice-water, then extracted with ethyl acetate(50 mL x 2) and further washed with water (75 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 230-400 mesh silica (product eluted with 1% methanol/ dichloromethane) to afford **Example 807** as light brown solid (33 mg).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 807	 5-(5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridin-3-yl)-1,3,4-oxadiazol-2(3*H*)-one	MS(ES): 557 (M+1) for $C_{24}H_{19}F_3N_8O_5$. 400 MHz, DMSO-d_6: δ 3.74 (s, 6H), 3.99 (s, 3H), 6.21 (t, J = 2.12 Hz, 1H), 7.04 (d, J = 2.52 Hz, 1H), 7.09 (s, 1H), 7.10 (s, 1H), 7.83 (d, J = 2.36 Hz, 1H), 8.25 (d, J = 2.36 Hz, 1H), 8.49 (s, 1H), 8.78 (s, 1H), 10.19 (s, 1H), 12.64 (s, 1H).	**Example 806** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carbohydrazide

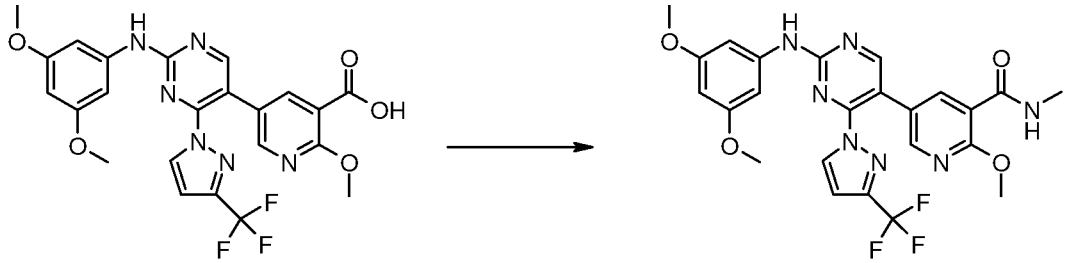
Example 808: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-methylpyridine-3-carboxamide



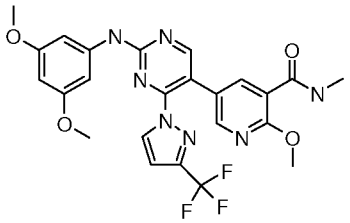
To a mixture of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 677**, 0.47 mmol, 250 mg), triethylamine (1.41 mmol, 0.2 mL, 0.143 mg) and methylamine hydrochloride (0.94 mmol, 64 mg) in dichloromethane was added T_3P (50 % w/w solution in EtOAc; 0.94 mmol, 0.6 mL, 300 mg) at 0 °C. The reaction mixture was slowly raised to room temperature and stirred 2 h. The mixture was then diluted with dichloromethane (15 mL), and the organic layer was successively washed with water (2x20 mL), 10 % aq sodium bicarbonate solution (15 mL) and brine. The organic layer was dried over sodium sulphate and concentrated to yield 180 mg of **Example 808**.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 808	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-methylpyridine-3-carboxamide	MS(ES): 544 (M+1) for $C_{25}H_{24}F_3N_7O_4$. 400 MHz, DMSO-d_6: δ 2.31 (s, 3H), 2.78 (d, *J* = 4.64 Hz, 3H), 3.73 (s, 6H), 3.96 (s, 3H), 6.21 (t, *J* = 2.16 Hz, 1H), 6.75 (s, 1H), 7.05 (d, *J* = 2.04 Hz, 2H), 7.78 (d, *J* = 2.48 Hz, 1H), 8.02 (d, *J* = 2.48 Hz, 1H), 8.21 (d, *J* = 4.72 Hz, 1H), 8.91 (s, 1H), 10.21 (s, 1H).	**Example 677** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

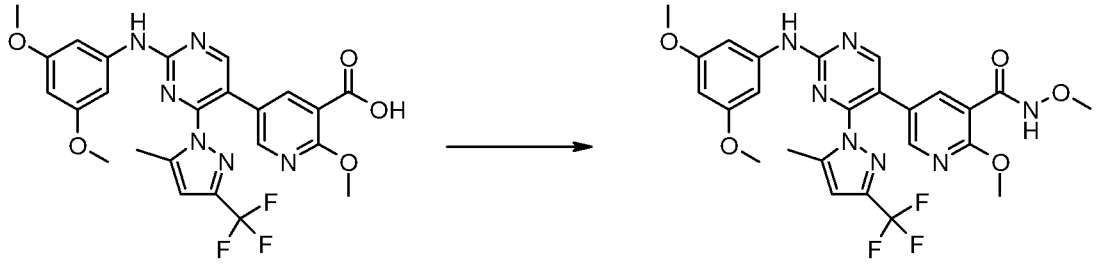
Example 809: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-methylpyridine-3-carboxamide



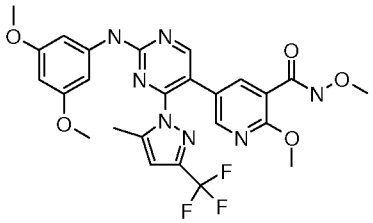
To a mixture of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.48 mmol, 250 mg), triethylamine (1.46 mmol, 0.20 mL, 145 mg) and methylamine hydrochloride (0.97 mmol, 66 mg) in dichloromethane (10 mL) was added T_3P (50 % w/w solution in EtOAc, 0.97 mmol, 0.62 mL, 310 mg) slowly at 0 °C. The reaction mixture was slowly raised to room temperature and stirred for 2 h. The reaction mixture was then diluted with dichloromethane (15 mL) and the dichloromethane layer was washed successively with water (2x20 mL), 10 % aq sodium bicarbonate solution (15 mL) and brine. The organic layer was dried over sodium sulphate and concentrated. The crude material was purified by silica gel column chromatography (230-400 mesh) using 2 % methanol/chloroform to yield 230 mg of **Example 809**.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 809	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-methylpyridine-3-carboxamide	MS(ES): 530 (M+1) for $C_{24}H_{22}F_3N_7O_4$. 400 MHz, DMSO-d_6: δ 2.80 (d, J = 4.64 Hz, 3H), 3.75 (s, 6H), 4.00 (s, 3H), 6.21 (t, J = 2.16 Hz, 1H), 7.02 (d, J = 2.60 Hz, 1H), 7.11 (d, J = 2.16 Hz, 2H), 7.93 (d, J = 2.48 Hz, 1H), 8.16 (d, J = 2.48 Hz, 1H), 8.24 (d, J = 4.68 Hz, 1H), 8.45 (d, J = 1.64 Hz, 1H), 8.76 (s, 1H), 10.18 (s, 1H).	**Example 675** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

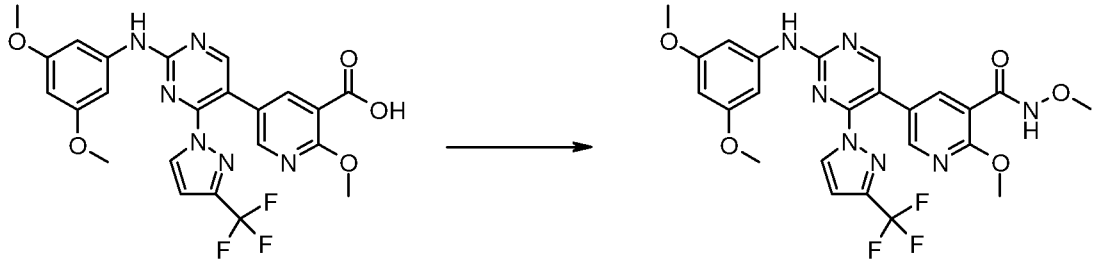
Example 810: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*,2-dimethoxypyridine-3-carboxamide



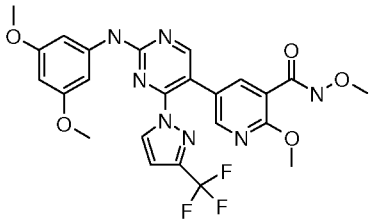
To a mixture of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 677**, 0.47 mmol, 250 mg), triethylamine (0.94 mmol, 0.13 mL, 94 mg) and methoxylamine hydrochloride (0.7 mmol, 59 mg) in dichloromethane, was added TBTU (0.56 mmol, 182 mg) slowly at 0 °C. The reaction mixture was slowly raised to room temperature and stirred for 2 h. The reaction mixture was then diluted with dichloromethane (15 mL) and the dichloromethane solution was washed successively with water (2x20 mL), 10 % aq sodium bicarbonate solution (20 mL) and brine. The organic layer was dried over sodium sulphate, and concentrated to yield 170 mg of **Example 810**.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 810	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*,2-dimethoxypyridine-3-carboxamide	MS(ES): 560 (M+1) for $C_{25}H_{24}F_3N_7O_5$. 400 MHz, DMSO-d_6: δ 2.31 (s, 3H), 3.68 (s, 3H), 3.73 (s, 6H), 3.93 (s, 3H), 6.22 (t, *J* = 2.00 Hz, 1H), 6.76 (s, 1H), 7.05 (d, *J* = 1.96 Hz, 2H), 7.65 (d, *J* = 2.36 Hz, 1H), 8.03 (d, *J* = 2.36 Hz, 1H), 8.93 (s, 1H), 10.22 (s, 1H), 11.31 (s, 1H).	**Example 677** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

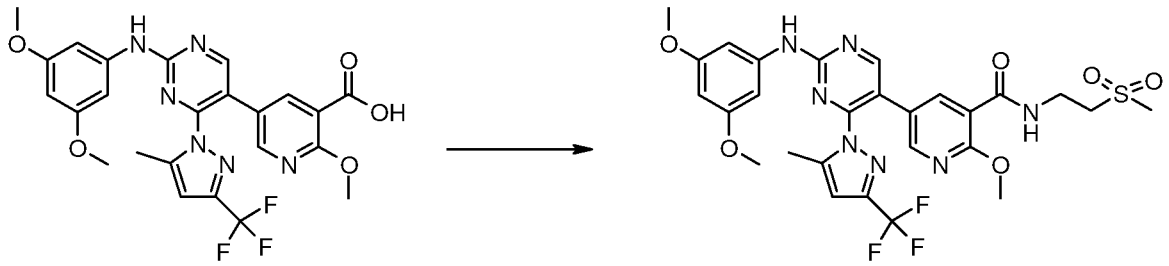
Example 811: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*,2-dimethoxypyridine-3-carboxamide



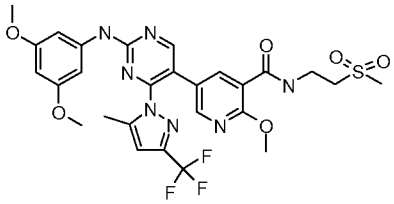
To a mixture of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.48 mmol, 250 mg), triethylamine (0.97 mmol, 0.14 mL, 98 mg) and methoxylamine hydrochloride (0.73 mmol, 61 mg) in dichloromethane, was added TBTU (0.58 mmol, 187 mg) slowly at 0 °C. The reaction mixture was slowly raised to room temperature and stirred for 2 h. The reaction mixture was then diluted with dichloromethane (15 mL) and the dichloromethane solution was washed successively with water (2x20 mL), 10 % aq sodium bicarbonate solution (20 mL) and brine. The organic layer was dried over sodium sulphate, and concentrated. The crude material was purified by silica gel column chromatography using 2 % methanol/chloroform to yield 220 mg of **Example 811.**

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 811	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*,2-dimethoxypyridine-3-carboxamide	MS(ES): 546 (M+1) for $C_{24}H_{22}F_3N_7O_5$. 400 MHz, DMSO-d_6: δ 3.69 (s, 3H), 3.75 (s, 6H), 3.96 (s, 3H), 6.21 (t, J = 2.16 Hz, 1H), 7.03 (d, J = 2.64 Hz, 1H), 7.11 (d, J = 2.16 Hz, 2H), 7.85 (d, J = 2.36 Hz, 1H), 8.16 (d, J = 2.44 Hz, 1H), 8.45 (d, J = 1.56 Hz, 1H), 8.76 (s, 1H), 10.18 (s, 1H), 11.31 (s, 1H).	**Example 675** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

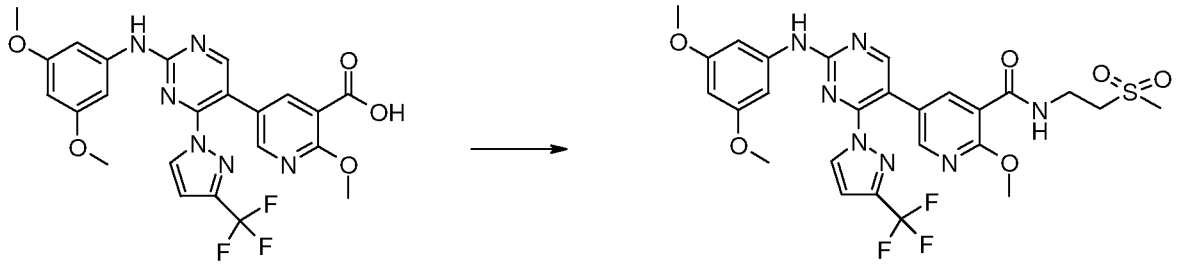
Example 812: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-[2-(methylsulfonyl)ethyl]pyridine-3-carboxamide



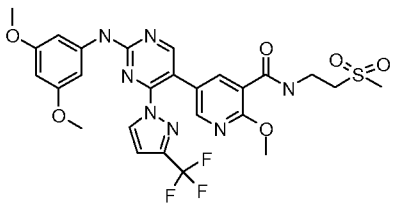
To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 677**, 0.28 mmol, 150 mg) and [2-(methylsulfonyl)ethyl]amine (0.71 mmol, 87 mg) in CH_2Cl_2 (5 mL), were added 2-chloro-1-methylpyridinium iodide (0.35 mmol, 90 mg), 4-(Dimethylamino)pyridine (0.056 mmol, 7 mg) and triethylamine (0.85 mmol, 85 mg), and the solution stirred for 90 min at RT. The reaction mixture was diluted with dichloromethane and further washed with 25% citric acid solution, water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 1% MeOH in $CHCl_3$) to afford 80 mg of **Example 812** as an off-white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 812	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-[2-(methylsulfonyl)ethyl]pyridine-3-carboxamide	MS(ES): 636 (M+1) for $C_{27}H_{28}F_3N_7O_6S$. 400 MHz, DMSO-d_6: δ 2.31 (s, 3H), 3.04 (s, 3H), 3.35 (t, *J* = 6.40 Hz, 2H), 3.69 (m, 2H, partly merges with water peak), 3.71 (s, 6H), 3.95 (s, 3H), 6.20 (d, *J* = 1.20 Hz, 1H), 6.73 (s, 1H), 7.04 (s, 2H), 7.81 (dd, *J* = 1.20, 2.48 Hz, 1H), 8.05 (dd, *J* = 1.16, 2.42 Hz, 1H), 8.59 (t, *J* = 5.84 Hz, 1H), 8.89 (d, *J* = 1.16 Hz, 1H), 10.19 (s, 1H).	**Example 677** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

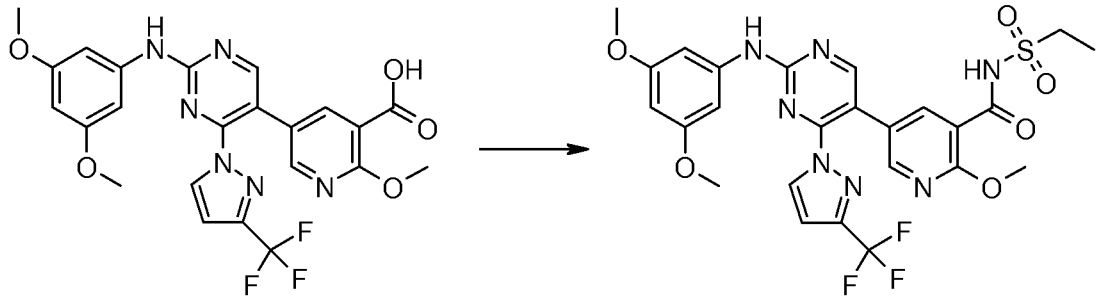
Example 813: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-[2-(methylsulfonyl)ethyl]pyridine-3-carboxamide



To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.29 mmol, 150 mg) and [2-(methylsulfonyl)ethyl]amine (0.72 mmol, 89 mg)in CH_2Cl_2 (5mL), were added 2-chloro-1-methylpyridinium iodide (0.36 mmol, 92 mg), 4-(Dimethylamino)pyridine (0.058 mmol, 7 mg) and triethylamine (0.87 mmol, 88 mg), and the solution stirred for 90 min at RT. The reaction mixture was diluted with dichloromethane and further washed with 25% citric acid solution, water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 1% MeOH in $CHCl_3$) to afford 95 mg of **Example 813** as an off-white solid.

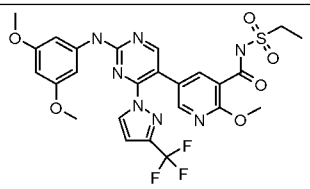
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 813	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-[2-(methylsulfonyl)ethyl]pyridine-3-carboxamide	MS(ES): 622(M+1) for $C_{26}H_{26}F_3N_7O_6S$. 400 MHz, DMSO-d_6: δ 3.04 (s, 3H), 3.36 (t, *J* = 6.76 Hz, 2H), 3.71 (m, 2H), 3.73 (s, 6H), 3.99 (s, 3H), 6.20 (t, *J* = 2.20 Hz, 1H), 7.02 (d, *J* = 2.60 Hz, 1H), 7.10 (d, *J* = 2.20 Hz, 2H), 7.97 (d, *J* = 2.52 Hz, 1H), 8.18 (d, *J* = 2.48 Hz, 1H), 8.45 (d, *J* = 1.68 Hz, 1H), 8.64 (s, 1H), 8.75 (s, 1H), 10.18 (s, 1H).	**Example 675** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

Example 814: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(ethylsulfonyl)-2-methoxypyridine-3-carboxamide

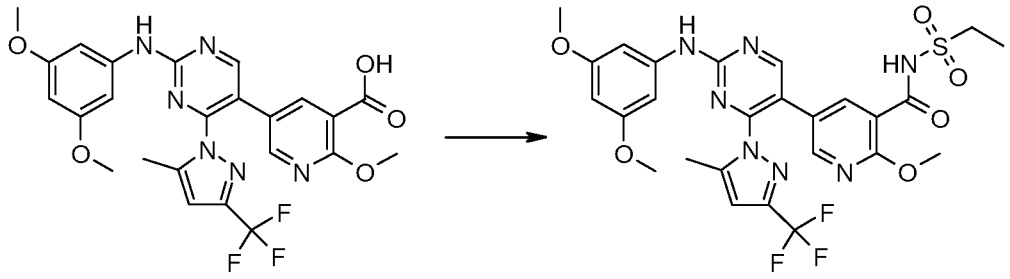


To a solution of 5-{2-[(3,5-dimethoxylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid **Example 675** (0.48 mmol, 0.250 g) in CH_2Cl_2 (25 mL), were added ethanesulfonamide (**Intermediate 328**, 1.16 mmol, 0.126 g), triethylamine (1.45 mmol, 0.204 mL), 2-chloro-1-methylpyridinium iodide (0.58 mmol, 0.148 g) and 4-(Dimethylamino)pyridine (0.097 mmol, 0.012 g) and stirred overnight at RT. The reaction mixture was diluted with dichloromethane (50 mL) and further washed with 25% citric acid solution (2 x 50 mL), water (100 mL) and brine (75 mL). The organic layer was dried over

Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 1-2% MeOH in $CHCl_3$) to afford 120 mg of white solid of **Example 814**.

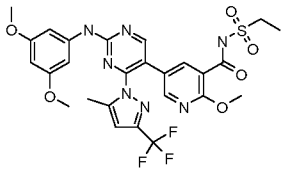
Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 814	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(ethylsulfonyl)-2-methoxypyridine-3-carboxamide	MS(ES): 608 (M+1) for $C_{25}H_{24}F_3N_7O_6S$. 400 MHz, DMSO-d_6: δ 1.26 (t, J = 7.32 Hz, 3H), 3.46 (q, J = 7.32 Hz, 2H), 3.73 (s, 6H), 3.95 (s, 3H), 6.20 (t, J = 2.08 Hz, 1H), 7.04 (d, J = 2.56 Hz, 1H), 7.10 (d, J = 2.08 Hz, 2H), 7.80 (d, J = 2.36 Hz, 1H), 8.19 (d, J = 2.36 Hz, 1H), 8.44 (d, J = 1.76 Hz, 1H), 8.77 (s, 1H), 10.19 (s, 1H), 11.70 (s, 1H).	**Intermediate 328** ethanesulfonamide and **Example 675** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

Example 815: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(ethylsulfonyl)-2-methoxypyridine-3-carboxamide

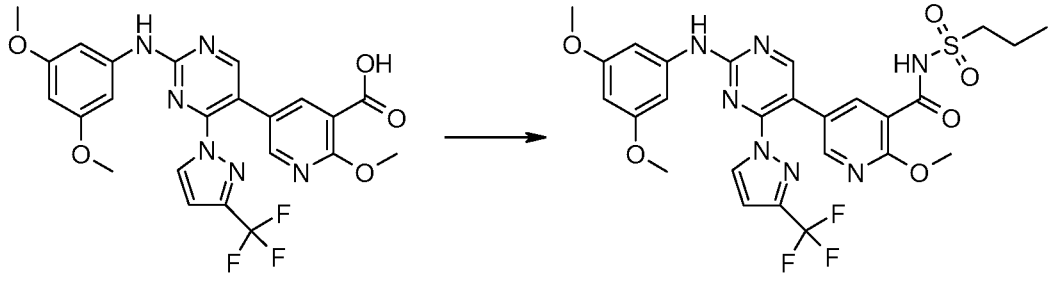


To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 677**, 0.19 mmol, 100 mg) in CH_2Cl_2 (10 mL), were added ethanesulfonamide (**Intermediate 328**, 0.47 mmol, 52 mg), triethylamine (0.56 mmol, 57 mg), 2-chloro-1-methylpyridinium iodide (0.23 mmol, 60 mg) and 4-(Dimethylamino)pyridine (0.037 mmol, 4.5 mg) and stirred at RT for 3-4 h. The reaction mixture was diluted with dichloromethane and further washed with water and brine. The organic

layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 1% MeOH in $CHCl_3$) to afford 40 mg of the title compound.

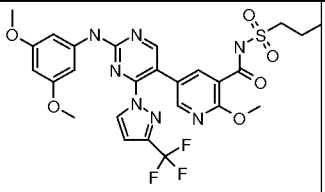
Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 815	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(ethylsulfonyl)-2-methoxypyridine-3-carboxamide	MS(ES): 622 (M+1) for $C_{26}H_{26}F_3N_7O_6S$. 400 MHz, DMSO-d_6: δ 1.25 (t, J = 7.36 Hz, 3H), 2.30 (s, 3H), 3.44 (q, J = 7.36 Hz, 2H), 3.72 (s, 6H), 3.92 (s, 3H), 6.21 (t, J = 2.00 Hz, 1H), 6.76 (s, 1H), 7.05 (d, J = 1.92 Hz, 2H), 7.62 (d, J = 2.40 Hz, 1H), 8.02 (d, J = 2.28 Hz, 1H), 8.94 (s, 1H), 10.22 (s, 1H), 11.72 (s, 1H).	**Intermediate 328** ethanesulfonamide and **Example 677** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

Example 816: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(propylsulfonyl)pyridine-3-carboxamide

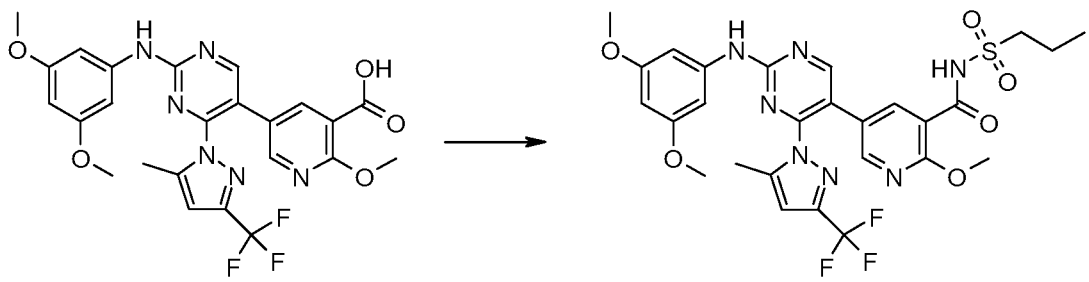


To a solution of 5-{2-[(3,5-dimethoxylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (0.48 mmol, 0.250 g) in CH_2Cl_2 (25 mL), were added propane-1-sulfonamide (**Intermediate 329**, 1.16 mmol, 0.143 g), triethylamine (1.45 mmol, 0.204 mL), 2-chloro-1-methylpyridinium iodide (0.58 mmol, 0.148 g) and 4-

(Dimethylamino)pyridine (0.097 mmol, 0.012 g) and stirred overnight at RT. The reaction mixture was diluted with dichloromethane (50 mL) and further washed with 25% citric acid solution (2 x 50 mL), water (100 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 1.5-2.5% MeOH in $CHCl_3$) to afford 170 mg of **Example 816** as a white solid.

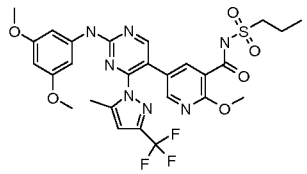
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 816	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(propylsulfonyl)pyridine-3-carboxamide	MS(ES): 622 (M+1) for $C_{26}H_{26}F_3N_7O_6S$. 400 MHz, DMSO-d_6: δ 1.00 (t, J = 7.44 Hz, 3H), 1.73 (q, J = 7.52 Hz, 2H), 3.44 (t, J = 7.64 Hz, 2H), 3.73 (s, 6H), 3.95 (s, 3H), 6.20 (t, J = 2.00 Hz, 1H), 7.04 (d, J = 2.56 Hz, 1H), 7.10 (d, J = 2.04 Hz, 2H), 7.80 (d, J = 2.28 Hz, 1H), 8.19 (d, J = 2.36 Hz, 1H), 8.44 (d, J = 1.88 Hz, 1H), 8.77 (s, 1H), 10.19 (s, 1H), 11.71 (s, 1H).	**Intermediate 329** propane-1-sulfonamide and **Example 675** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

Example 817: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(propylsulfonyl)pyridine-3-carboxamide

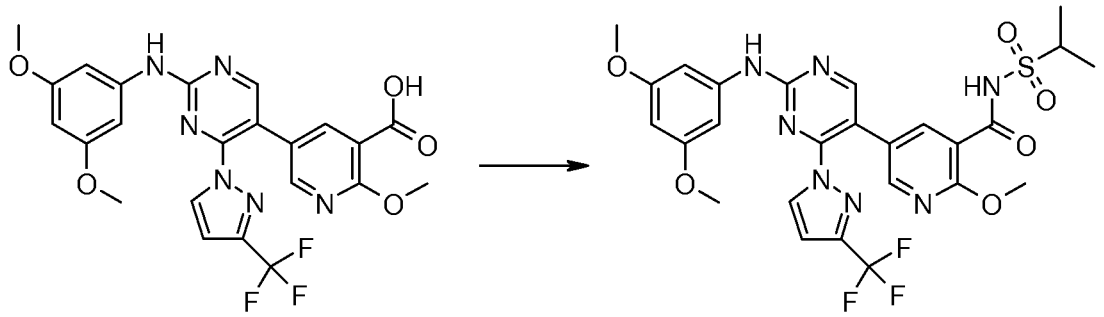


To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 677**, 0.19 mmol,

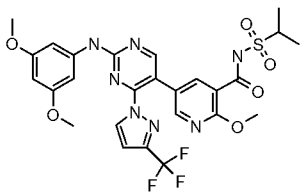
100 mg) in CH_2Cl_2 (10 mL), were added propane-1-sulfonamide (**Intermediate 329**, 0.47 mmol, 60 mg), triethylamine (0.56 mmol, 57 mg), 2-chloro-1-methylpyridinium iodide (0.23 mmol, 60 mg) and 4-(Dimethylamino)pyridine (0.037 mmol, 4.5 mg) and stirred at RT for 1 h. The reaction mixture was diluted with dichloromethane and further washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 1% MeOH in $CHCl_3$) to afford 40 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 817	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(propylsulfonyl)pyridine-3-carboxamide	MS(ES): 636 (M+1) for $C_{27}H_{28}F_3N_7O_6S$. 400 MHz, DMSO-d_6: δ 1.01 (t, J = 7.44 Hz, 3H), 1.71-1.76 (m, 2H), 2.32 (s, 3H), 3.43 (t, J = 7.96 Hz, 2H), 3.73 (s, 6H), 3.93 (s, 3H), 6.22 (t, J = 2.16 Hz, 1H), 6.77 (s, 1H), 7.06 (d, J = 2.12 Hz, 2H), 7.63 (d, J = 2.44 Hz, 1H), 8.03 (d, J = 2.44 Hz, 1H), 8.94 (s, 1H), 10.23 (s, 1H), 11.75 (s, 1H).	**Intermediate 329** propane-1-sulfonamide and **Example 677** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

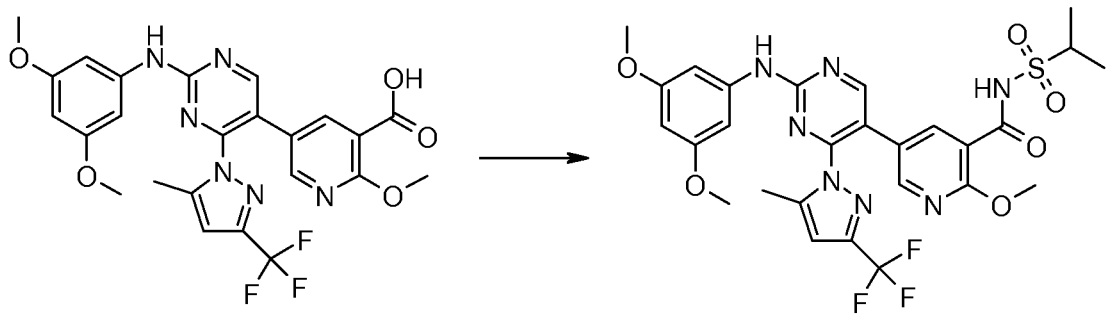
Example 818: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(propan-2-ylsulfonyl)pyridine-3-carboxamide



To a solution of 5-{2-[(3,5-dimethoxylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.38 mmol, 0.2 g) in CH_2Cl_2 (10 mL), were added propane-2-sulfonamide (**Intermediate 330**, 0.58 mmol, 0.07 g), triethylamine (0.86 mmol, 0.12 mL, 86 mg), 2-chloro-1-methylpyridinium iodide (0.45 mmol, 0.116 g) and 4-(Dimethylamino)pyridine (0.06 mmol, 7 mg) and stirred at RT for 3-4 h. The reaction mixture was diluted with dichloromethane and further washed with 25% citric acid solution, water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 1% MeOH in $CHCl_3$) to afford 100 mg of the title compound.

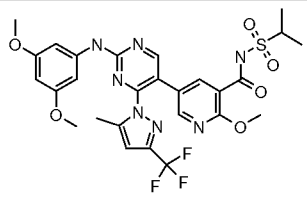
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 818	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(propan-2-ylsulfonyl)pyridine-3-carboxamide	MS(ES): 622 (M+1) for $C_{26}H_{26}F_3N_7O_6S$. 400 MHz, $CDCl_3$: δ 1.49 (d, *J* = 6.92 Hz, 6H), 3.84 (s, 6H), 3.98-3.99 (m, 1H), 4.22 (s, 3H), 6.28 (t, *J* = 2.08 Hz, 1H), 6.67 (d, *J* = 2.60 Hz, 1H), 6.88 (d, *J* = 2.12 Hz, 2H), 7.35 (s, 1H), 8.26 (d, *J* = 2.48 Hz, 1H), 8.31 (d, *J* = 2.52 Hz, 1H), 8.48 (s, 1H), 8.49 (d, *J* = 1.84 Hz, 1H), 9.91 (s, 1H).	**Intermediate 330** propane-2-sulfonamide and **Example 675** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

Example 819: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(propan-2-ylsulfonyl)pyridine-3-carboxamide

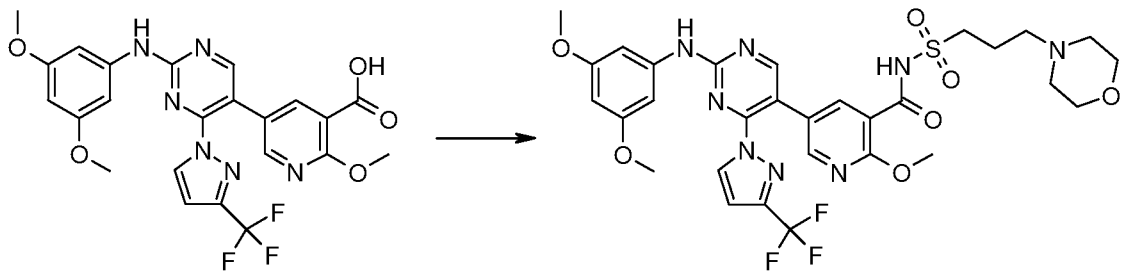


To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 677**, 0.37 mmol, 0.2 g) in CH_2Cl_2 (10 mL), were added propane-2-sulfonamide (**Intermediate 330**, 0.56 mmol, 0.07 g), triethylamine (1.1 mmol, 0.15 mL), 2-chloro-1-methylpyridinium iodide (0.45 mmol, 0.116 g) and 4-(Dimethylamino)pyridine (0.06 mmol, 7 mg) and stirred at RT for 3-4 h. The reaction mixture was diluted with dichloromethane and further washed with 25% citric acid

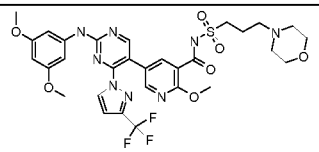
solution, water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 1% MeOH in $CHCl_3$) to afford 130 mg of the title compound.

Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 819	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(propan-2-ylsulfonyl)pyridine-3-carboxamide	MS(ES): 636 (M+1) for $C_{27}H_{28}F_3N_7O_6S$. 400 MHz, $CDCl_3$: δ 1.48 (d, *J* = 6.92 Hz, 6H), 2.47 (s, 3H), 3.81 (s, 6H), 3.93-3.97 (m, 1H), 4.18 (s, 3H), 6.26 (t, *J* = 2.08 Hz, 1H), 6.44 (s, 1H), 6.87 (d, *J* = 2.12 Hz, 2H), 7.36 (s, 1H), 8.03 (d, *J* = 2.52 Hz, 1H), 8.08 (d, *J* = 2.52 Hz, 1H), 8.63 (s, 1H), 9.84 (s, 1H).	**Intermediate 330** propane-2-sulfonamide and **Example 677** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

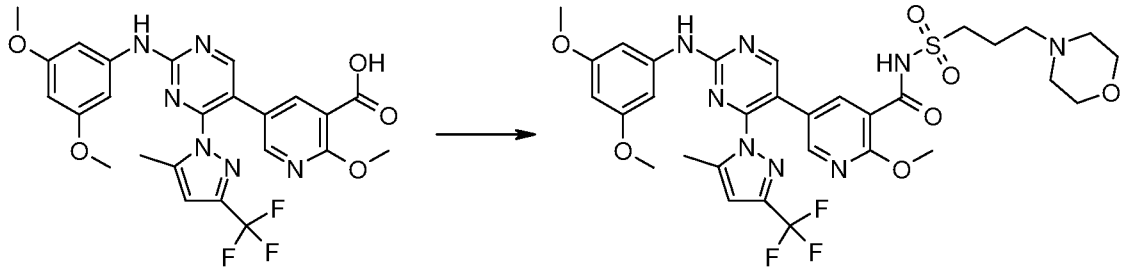
Example 820: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-{[3-(morpholin-4-yl)propyl]sulfonyl}pyridine-3-carboxamide



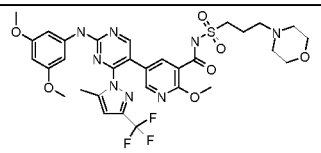
To a solution of 5-{2-[(3,5-dimethoxylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.38 mmol, 0.2 g) and 4-(Dimethylamino)pyridine (0.06 mmol, 7 mg) in CH_2Cl_2 (10 mL), were added 3-(morpholin-4-yl)propane-1-sulfonamide (**Intermediate 332**, 0.58 mmol, 0.12 g), triethylamine (0.86 mmol, 0.12 mL, 86 mg), 2-chloro-1-methylpyridinium iodide (0.45 mmol, 0.116 g) and stirred at RT for 3-4 h. The reaction mixture was diluted with dichloromethane and further washed with 25% citric acid solution, water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 1% MeOH in $CHCl_3$) to afford 70 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 820	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-{[3-(morpholin-4-yl)propyl]sulfonyl}pyridine-3-carboxamide	MS(ES): 707 (M+1) for $C_{30}H_{33}F_3N_8O_7S$. 400 MHz, DMSO-d_6: δ 1.91 (br s, 2H), 2.57-2.63 (m, 5H), 3.39 (m, 3H), 3.61 (s, 4H), 3.74 (s, 6H), 3.91 (s, 3H), 6.20 (s, 1H), 7.02 (s, 1H), 7.10 (s, 2H), 7.76 (s, 1H), 8.08 (s, 1H), 8.41 (s, 1H), 8.74 (s, 1H), 10.18 (s, 1H).	**Intermediate 332** 3-(morpholin-4-yl)propane-1-sulfonamide and **Example 675** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

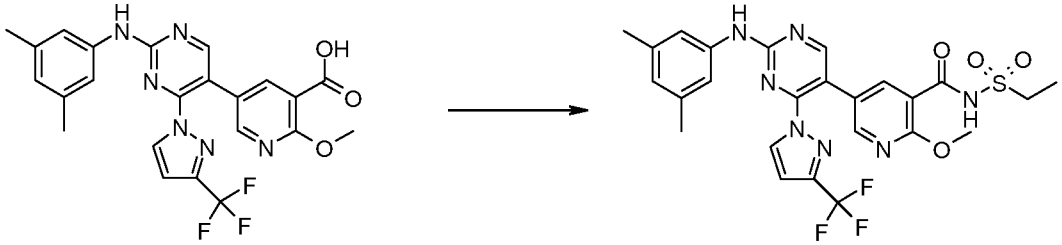
Example 821: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-{[3-(morpholin-4-yl)propyl]sulfonyl}pyridine-3-carboxamide



To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 677**, 0.37 mmol, 0.2 g) and 4-(Dimethylamino)pyridine (0.06 mmol, 7 mg) in CH_2Cl_2 (10 mL) were added 3-(morpholin-4-yl)propane-1-sulfonamide (**Intermediate 332**, 0.58 mmol, 0.12 g), triethylamine (1.1 mmol, 0.15 mL), 2-chloro-1-methylpyridinium iodide (0.45 mmol, 0.116 g) and stirred at RT for 3-4 h. The reaction mixture was diluted with dichloromethane and further washed with 25% citric acid solution, water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 3% MeOH in $CHCl_3$) to afford 130 mg of the title compound.

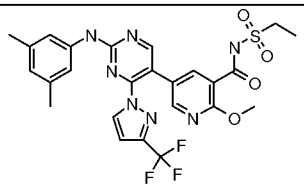
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 821	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-{[3-(morpholin-4-yl)propyl]sulfonyl}pyridine-3-carboxamide	MS(ES): 721 (M+1) for $C_{31}H_{35}F_3N_8O_7S$. 400 MHz, $CDCl_3$: δ 2.15 (br s, 2H), 2.46 (s, 3H), 2.56 (br s, 6H), 3.66 (t, *J* = 7.76 Hz, 2H), 3.77 (s, 4H), 3.81 (s, 6H), 4.17 (s, 3H), 6.26 (t, *J* = 2.04 Hz, 1H), 6.44 (s, 1H), 6.87 (d, *J* = 2.08 Hz, 2H), 7.35 (s, 1H), 8.05 (d, *J* = 2.52 Hz, 1H), 8.08 (d, *J* = 2.52 Hz, 1H), 8.63 (s, 1H).	**Intermediate 332** 3-(morpholin-4-yl) propane-1-sulfonamide and **Example 677** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

Example 822: 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(ethylsulfonyl)-2-methoxypyridine-3-carboxamide

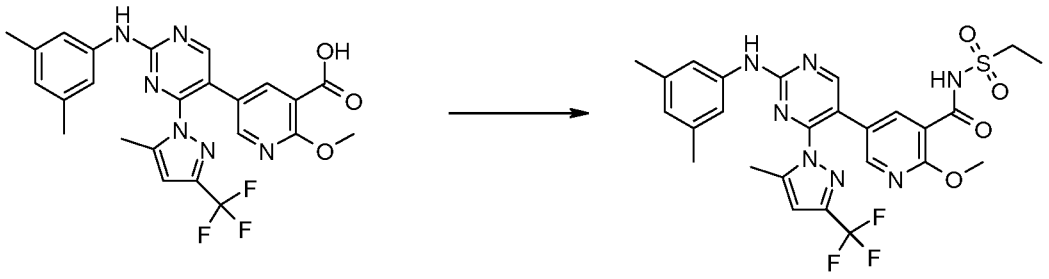


To a solution of 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 648**, 0.52 mmol, 0.250 g) and 4-(Dimethylamino)pyridine (0.104 mmol, 0.013 g) in CH_2Cl_2 (25 mL) were added ethanesulfonamide (**Intermediate 328**, 1.3 mmol, 0.14 g), triethylamine (1.61 mmol, 0.225 mL),

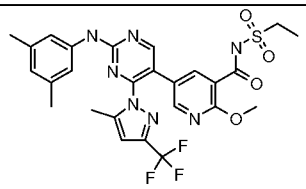
2-chloro-1-methylpyridinium iodide (0.63 mmol, 0.16 g) and stirred overnight at RT. The reaction mixture was diluted with dichloromethane (50 mL) and further washed with 25% citric acid solution (2 x 50 mL), water (100 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 1-1.5% methanol/chloroform) to afford 208 mg of white solid with 94 % purity by LCMS. This was further purified using RP-HPLC (Atlantis C18 column(19 x 250 mm, 10 µm); using a binary solvent mixture of 20 mM NH_4OAc (A)/MeOH (B) (0-20 min: 10-65% B, 20-30 min: 65% B and 30-45 min: 65-100% B; 45-50 min: 100% B flow rate of 15 mL/min; Separation was monitored at 210, 254 and 300 nm) to give 110mg of the title compound.

Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 822	 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(ethylsulfonyl)-2-methoxypyridine-3-carboxamide	MS(ES): 576 (M+1) for $C_{25}H_{24}F_3N_6O_4S$. 400 MHz, DMSO-d_6: δ 1.26 (t, J = 7.24 Hz, 3H), 2.28 (s, 6H), 3.46 (q, J = 7.20 Hz, 2H), 3.96 (s, 3H), 6.70 (s, 1H), 7.04 (s, 1H), 7.43 (s, 2H), 7.80 (s, 1H), 8.20 (d, J = 1.72 Hz, 1H), 8.46 (s, 1H), 8.75 (s, 1H), 10.10 (s, 1H), 11.69 (s, 1H).	**Intermediate 328** Ethanesulfonamide and **Example 648** 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

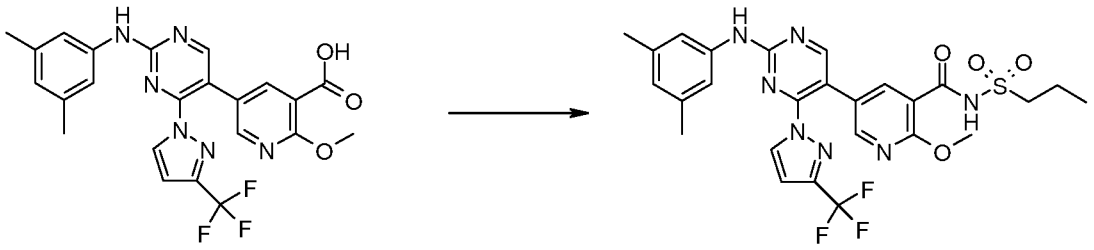
Example 823: 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(ethylsulfonyl)-2-methoxypyridine-3-carboxamide



To a solution of 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 646**, 0.3 mmol, 0.150 g) and 4-(Dimethylamino)pyridine (0.06 mmol, 7 mg) in CH_2Cl_2 were added ethanesulfonamide (**Intermediate 328**, 0.75 mmol, 0.082 g), triethylamine (0.9 mmol, 0.125 mL), 2-chloro-1-methylpyridinium iodide (0.36 mmol, 0.095 g) and stirred at RT for 3-4 h. The reaction mixture was diluted with dichloromethane and further washed with 25% citric acid solution, water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 1% MeOH/$CHCl_3$) to afford 130 mg of the title compound.

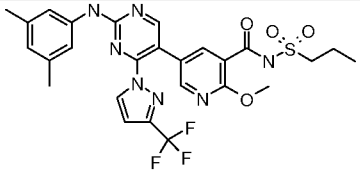
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 823	 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(ethylsulfonyl)-2-methoxypyridine-3-carboxamide	MS(ES): 590 (M+1) for $C_{26}H_{26}F_3N_7O_4S$. 400 MHz, $CDCl_3$: δ 1.45 (t, *J* = 7.40 Hz, 3H), 2.35 (s, 6H), 2.50 (s, 3H), 3.57 (q, *J* = 7.36 Hz, 2H), 4.18 (s, 3H), 6.44 (s, 1H), 6.81 (s, 1H), 7.24 (s, 2H), 7.32 (s, 1H), 8.04 (d, *J* = 2.56 Hz, 1H), 8.09 (d, *J* = 2.56 Hz, 1H), 8.61 (s, 1H), 9.94 (s, 1H).	**Intermediate 328** Ethanesulfonamide and **Example 646** 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

Example 824: 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(propylsulfonyl)pyridine-3-carboxamide

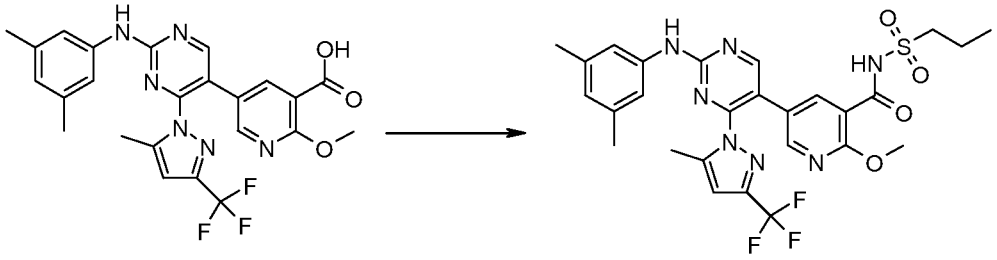


To a solution of 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 648**, 0.52 mmol, 0.250 g) and 4-(Dimethylamino)pyridine (0.61 mmol, 0.075 g) in CH_2Cl_2 (25 mL) were added propane-1-sulfonamide (**Intermediate 328**, 1.3 mmol, 0.16 g), triethylamine (1.61 mmol, 0.225 mL), 2-chloro-1-methylpyridinium iodide (0.63 mmol, 0.16 g) and stirred overnight at RT. The reaction mixture was diluted with dichloromethane (50 mL) and further washed with 25% citric acid

solution (2 x 50 mL), water (100 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 230-400 mesh silica (product eluted with 40-45% ethyl acetate/hexanes) to afford 200 mg of white solid with 81 % purity by LCMS. This was further purified using RP-HPLC (Atlantis C18 column(19 x 250 mm, 10 µm); using a binary solvent mixture of 20 mM NH_4OAc (A)/MeOH (B) (0-20 min: 10-65% B, 20-30 min: 65% B and 30-45 min: 65-100% B; 45-50 min: 100% B flow rate of 15 mL/min; Separation was monitored at 210, 254 and 300 nm) to give 125 mg of **Example 824**.

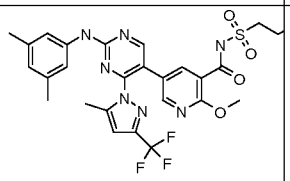
Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 824	 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(propylsulfonyl)pyridine-3-carboxamide	MS(ES): 590 (M+1) for $C_{26}H_{26}F_3N_7O_4S$. 400 MHz, DMSO-d_6: δ 1.00 (t, J = 7.36 Hz, 3H), 1.71-1.77 (m, 2H), 2.28 (s, 6H), 3.44 (t, J = 7.64 Hz, 2H), 3.96 (s, 3H), 6.70 (s, 1H), 7.04 (s, 1H), 7.43 (s, 2H), 7.80 (s, 1H), 8.21 (s, 1H), 8.46 (s, 1H), 8.75 (s, 1H), 10.09 (s, 1H), 11.70 (s, 1H).	**Intermediate 328** propane-1-sulfonamide and **Example 648** 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

Example 825: 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(propylsulfonyl)pyridine-3-carboxamide

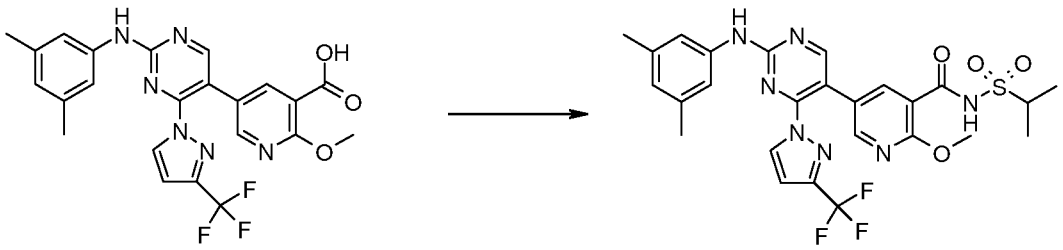


To a solution of 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 646**, 0.3 mmol, 0.150 g) and 4-(Dimethylamino)pyridine (0.06 mmol, 7 mg) in CH_2Cl_2 were added propane-1-sulfonamide (**Intermediate 329**, 0.75 mmol, 0.092 g), triethylamine (0.9 mmol, 0.125 mL, 92 mg), 2-chloro-1-methylpyridinium iodide (0.37 mmol, 0.095 g) and stirred at RT for 3-4 h. The reaction mixture was diluted with dichloromethane and further washed with 25% citric acid

solution, water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 1% MeOH/$CHCl_3$) to afford 90 mg of the title compound.

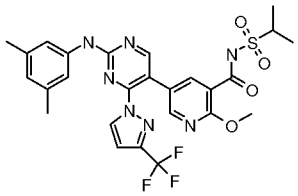
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 825	 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(propylsulfonyl)pyridine-3-carboxamide	MS(ES): 604 (M+1) for $C_{27}H_{28}F_3N_7O_4S$. 400 MHz, $CDCl_3$: δ 1.10 (t, *J* = 7.48 Hz, 3H), 1.93 (q, *J* = 7.56 Hz, 2H), 2.35 (s, 6H), 2.50 (s, 3H), 3.50-3.54 (m, 2H), 4.18 (s, 3H), 6.44 (s, 1H), 6.81 (s, 1H), 7.23 (s, 2H), 7.44 (br s, 1H), 8.04 (d, *J* = 2.52 Hz, 1H), 8.09 (d, *J* = 2.52 Hz, 1H), 8.60 (s, 1H), 9.96 (s, 1H).	**Intermediate 329** propane-1-sulfonamide and **Example 646** 5-{2-[(3,5-dimethylphenyl) amino]-4-[5-methyl-3-(trifluoromethyl) -1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine -3-carboxylic acid

Example 826: 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(propan-2-ylsulfonyl)pyridine-3-carboxamide

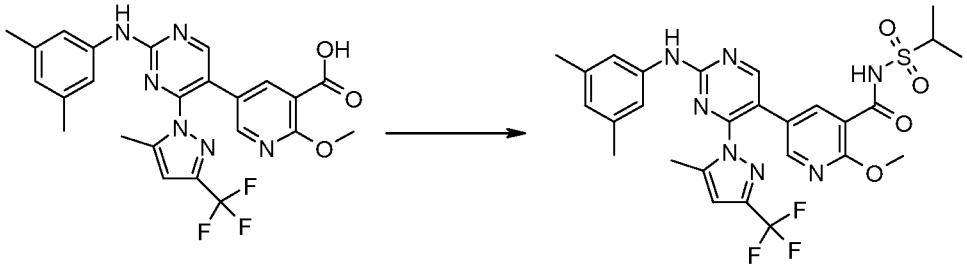


To a solution of 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 648**, 0.412 mmol, 0.200 g) and 4-(Dimethylamino)pyridine (0.082 mmol, 0.010 g) in CH_2Cl_2 (25 mL) were added propane-2-sulfonamide (**Intermediate 330**, 0.99 mmol, 0.122 g), triethylamine (1.236 mmol, 0.173 mL), 2-chloro-1-methylpyridinium iodide (0.49 mmol, 0.126 g) and stirred overnight at RT. The reaction mixture was diluted with dichloromethane (50 mL) and further washed with 25% citric acid solution (2 x 50 mL), water (100 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted

with 1.5-2.5% MeOH in $CHCl_3$) to afford 110 mg of white solid with 86 % purity by LCMS. This was further purified using RP-HPLC (kromasil C18 column(50 x 250 mm, 10 µm); using a binary solvent mixture of 0.1% TFA in water (A)/MeOH (B) (0-20 min: 10-70% B, 20-30 min: 70-80% B and 30-40 min: 80-90% B; 40-50 min: 90% B,50-55 min: 90-100%B flow rate of 40 mL/min; Separation was monitored at 210 and 290 nm) to give 40 mg of **Example 826**.

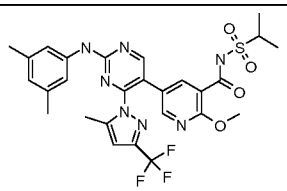
Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 826	 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(propan-2-ylsulfonyl)pyridine-3-carboxamide	MS(ES): 590 (M+1) for $C_{26}H_{26}F_3N_7O_4S$. 400 MHz, DMSO-d_6: δ 1.32 (d, *J* = 6.84 Hz, 6H), 2.27 (s, 6H), 3.70-3.71 (m, 1H), 3.95 (s, 3H), 6.69 (s, 1H), 7.02 (d, *J* = 2.60 Hz, 1H), 7.42 (s, 2H), 7.75 (d, *J* = 2.36 Hz, 1H), 8.19 (d, *J* = 2.40 Hz, 1H), 8.45 (d, *J* = 1.56 Hz, 1H), 8.74 (s, 1H), 10.08 (s, 1H), 11.66 (s, 1H).	**Intermediate 330** propane-2-sulfonamide and **Example 648** 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

Example 827: 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(propan-2-ylsulfonyl)pyridine-3-carboxamide

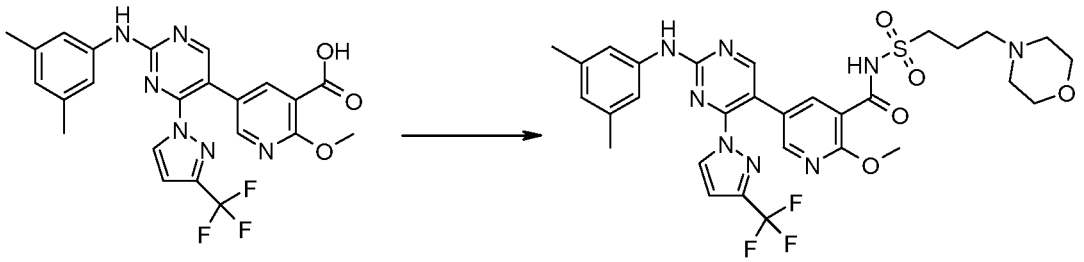


To a solution of 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 646**, 0.3 mmol, 0.150 g) in CH_2Cl_2 (10 mL), were added propane-2-sulfonamide (**Intermediate 330**, 0.45 mmol, 0.055 g), triethylamine (0.9 mmol, 0.125 mL, 92 mg), 2-chloro-1-methylpyridinium iodide (0.37 mmol,

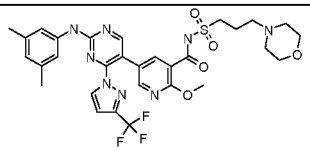
0.095 g) and 4-(Dimethylamino)pyridine (0.06 mmol, 7 mg), and refluxed at 45 °C for 30'. The reaction mixture was cooled, diluted with dichloromethane and further washed with 25% citric acid solution, water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 1% MeOH/$CHCl_3$) to afford 95 mg of the title compound.

Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 827	 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(propan-2-ylsulfonyl)pyridine-3-carboxamide	MS(ES): 604 (M+1) for $C_{27}H_{28}F_3N_7O_4S$. 400 MHz, $CDCl_3$: δ 1.48 (d, *J* = 6.84 Hz, 6H), 2.35 (s, 6H), 2.50 (s, 3H), 3.95 (t, *J* = 6.80 Hz, 1H), 4.18 (s, 3H), 6.44 (s, 1H), 6.81 (s, 1H), 7.24 (s, 2H), 7.34 (br s, 1H), 8.02 (s, 1H), 8.09 (d, *J* = 2.16 Hz, 1H), 8.64 (br s, 1H), 9.85 (s, 1H).	**Intermediate 330** propane-2-sulfonamide and **Example 646** 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

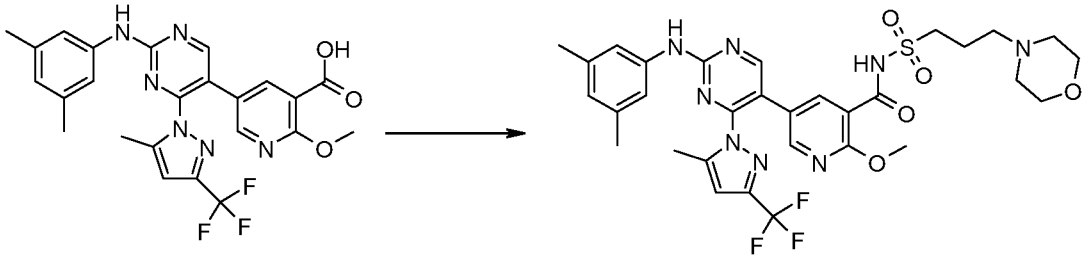
Example 828: 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-{[3-(morpholin-4-yl)propyl]sulfonyl}pyridine-3-carboxamide



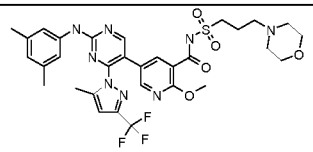
To a solution of 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 648**, 0.52 mmol, 0.250 g) and 4-(Dimethylamino)pyridine (0.104 mmol, 0.013 g) in CH_2Cl_2 (25 mL) were added 3-(morpholin-4-yl)propane-1-sulfonamide (**Intermediate 332**, 1.25 mmol, 0.26 g), triethylamine (1.61 mmol, 0.225 mL), 2-chloro-1-methylpyridinium iodide (0.63 mmol, 0.16 g) and stirred overnight at RT. The reaction mixture was diluted with dichloromethane (50 mL) and further washed with 25% citric acid solution (2 x 50 mL), water (100 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 5-7% methanol/chloroform) to afford 170 mg of **Example 828**.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 828	 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-{[3-(morpholin-4-yl)propyl]sulfonyl}pyridine-3-carboxamide	MS(ES): 675 (M+1) for $C_{30}H_{33}F_3N_8O_5S$. 400 MHz, DMSO-d_6: δ 1.92 (t, *J* = 7.40 Hz, 2H), 2.26 (s, 6H), 2.63 (m, 6H), 3.42 (t, *J* = 7.56 Hz, 2H), 3.61 (s, 4H), 3.91 (s, 3H), 6.68 (s, 1H), 7.02 (d, *J* = 2.48 Hz, 1H), 7.41 (s, 2H), 7.75 (d, *J* = 2.32 Hz, 1H), 8.09 (d, *J* = 2.40 Hz, 1H), 8.43 (s, 1H), 8.71 (s, 1H), 10.08 (s, 1H).	**Intermediate 332** 3-(morpholin-4-yl)propane-1-sulfonamide and **Example 648** 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

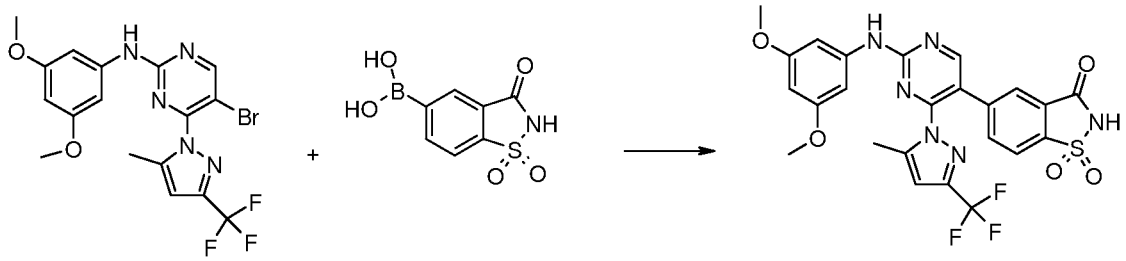
Example 829: 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-{[3-(morpholin-4-yl)propyl]sulfonyl}pyridine-3-carboxamide



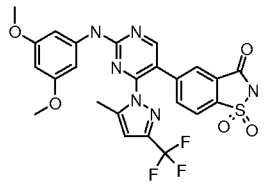
To a solution of 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 646,** 0.4 mmol, 0.2 g) and 4-(Dimethylamino)pyridine (0.08 mmol, 9 mg) in CH_2Cl_2 were added 3-(morpholin-4-yl)propane-1-sulfonamide (**Intermediate 332**, 0.8 mmol, 0.17 g), triethylamine (1.2 mmol, 0.16 mL, 121 mg), 2-chloro-1-methylpyridinium iodide (0.48 mmol, 0.122 g) and stirred at RT for 3-4 h. The reaction mixture was diluted with dichloromethane and further washed with 25% citric acid solution, water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 4% MeOH/$CHCl_3$) to afford 120 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 829	 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-{[3-(morpholin-4-yl)propyl]sulfonyl}pyridine-3-carboxamide	MS(ES): 689 (M+1) for $C_{31}H_{35}F_3N_8O_5S$. 400 MHz, $CDCl_3$: δ 1.93 (t, *J* = 7.20 Hz, 2H), 2.26 (s, 6H), 2.35 (s, 3H), 2.61-2.68 (m, 6H), 3.38-3.42 (m, 2H), 3.63 (br s, 4H), 3.89 (s, 3H), 6.69 (s, 1H), 6.76 (s, 1H), 7.37 (s, 2H), 7.62 (d, *J* = 2.08 Hz, 1H), 7.90 (d, *J* = 2.12 Hz, 1H), 8.88 (s, 1H), 10.11 (s, 1H).	**Intermediate 332** 3-(morpholin-4-yl)propane-1-sulfonamide and **Example 646** 5-{2-[(3,5-dimethylphenyl) amino]-4-[5-methyl-3-(trifluoromethyl) -1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine -3-carboxylic acid

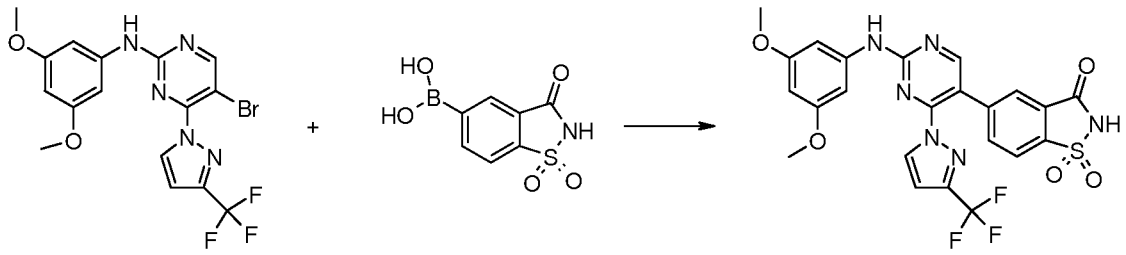
Example 830: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1,2-benzothiazol-3(2*H*)-one 1,1-dioxide



A solution of 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 216**, 0.96 mmol, 440 mg), (1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzothiazol-5-yl)boronic acid (**Intermediate 335**, 1.32 mmol, 300 mg), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (0.19 mmol, 158 mg) and sodium carbonate (0.96 mmol, 103 mg) in acetonitrile (5 mL)/water (1 mL) was degassed and heated to 90 °C for 20 min under nitrogen. Solvent was removed *in vacuo* and the residue obtained was taken in ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using 10% methanol/chloroform to yield 157 mg of the title compound.

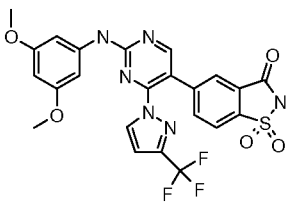
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 830	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1,2-benzothiazol-3(2*H*)-one 1,1-dioxide	MS(ES): 561 (M+1) for $C_{24}H_{19}F_3N_6O_5S$. 400 MHz, DMSO-d_6: δ 2.20 (s, 3H), 3.71 (s, 6H), 6.20 (t, J = 2.12 Hz, 1H), 6.70 (s, 1H), 7.05 (d, J = 2.08 Hz, 2H), 7.19 (dd, J = 1.44, 7.82 Hz, 1H), 7.28 (s, 1H), 7.56 (d, J = 7.80 Hz, 1H), 8.91 (s, 1H), 10.24 (s, 1H).	**Intermediate 216** 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

Example 831: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1,2-benzothiazol-3(2*H*)-one 1,1-dioxide

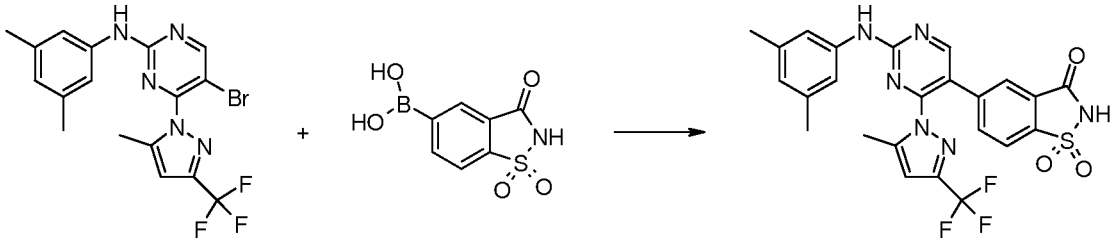


A solution of 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 215**, 0.97 mmol, 430 mg), (1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzothiazol-5-yl)boronic acid (**Intermediate 335**, 1.32 mmol, 300 mg), [1,1′-

bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (0.19 mmol, 160 mg) and sodium carbonate (0.97 mmol, 103 mg) in acetonitrile (5 mL)/water (1 mL) was degassed and heated to 90 °C for 20 min under nitrogen. Solvent was removed *in vacuo* and the residue obtained was taken in ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using 9% methanol/chloroform to yield 190 mg of the title compound.

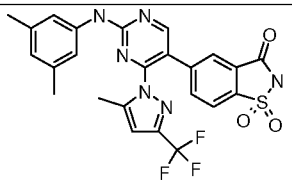
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 831	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1,2-benzothiazol-3(2*H*)-one 1,1-dioxide	MS(ES): 547 (M+1) for $C_{23}H_{17}F_3N_6O_5S$. 400 MHz, DMSO-d_6: δ 3.73 (s, 6H), 6.19 (t, J = 2.20 Hz, 1H), 6.97 (d, J = 2.64 Hz, 1H), 7.12 (d, J = 2.20 Hz, 2H), 7.32 (dd, J = 1.56, 7.78 Hz, 1H), 7.37 (d, J = 0.92 Hz, 1H), 7.60 (d, J = 7.80 Hz, 1H), 8.29 (t, J = 1.68 Hz, 1H), 8.76 (s, 1H), 10.21 (s, 1H) .	**Intermediate 215** 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

Example 832: 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1,2-benzothiazol-3(2*H*)-one 1,1-dioxide

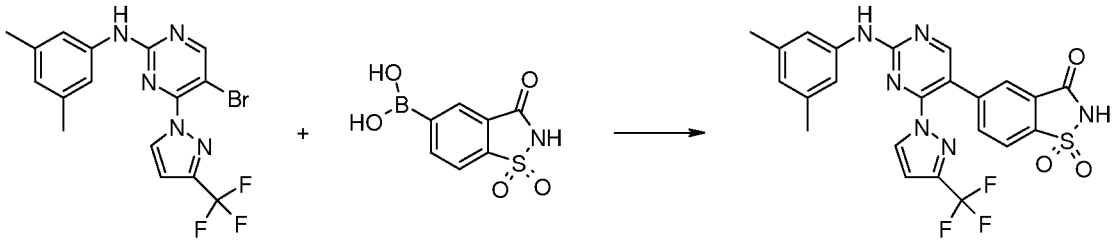


A solution of 5-bromo-*N*-(3,5-dimethylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 218**, 0.97 mmol, 413 mg), (1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzothiazol-5-yl)boronic acid (**Intermediate 335**, 1.32 mmol, 300 mg), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (0.19 mmol, 158 mg) and sodium carbonate (0.97 mmol, 103 mg) in acetonitrile (5 mL)/water (1 mL) was degassed and heated to 90 °C for 20 min under nitrogen. Solvent was removed *in vacuo* and the

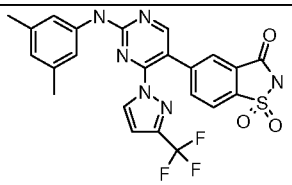
residue was taken in ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using 10% methanol/chloroform to yield 195 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 832	 5-{2-[(3,5-dimethylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1,2-benzothiazol-3(2*H*)-one 1,1-dioxide	MS(ES): 529 (M+1) for $C_{24}H_{19}F_3N_6O_3S$. 400 MHz, DMSO-d_6: δ 2.24 (s, 6H), 2.26 (s, 3H), 6.69 (d, J = 6.16 Hz, 2H), 7.19 (d, J = 7.80 Hz, 1H), 7.26 (s, 1H), 7.37 (s, 2H), 7.55 (d, J = 7.76 Hz, 1H), 8.86 (s, 1H), 10.12 (s, 1H).	**Intermediate 218** 5-bromo-*N*-(3,5-dimethylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

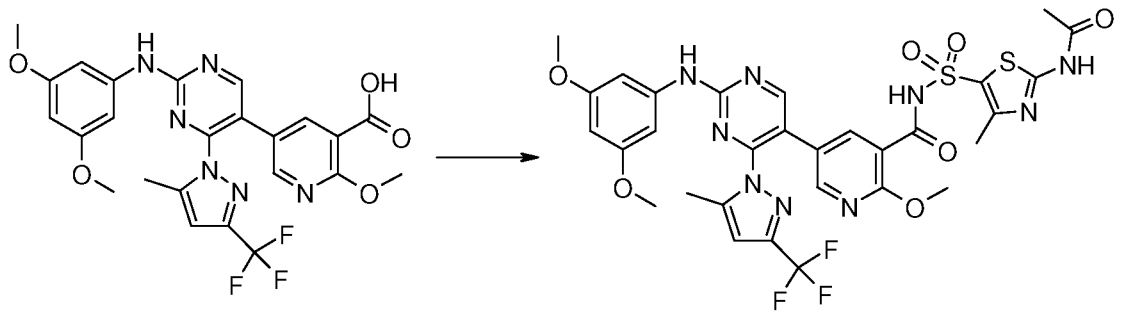
Example 833: 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1,2-benzothiazol-3(2*H*)-one 1,1-dioxide



A solution of 5-bromo-*N*-(3,5-dimethylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 217**, 0.97 mmol, 399 mg), (1,1-dioxido-3-oxo-2,3-dihydro-1,2-benzothiazol-5-yl)boronic acid (**Intermediate 335**, 1.32 mmol, 300 mg), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (0.19 mmol, 158 mg) and sodium carbonate (0.97 mmol, 103 mg) in acetonitrile (5 mL)/water (1 mL) was degassed and heated to 90 °C for 20 min under nitrogen. Solvent was removed *in vacuo* and the residue obtained was taken in ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using 9 % methanol/chloroform to yield 200 mg of the title compound.

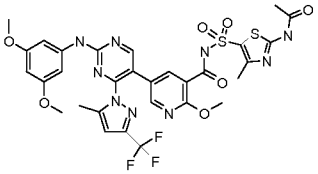
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 833	 5-{2-[(3,5-dimethylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1,2-benzothiazol-3(2*H*)-one 1,1-dioxide	MS(ES): 515 (M+1) for $C_{23}H_{17}F_3N_6O_3S$. 400 MHz, DMSO-d_6: δ 2.26 (s, 6H), 6.67 (s, 1H), 6.97 (d, J = 2.44 Hz, 1H), 7.33 (d, J = 1.20 Hz, 1H), 7.35 (s, 1H), 7.43 (s, 2H), 7.59 (d, J = 7.76 Hz, 1H), 8.32 (s, 1H), 8.73 (s, 1H), 10.11 (s, 1H).	**Intermediate 217** 5-bromo-*N*-(3,5-dimethylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

Example 834: *N*-{[2-(acetylamino)-4-methyl-1,3-thiazol-5-yl]sulfonyl}-5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxamide

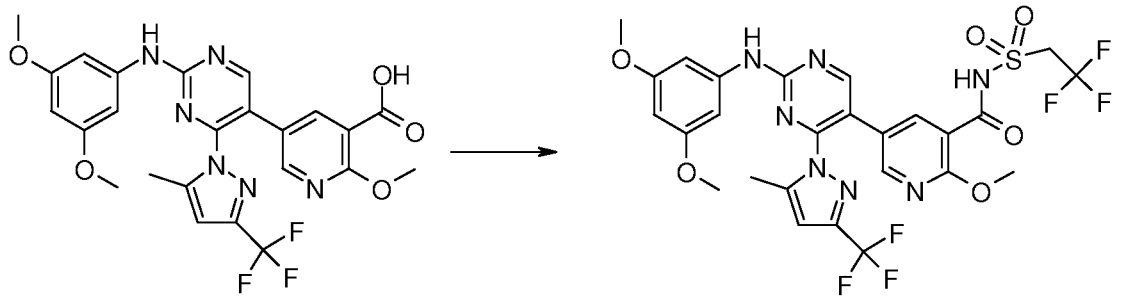


To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.19 mmol, 0.100 g) and *N*-(4-methyl-5-sulfamoyl-1,3-thiazol-2-yl)acetamide (**Intermediate 336**, 0.38 mmol, 0.089 g) in CH_2Cl_2 (25 mL), were added triethylamine (0.57 mmol, 0.08 mL), 2-chloro-1-methylpyridinium iodide (0.23 mmol, 58 mg) and 4-(Dimethylamino)pyridine (0.038 mmol, 5 mg) and stirred for 4-5 h at RT. The reaction mixture was diluted with dichloromethane (50 mL) and further washed with 25% citric acid solution (2 x 50mL), water (100 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 4-5% methanol/chloroform) to afford 110 mg of white solid with 89 % purity by LCMS. This was further purified using RP-HPLC (Kromasil C18

column(50 x 250 mm, 10 µm); using a binary solvent mixture of 0.1% TFA in water(A)/MeOH (B) (0-20 min: 10-70% B, 20-30 min: 70-80% B and 30-40 min: 80% B; 40-45 min: 80-100% B, 45-50 min: 100% B, 50-52 min:100-10 B, flow rate of 40 mL/min; Separation was monitored at 210 and 300 nm) to give 55 mg of the title compound.

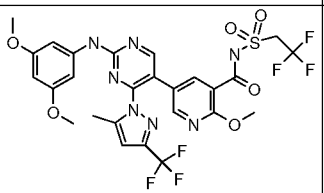
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 834	 *N*-{[2-(acetylamino)-4-methyl-1,3-thiazol-5-yl]sulfonyl}-5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxamide	MS(ES): 748 (M+1) for $C_{30}H_{28}F_3N_9O_7S_2$. 400 MHz, DMSO-d_6: δ 2.20 (s, 3H), 2.30 (s, 3H), 2.54 (s, 3H), 3.72 (s, 6H), 3.90 (s, 3H), 6.21 (s, 1H), 6.72 (s, 1H), 7.04 (d, *J* = 1.36 Hz, 2H), 7.59 (d, *J* = 2.08 Hz, 1H), 7.97 (d, *J* = 1.72 Hz, 1H), 8.91 (s, 1H), 10.21 (s, 1H), 12.41 (s, 1H), 12.69 (s, 1H).	**Intermediate 336** *N*-(4-methyl-5-sulfamoyl-1,3-thiazol-2-yl)acetamide

Example 835: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-[(2,2,2-trifluoroethyl)sulfonyl]pyridine-3-carboxamide

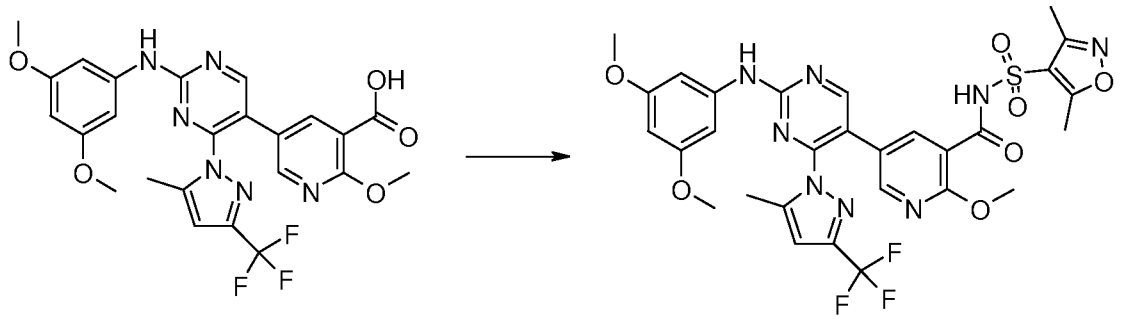


To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.19 mmol, 0.100 g) and 2,2,2-trifluoroethanesulfonamide (**Intermediate 337**, 0.43 mmol, 0.07 g) in CH_2Cl_2

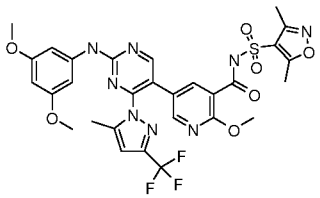
(25 mL), were added triethylamine (0.94 mmol, 0.14 mL), 2-chloro-1-methylpyridinium iodide (0.23 mmol, 60 mg) and 4-(Dimethylamino)pyridine (0.08 mmol, 10 mg) and stirred for 1 h at RT. The reaction mixture was diluted with dichloromethane (50 mL) and further washed with 25% citric acid solution (2 x 50 mL), water (100 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 2% methanol/chloroform) to afford 45 mg of the title compound as a white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 835	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-[(2,2,2-trifluoroethyl)sulfonyl]pyridine-3-carboxamide	MS(ES): 676 (M+1) for $C_{26}H_{23}F_6N_7O_6S$. 400 MHz, DMSO-d_6: δ 2.30 (s, 3H), 3.73 (s, 6H), 3.92 (s, 3H), 4.79-4.80 (m, 2H), 6.22 (s, 1H), 6.75 (s, 1H), 7.06 (d, *J* = 1.68 Hz, 2H), 7.60 (d, *J* = 2.32 Hz, 1H), 8.05 (s, 1H), 8.93 (s, 1H), 10.23 (s, 1H).	**Intermediate 337** 2,2,2-trifluoroethanesulfonamide

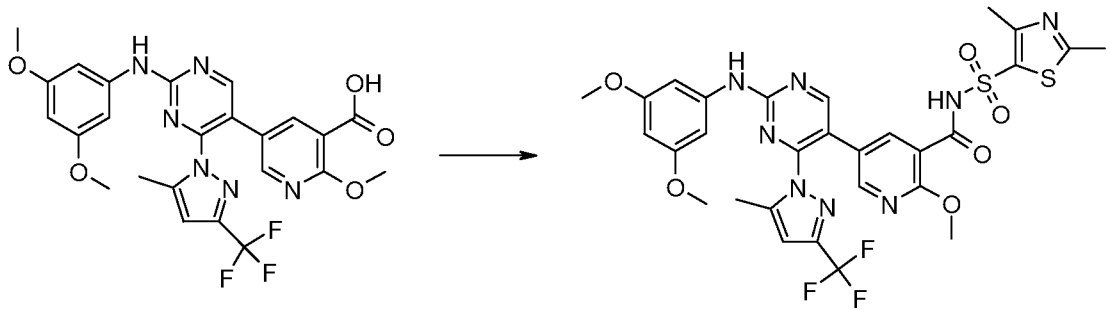
Example 836: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]-2-methoxypyridine-3-carboxamide



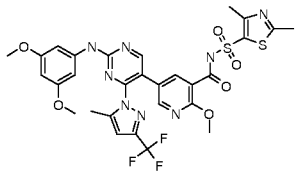
To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.28 mmol, 0.15 g) and 3,5-dimethyl-1,2-oxazole-4-sulfonamide (**Intermediate 338**, 0.42 mmol, 74 mg) in CH_2Cl_2 (10 mL), were added triethylamine (0.84 mmol, 0.12 mL), 2-chloro-1-methylpyridinium iodide (0.3 mmol, 78 mg) and 4-(Dimethylamino)pyridine (0.05 mmol, 6 mg) and stirred for 2 h at RT. The reaction mixture was diluted with dichloromethane (50 mL) and further washed with 25% citric acid solution, water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 2% methanol/chloroform) to afford 85 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 836	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]-2-methoxypyridine-3-carboxamide	MS(ES): 689 (M+1) for $C_{29}H_{27}F_3N_8O_7S$. 400 MHz, DMSO-d_6: δ 2.29 (s, 3H), 2.40 (s, 3H), 2.68 (s, 3H), 3.72 (s, 6H), 3.90 (s, 3H), 6.21 (d, J = 2.08 Hz, 1H), 6.74 (s, 1H), 7.04 (d, J = 1.96 Hz, 2H), 7.60 (d, J = 2.36 Hz, 1H), 7.97 (s, 1H), 8.91 (s, 1H), 10.22 (s, 1H), 12.62 (br s, 1H).	**Intermediate 338** 3,5-dimethyl-1,2-oxazole-4-sulfonamide

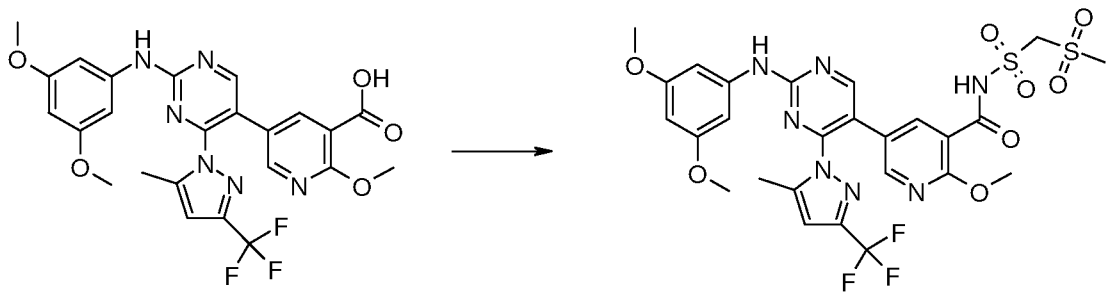
Example 837: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]-2-methoxypyridine-3-carboxamide



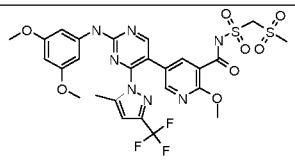
To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.37 mmol, 0.200 g) in CH_2Cl_2 (10 mL), were added 2,4-dimethyl-1,3-thiazole-5-sulfonamide (**Intermediate 339**, 0.56 mmol, 0.11 g), triethylamine (0.84 mmol, 0.12 mL), 2-chloro-1-methylpyridinium iodide (0.44 mmol, 0.11 g) and 4-(Dimethylamino)pyridine (0.05 mmol, 6 mg) and stirred at RT for 2 h. The reaction mixture was diluted with dichloromethane and further washed with 10% citric acid solution, water and brine. The organic layer was dried over Na_2SO_4 and concentrated. This was further purified using RP-HPLC (Kromasil C18 column(250 x 50 mm, 10 µm); using a binary solvent mixture of 10 mM NH_4OAc (A)/MeOH (B) (0-20 min: 20-70% B, 20-30 min:70-80% B and 30-35 min: 80-100% B; 35-40 min: 100% B flow rate of 40 mL/min; Separation was monitored at 210, 254 and 300 nm) to afford 100 mg of the title compound.

Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 837	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]-2-methoxypyridine-3-carboxamide	MS(ES): 705 (M+1) for $C_{29}H_{27}F_3N_8O_6S_2$. 400 MHz, DMSO-d_6: δ 2.30 (s, 3H), 2.58 (s, 3H), 2.68 (s, 3H), 3.72 (s, 6H), 3.90 (s, 3H), 6.21 (t, *J* = 2.16 Hz, 1H), 6.74 (s, 1H), 7.04 (d, *J* = 2.08 Hz, 2H), 7.60 (d, *J* = 2.44 Hz, 1H), 7.96 (s, 1H), 8.91 (s, 1H), 10.21 (s, 1H), 12.54 (s, 1H).	**Intermediate 339** 2,4-dimethyl-1,3-thiazole-5-sulfonamide

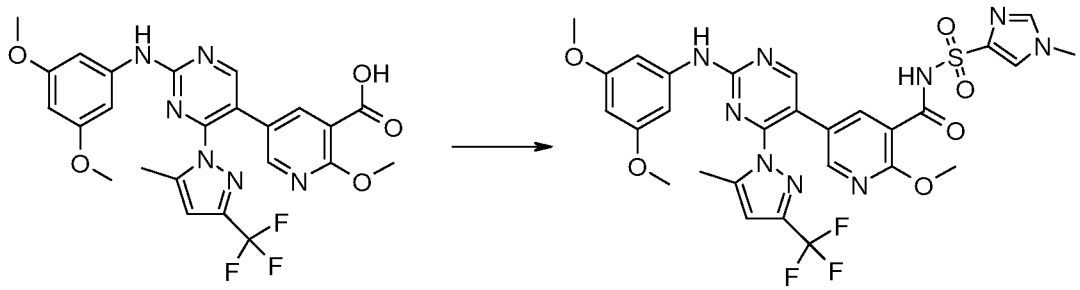
Example 838: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-{[(methylsulfonyl)methyl]sulfonyl}pyridine-3-carboxamide



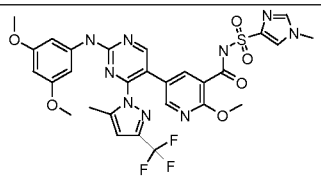
To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.23 mmol, 0.125 g) and 1-(methylsulfonyl)methanesulfonamide (**Intermediate 340**, 0.34 mmol, 0.06 g) in CH_2Cl_2 (10 mL), were added triethylamine (0.6 mmol, 0.1 mL), 2-chloro-1-methylpyridinium iodide (0.27 mmol, 0.07 g) and 4-(Dimethylamino)pyridine (0.04 mmol, 5 mg) and stirred at RT for 2 h. The reaction mixture was diluted with dichloromethane and further washed with 10% citric acid solution, water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 2% MeOH in $CHCl_3$) to afford 70 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 838	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-{[(methylsulfonyl)methyl]sulfonyl}pyridine-3-carboxamide	MS(ES): 684 (M-1) for $C_{26}H_{26}F_3N_7O_8S_2$. 400 MHz, DMSO-d_6: δ 2.31 (s, 3H), 3.24 (s, 3H), 3.72 (s, 6H), 3.91 (s, 3H), 5.44 (s, 2H), 6.21 (t, *J* = 2.00 Hz, 1H), 6.75 (s, 1H), 7.05 (d, *J* = 1.88 Hz, 2H), 7.72 (d, *J* = 2.40 Hz, 1H), 7.95 (d, *J* = 2.28 Hz, 1H), 8.90 (s, 1H), 10.22 (s, 1H).	**Intermediate 340** 1-(methylsulfonyl)methanesulfonamide and **Example 675** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid

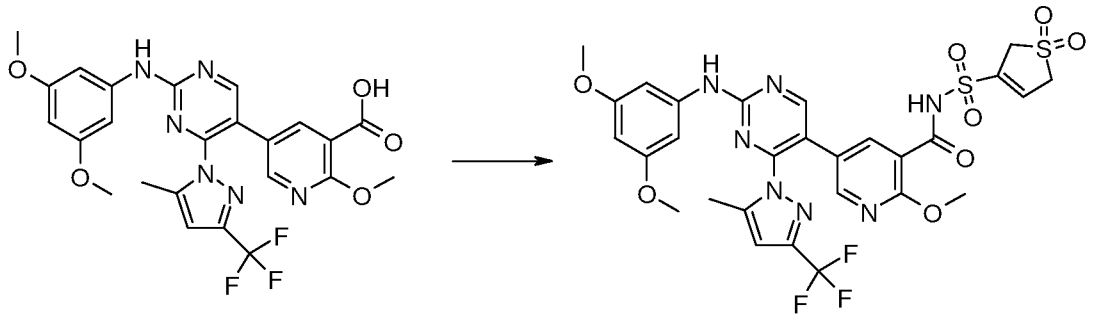
Example 839: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-[(1-methyl-1*H*-imidazol-4-yl)sulfonyl]pyridine-3-carboxamide



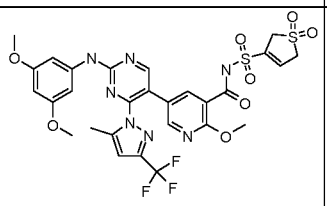
To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.28 mmol, 0.15 g) and 1-methyl-1*H*-imidazole-4-sulfonamide (**Intermediate 341**, 0.84 mmol, 0.14 g) in CH_2Cl_2 (10 mL), were added triethylamine (1.69 mmol, 0.23 mL), 2-chloro-1-methylpyridinium iodide (0.35 mmol, 0.09 g) and 4-(Dimethylamino)pyridine (0.056 mmol, 7 mg) and stirred at RT for 2 h. The reaction mixture was diluted with dichloromethane and further washed with 5 % citric acid solution, water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 2% MeOH in $CHCl_3$) to afford 150 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 839	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-[(1-methyl-1*H*-imidazol-4-yl)sulfonyl]pyridine-3-carboxamide	MS(ES): 674 (M+1) for $C_{28}H_{26}F_3N_9O_6S$. 400 MHz, DMSO-d_6: δ 2.29 (s, 3H), 3.71 (s, 3H), 3.73 (s, 6H), 3.88 (s, 3H), 6.20 (d, J = 2.04 Hz, 1H), 6.73 (s, 1H), 7.04 (d, J = 1.88 Hz, 2H), 7.60 (d, J = 2.32 Hz, 1H), 7.81 (s, 1H), 7.90 (s, 1H), 8.01 (s, 1H), 8.90 (s, 1H), 10.21 (s, 1H), 11.95 (s, 1H).	**Intermediate 341** 1-methyl-1*H*-imidazole-4-sulfonamide

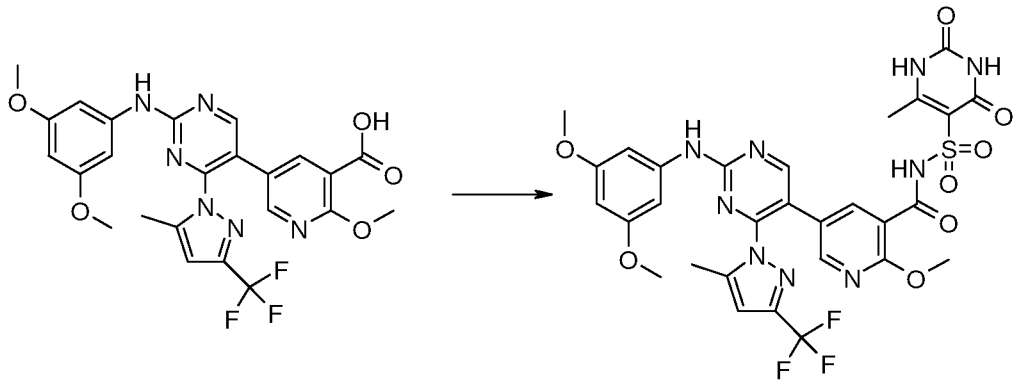
Example 840: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-[(1,1-dioxido-2,5-dihydrothiophen-3-yl)sulfonyl]-2-methoxypyridine-3-carboxamide



To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.56 mmol, 0.3 g) and 2,5-dihydrothiophene-3-sulfonamide 1,1-dioxide (**Intermediate 343**, 0.85 mmol, 0.17 g) in DMSO (10 mL), were added triethylamine (1.68 mmol, 0.23 mL), 2-chloro-1-methylpyridinium iodide (0.7 mmol, 0.18 g) and 4-(Dimethylamino)pyridine (0.11 mmol, 14 mg) and stirred at RT for 1 h. The reaction mixture was diluted with water and extracted into ethyl acetate. The organic layer was further washed with 10% citric acid solution, water and brine, dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 2% MeOH in $CHCl_3$) to afford 200 mg of the title compound as a 7:3 mixture of two isomers.

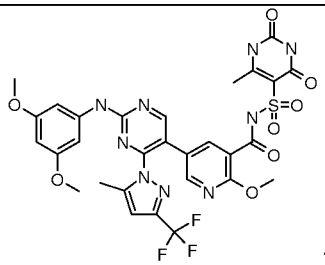
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 840	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-[(1,1-dioxido-2,5-dihydrothiophen-3-yl)sulfonyl]-2-methoxypyridine-3-carboxamide	MS(ES): 710 (M+1) for $C_{28}H_{26}F_3N_7O_8S_2$. 400 MHz, DMSO-d_6: δ 2.33 (s, 3H), 3.73 (s, 6H), 3.93 (m, 3H), 4.20 (br s, 2H), 4.34 (br s, 2H), 6.22 (s, 1H), 6.76-6.78 (m, 1H), 7.05 (s, 2H), 7.16 (br s, 1H), 7.73 (d, J = 2.32 Hz, 1H), 7.93-7.96 (m, 1H), 8.93 (d, J = 2.04 Hz, 1H), 10.23 (s, 1H), 12.37 (br s, 1H).	**Intermediate 343** 2,5-dihydrothiophene-3-sulfonamide 1,1-dioxide

Example 841: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-[(6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)sulfonyl]pyridine-3-carboxamide

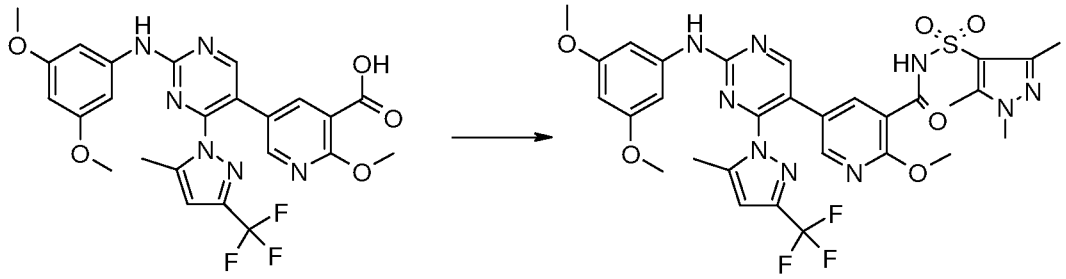


To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.28 mmol, 0.15 g) and 6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonamide (**Intermediate 345**, 0.42 mmol, 0.09 g) in DMSO (6 mL), were added triethylamine (1.4 mmol, 0.2 mL), 2-chloro-1-methylpyridinium iodide (0.42 mmol, 0.11 g) and 4-(Dimethylamino)pyridine (0.08 mmol, 10

mg) and stirred at RT for 1 h. The reaction mixture was diluted with water and extracted into ethyl acetate. The organic layer was further washed with 10% citric acid solution, water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude mass was purified by 60-120 mesh silica (product eluted with 2% MeOH in $CHCl_3$) to afford 70 mg of the title compound.

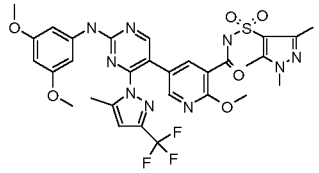
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 841	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-[(6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)sulfonyl]pyridine-3-carboxamide	MS(ES): 718 (M+1) for $C_{29}H_{26}F_3N_9O_8S$. 400 MHz, DMSO-d_6: δ 2.29 (s, 3H), 2.52 (s, 3H), 3.71 (s, 6H), 3.87 (s, 3H), 6.20 (s, 1H), 6.73 (s, 1H), 7.04 (s, 2H), 7.64 (s, 1H), 7.85 (br s, 1H), 8.90 (s, 1H), 10.21 (s, 1H), 11.53 (br s, 1H), 11.97 (br s, 1H).	**Intermediate 345** 6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonamide

Example 842: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-[(1,3,5-trimethyl-1*H*-pyrazol-4-yl)sulfonyl]pyridine-3-carboxamide

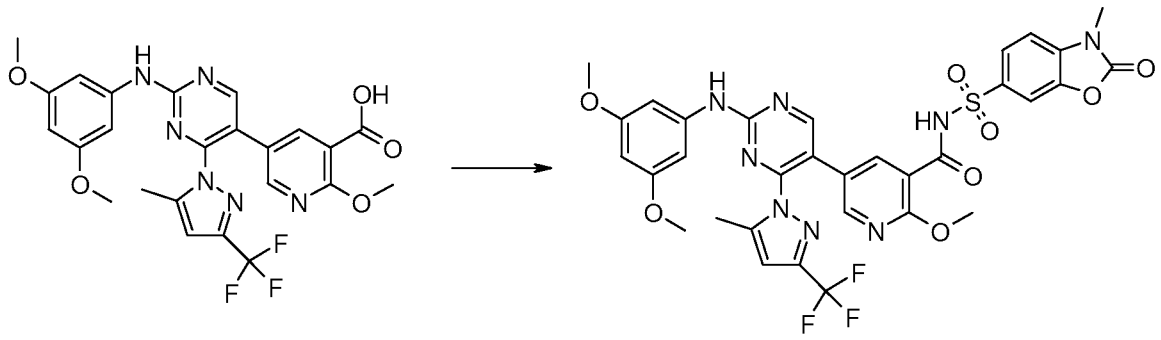


To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.31 mmol,

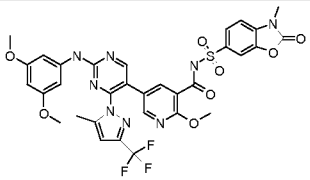
0.165 g) and 1,3,5-trimethyl-1*H*-pyrazole-4-sulfonamide (**Intermediate 346**, 0.78 mmol, 0.147 g) in CH_2Cl_2 (15 mL), were added triethylamine (0.933 mmol, 0.1302 mL), 2-chloro-1-methylpyridinium iodide (0.38 mmol, 99 mg) and 4-(Dimethylamino)pyridine (0.062 mmol, 8 mg) and stirred at RT for 90 min. The reaction mixture was diluted with dichloromethane (30 mL) and further washed with 25% citric acid solution (2 x 25 mL), water (50 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 1-2% MeOH in $CHCl_3$) to afford 60 mg of the title compound as a white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 842	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-[(1,3,5-trimethyl-1*H*-pyrazol-4-yl)sulfonyl]pyridine-3-carboxamide	MS (ES): 702 (M+1) for $C_{30}H_{30}F_3N_9O_6S$. 400 MHz, DMSO-d_6: δ 2.29 (s, 3H), 2.31 (s, 3H), 2.47 (s, 3H), 3.74 (s, 9H), 3.89 (s, 3H), 6.21 (t, *J* = 2.12 Hz, 1H), 6.74 (s, 1H), 7.04 (d, *J* = 2.12 Hz, 2H), 7.61 (d, *J* = 2.44 Hz, 1H), 7.92 (d, *J* = 2.40 Hz, 1H), 8.91 (s, 1H), 10.21 (s, 1H), 12.04 (s, 1H).	**Intermediate 346** 1,3,5-trimethyl-1*H*-pyrazole-4-sulfonamide

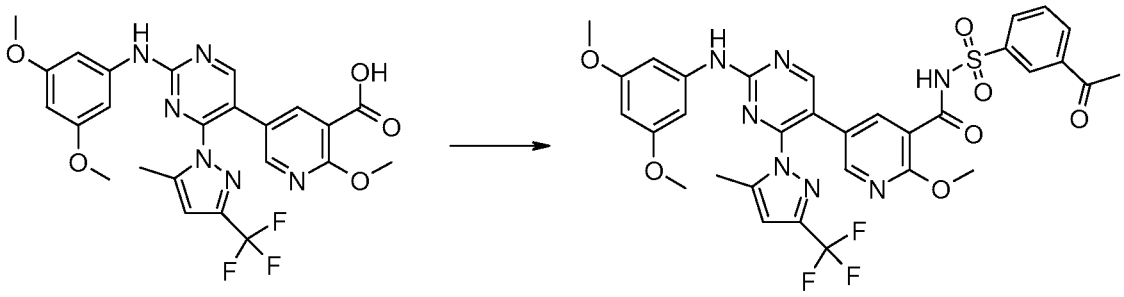
Example 843: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-[(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)sulfonyl]pyridine-3-carboxamide



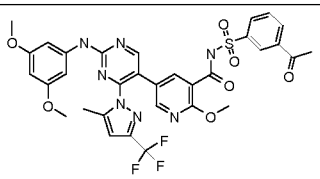
To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.38 mmol, 0.2 g) and 3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-sulfonamide (**Intermediate 347**, 0.46 mmol, 0.1 g) in CH_2Cl_2 (25 mL) were added triethylamine (1.14 mmol, 0.16 mL), 2-chloro-1-methylpyridinium iodide (0.46 mmol, 0.116 g) and 4-(Dimethylamino)pyridine (0.076 mmol, 10 mg) and stirred for 90 min at RT. The reaction mixture was diluted with dichloromethane (50 mL) and further washed with 25 % citric acid solution (2 x 50mL), water (100 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 1-1.5% methanol/chloroform) to afford 200 mg of white solid **Example 843**.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 843	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-[(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)sulfonyl]pyridine-3-carboxamide	MS(ES): 741 (M+1) for $C_{32}H_{27}F_3N_8O_8S$. 400 MHz, DMSO-d_6: δ 2.30 (s, 3H), 3.40 (s, 3H), 3.72 (s, 6H), 3.91 (s, 3H), 6.21 (t, J = 2.08 Hz, 1H), 6.70 (s, 1H), 7.04 (d, J = 2.04 Hz, 2H), 7.51 (d, J = 8.36 Hz, 1H), 7.57 (d, J = 2.40 Hz, 1H), 7.85 (d, J = 1.52 Hz, 1H), 7.89-7.91 (m, 1H), 7.97 (d, J = 2.40 Hz, 1H), 8.89 (s, 1H), 10.20 (s, 1H), 12.17 (s, 1H).	**Intermediate 347** 3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-sulfonamide

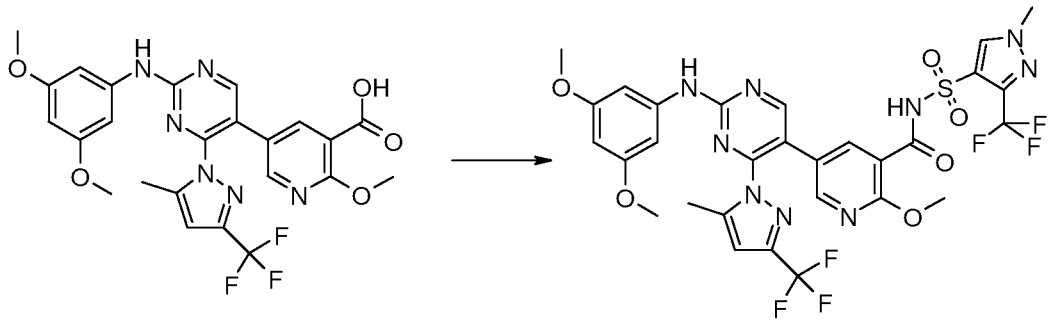
Example 844: *N*-[(3-acetylphenyl)sulfonyl]-5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxamide



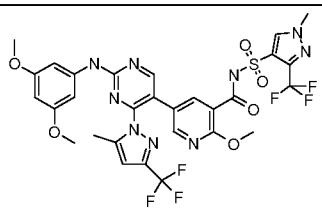
To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.19 mmol, 0.100 g) and 3-acetylbenzenesulfonamide (**Intermediate 348**, 0.37 mmol, 75 mg) in CH_2Cl_2 (10 mL), were added triethylamine (0.57 mmol, 0.08 mL), 2-chloro-1-methylpyridinium iodide (0.23 mmol, 60 mg) and 4-(Dimethylamino)pyridine (0.03 mmol, 5 mg) and stirred for 1 h at RT. The reaction mixture was diluted with dichloromethane (50 mL) and further washed with water (100 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude mass was purified by 60-120 mesh silica (product eluted with 1.5% methanol/chloroform) to afford 60 mg of the title compound as a white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 844	 *N*-[(3-acetylphenyl)sulfonyl]-5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxamide	MS(ES): 712 (M+1) for $C_{32}H_{28}F_3N_7O_7S$. 400 MHz, DMSO-d_6: δ 2.30 (s, 3H), 2.67 (s, 3H), 3.72 (s, 6H), 3.90 (s, 3H), 6.21 (t, J = 2.12 Hz, 1H), 6.69 (s, 1H), 7.04 (d, J = 2.12 Hz, 2H), 7.56 (d, J = 2.44 Hz, 1H), 7.84 (t, J = 7.84 Hz, 1H), 7.98 (d, J = 2.40 Hz, 1H), 8.22 (d, J = 8.44 Hz, 1H), 8.34 (d, J = 7.88 Hz, 1H), 8.46 (d, J = 1.64 Hz, 1H), 8.89 (s, 1H), 10.20 (s, 1H), 12.36 (br s, 1H).	**Intermediate 348** 3-acetylbenzenesulfonamide

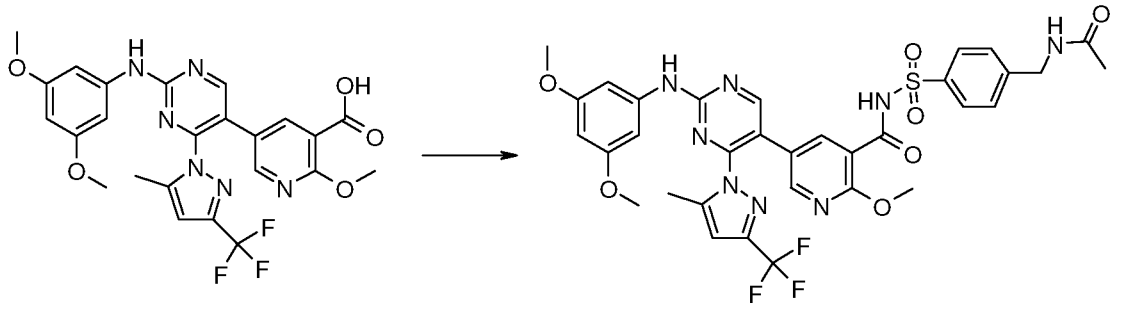
Example 845: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-{[1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]sulfonyl}pyridine-3-carboxamide



To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.19 mmol, 0.100 g) and 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-4-sulfonamide (**Intermediate 349**, 0.38 mmol, 0.087 g) in CH_2Cl_2 (25 mL), were added 2-chloro-1-methylpyridinium iodide (0.23 mmol, 58 mg), triethylamine (0.57 mmol, 0.08 mL) and 4-(Dimethylamino)pyridine (0.038 mmol, 5 mg) and stirred for 4-5 h at RT. The reaction mixture was diluted with dichloromethane (50 mL) and further washed with 25% citric acid solution (2 x 50mL), water (100 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 4-5% methanol/chloroform) to afford 110 mg of white solid in 78 % purity by LCMS. This was further purified using RP-HPLC (Kromasil C18 column(50 x 250 mm, 10 µm); using a binary solvent mixture of 0.1% TFA in water(A)/MeOH (B) (0-20 min: 10-70% B, 20-30 min: 70-80% B and 30-40 min: 80% B; 40-45 min: 80-100% B, 45-50 min: 100% B, 50-52 min:100-10 B, flow rate of 40 mL/min; Separation was monitored at 210 and 300 nm) to give 63 mg of **Example 845**.

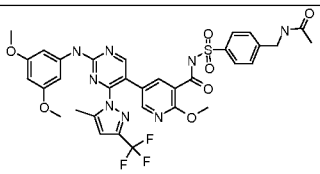
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 845	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-{[1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]sulfonyl}pyridine-3-carboxamide	MS(ES): 742 (M+1) for $C_{29}H_{25}F_6N_9O_6S$. 400 MHz, DMSO-d_6: δ 2.29 (s, 3H), 3.71 (s, 6H), 3.87 (s, 3H), 3.99 (s, 3H), 6.20 (t, J = 2.08 Hz, 1H), 6.70 (s, 1H), 7.03 (d, J = 2.00 Hz, 2H), 7.54 (d, J = 2.40 Hz, 1H), 7.98 (d, J = 2.28 Hz, 1H), 8.75 (s, 1H), 8.90 (s, 1H), 10.21 (s, 1H), 12.45 (s, 1H).	**Intermediate 349** 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-4-sulfonamide

Example 846: *N*-({4-[(acetylamino)methyl]phenyl}sulfonyl)-5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxamide

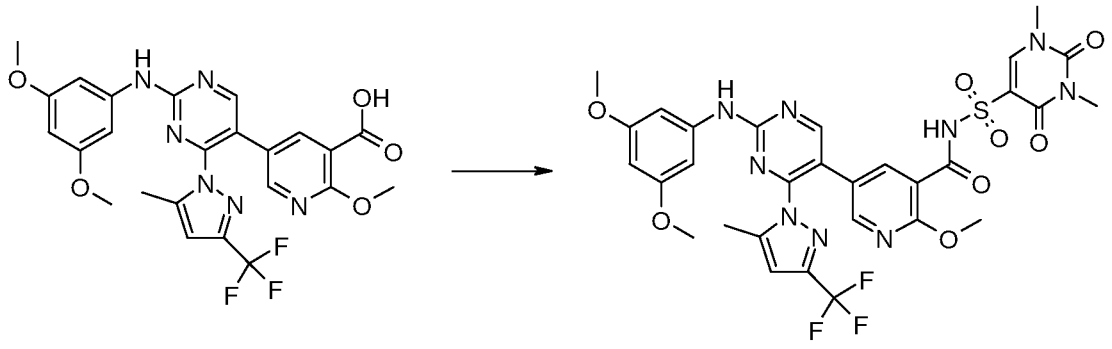


To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.19 mmol, 0.100 g) and *N*-(4-sulfamoylbenzyl)acetamide (**Intermediate 351** 0.23 mmol, 52 mg) in CH_2Cl_2 (25 mL) were added triethylamine (0.57 mmol, 0.08 mL), 2-chloro-1-methylpyridinium iodide (0.23 mmol, 58 mg) and 4-(Dimethylamino)pyridine (0.038 mmol, 5 mg) and stirred for 4-5 h at RT. The reaction mixture was diluted with dichloromethane (50 mL) and further washed with

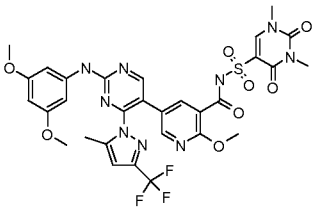
25% citric acid solution (2 x 50mL), water (100 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by RP-HPLC (Kromasil C18 column(50 x 250 mm, 10 µm); using a binary solvent mixture of 0.1% HCOOH in water(A)/MeOH (B) (0-20 min: 20-70% B, 20-30 min: 70-80% B and 30-45 min: 80-100% B; 45-55 min: 100% B, 55-57 min: 100-20% B, flow rate of 40 mL/min; Separation was monitored at 210,280 and 320 nm) to give 62 mg of **Example 846**.

Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 846	 *N*-({4-[(acetylamino)methyl]phenyl}sulfonyl)-5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxamide	MS(ES): 741 (M+1) for $C_{33}H_{31}F_3N_8O_7S$. 400 MHz, DMSO-d_6: δ 1.90 (s, 3H), 2.31 (s, 3H), 3.72 (s, 6H), 3.90 (s, 3H), 4.35 (d, *J* = 5.96 Hz, 2H), 6.21 (t, *J* = 2.00 Hz, 1H), 6.72 (s, 1H), 7.04 (d, *J* = 1.80 Hz, 2H), 7.50 (d, *J* = 8.20 Hz, 2H), 7.60 (d, *J* = 2.20 Hz, 1H), 7.91-7.93 (m, 3H), 8.49 (t, *J* = 5.80 Hz, 1H), 8.90 (s, 1H), 10.20 (s, 1H), 12.18 (s, 1H).	**Intermediate 51** *N*-(4-sulfamoylbenzyl)acetamide

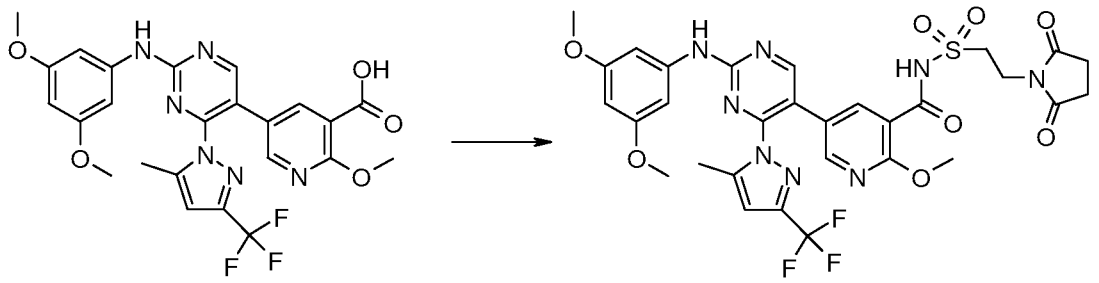
Example 847: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-[(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)sulfonyl]-2-methoxypyridine-3-carboxamide



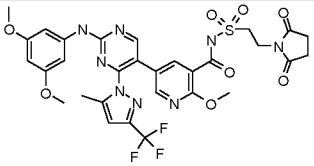
To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.19 mmol, 0.100 g) and 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonamide (**Intermediate 352** 0.23 mmol, 48 mg) in CH_2Cl_2 (25 mL) were added triethylamine (0.57 mmol, 0.08 mL), 2-chloro-1-methylpyridinium iodide (0.23 mmol, 58 mg) and 4-(Dimethylamino)pyridine (0.038 mmol, 5 mg) and stirred 4-5 h at RT. The reaction mixture was diluted with dichloromethane (50 mL) and further washed with 25% citric acid solution (2 x 50 mL), water (100 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by RP-HPLC (Kromasil C18 column(50 x 250 mm, 10 µm); using a binary solvent mixture of 0.1% HCOOH in water(A)/MeOH (B) (0-20 min: 20-70% B, 20-30 min: 70-80% B and 30-45 min: 80-100% B; 45-55 min: 100% B, 55-57 min: 100-20% B, flow rate of 40 mL/min; Separation was monitored at 210, 280 and 320 nm) to give 55 mg of **Example 847**.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 847	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-[(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)sulfonyl]-2-methoxypyridine-3-carboxamide	MS(ES): 730 (M-1) for $C_{30}H_{28}F_3N_9O_8S$. 400 MHz, DMSO-d_6: δ 2.31 (s, 3H), 3.19 (s, 3H), 3.50 (s, 3H), 3.72 (s, 6H), 3.90 (s, 3H), 6.22 (t, J = 2.12 Hz, 1H), 6.73 (s, 1H), 7.05 (d, J = 2.00 Hz, 2H), 7.64 (d, J = 2.40 Hz, 1H), 7.94 (d, J = 2.32 Hz, 1H), 8.76 (s, 1H), 8.93 (s, 1H), 10.24 (s, 1H).	**Intermediate 352** 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-sulfonamide

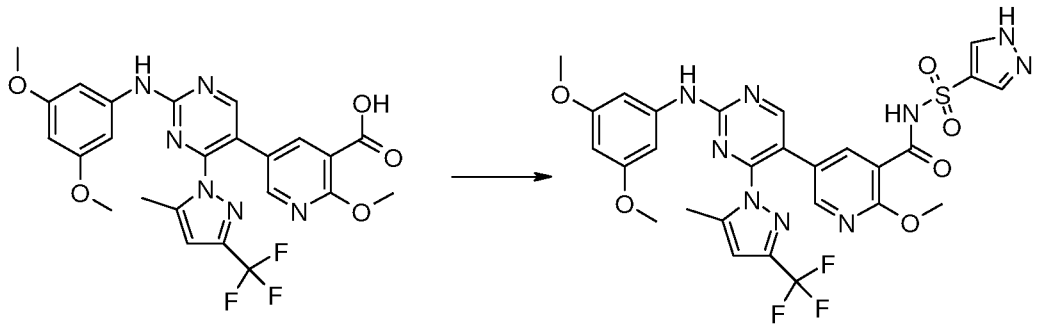
Example 848: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-{[2-(2,5-dioxopyrrolidin-1-yl)ethyl]sulfonyl}-2-methoxypyridine-3-carboxamide



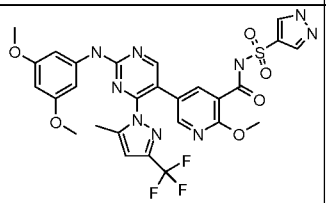
To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.36 mmol, 0.19 g) and 2-(2,5-dioxopyrrolidin-1-yl)ethanesulfonamide (**Intermediate 353**, 0.9 mmol, 0.19 g) in DMSO (10 mL), were added triethylamine (1.07 mmol, 0.15 mL), 2-chloro-1-methylpyridinium iodide (0.45 mmol, 0.12 g) and 4-(Dimethylamino)pyridine (0.07 mmol, 10 mg) and stirred at RT for 1 h. The reaction mixture was diluted with water and extracted into ethyl acetate. The organic layer was further washed with 10% citric acid solution, water and brine, dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 2% MeOH in $CHCl_3$) followed by washing with water and 1.5 N HCl to afford 58 mg of the title compound (0.08 mmol, 22 %).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 848	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-{[2-(2,5-dioxopyrrolidin-1-yl)ethyl]sulfonyl}-2-methoxypyridine-3-carboxamide	MS(ES):719 (M+1) for $C_{30}H_{29}F_3N_8O_8S$. 400 MHz, DMSO-d_6: δ 2.34 (s, 3H), 2.60 (s, 3H), 3.68-3.70 (m, 2H), 3.73 (s, 6H), 3.78 (t, *J* = 4.72 Hz, 2H), 3.94 (s, 3H), 6.22 (s, 1H), 6.77 (s, 1H), 7.05 (d, *J* = 2.00 Hz, 2H), 7.75 (d, *J* = 2.40 Hz, 1H), 7.97 (d, *J* = 2.04 Hz, 1H), 8.93 (s, 1H), 10.23 (s, 1H), 11.93 (br s, 1H).	**Intermediate 353** 2-(2,5-dioxopyrrolidin-1-yl)ethanesulfonamide

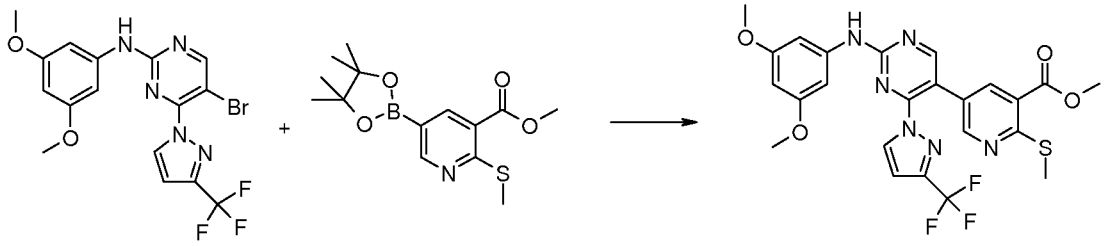
Example 849: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(1*H*-pyrazol-4-ylsulfonyl)pyridine-3-carboxamide



To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxypyridine-3-carboxylic acid (**Example 675**, 0.38 mmol, 0.2 g) and 1*H*-pyrazole-4-sulfonamide (**Intermediate 354**, 0.45 mmol, 0.07 g) in CH_2Cl_2 (25 mL) were added triethylamine (1.14 mmol, 0.16 mL), 2-chloro-1-methylpyridinium iodide (0.46 mmol, 0.116 g) and 4-(Dimethylamino)pyridine (0.076 mmol, 10 mg) and stirred for 4-5 h at RT. The reaction mixture was diluted with dichloromethane (50 mL) and further washed with 25 % citric acid solution (2 x 50mL), water (100 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 5-6% methanol/chloroform) to afford 36 mg of white solid **Example 849**.

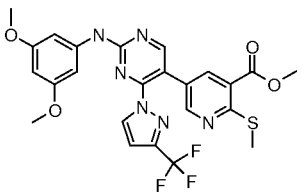
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 849	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-methoxy-*N*-(1*H*-pyrazol-4-ylsulfonyl)pyridine-3-carboxamide	MS(ES): 660 (M+1) for $C_{27}H_{24}F_3N_9O_6S$. 400 MHz, DMSO-d_6: δ 2.29 (s, 3H), 3.71 (s, 6H), 3.89 (s, 3H), 6.20 (t, J = 2.16 Hz, 1H), 6.71 (s, 1H), 7.03 (d, J = 2.12 Hz, 2H), 7.62 (d, J = 2.44 Hz, 1H), 7.93 (d, J = 2.24 Hz, 2H), 8.47 (s, 1H), 8.90 (s, 1H), 10.20 (s, 1H), 11.99 (s, 1H), 13.74 (s, 1H).	**Intermediate 354** 1*H*-pyrazole-4-sulfonamide

Example 850: methyl 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)pyridine-3-carboxylate

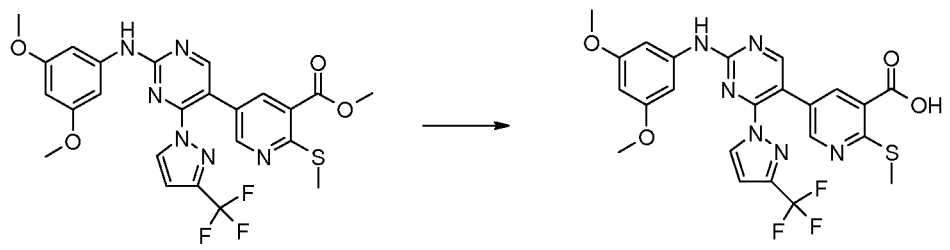


A suspension of 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 215**, 0.45 mmol, 0.2 g), a mixture of methyl 2-(methylsulfanyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate and [5-(methoxycarbonyl)-6-(methylsulfanyl)pyridin-3-yl]boronic acid (**Intermediate 359**, 0.58 mmol based on the boronic ester, 0.180 g), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (0.04 mmol, 0.0367 g) and sodium carbonate (0.45 mmol, 0.0477 g) in acetonitrile/water (5 : 1) was degassed and heated to 90 °C for 30 min under an inert atmosphere. The reaction mass was

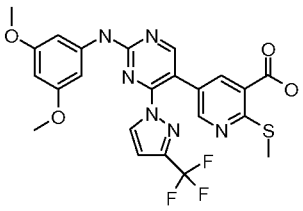
passed through a celite bed and solvent was concentrated *in vacuo*. The resultant residue taken in EtOAc (50 mL) was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude mass was further purified by silica gel column chromatography (product eluted with 3 % Et_3N EtOAc) to yield 0.22 g of the product.

Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 850	 methyl 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)pyridine-3-carboxylate	MS(ES): 547 (M+1) for $C_{24}H_{21}F_3N_6O_4S$. 400 MHz, DMSO-d_6: δ 2.47 (s, 3H), 3.75 (s, 6H), 3.81 (s, 3H), 6.22 (t, *J* = 2.20 Hz, 1H), 7.06 (d, *J* = 2.52 Hz, 1H), 7.10 (d, *J* = 2.16 Hz, 2H), 7.94 (d, *J* = 2.32 Hz, 1H), 8.51 (d, *J* = 1.40 Hz, 1H), 8.58 (d, *J* = 2.32 Hz, 1H), 8.83 (s, 1H), 10.23 (s, 1H).	**Intermediate 215** 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine and **Intermediate 359** mixture of methyl 2-(methylsulfanyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate and [5-(methoxycarbonyl)-6-(methylsulfanyl)pyridin-3-yl]boronic acid

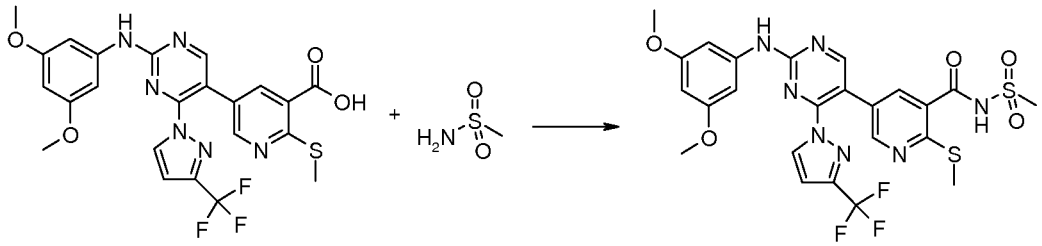
Example 851: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)pyridine-3-carboxylic acid



To 160 mg of methyl 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)pyridine-3-carboxylate (**Example 850**, 0.29 mmol) taken in a mixture of THF (5 mL) and water (5 mL), was added Sodium hydroxide (0.73 mmol, 0.029 g) and stirred at room temperature for 3 h. The mixture was carefully acidified with 1 N HCl and the solid obtained was filtered, dried to yield the desired product (0.13 g).

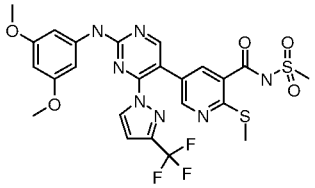
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 851	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)pyridine-3-carboxylic acid	MS(ES): 533 (M+1) for $C_{23}H_{19}F_3N_6O_4S$. 400 MHz, DMSO-d_6: δ 2.44 (s, 3H), 3.75 (s, 6H), 6.22 (t, *J* = 2.12 Hz, 1H), 7.05 (d, *J* = 2.60 Hz, 1H), 7.11 (d, *J* = 2.12 Hz, 2H), 7.91 (d, *J* = 2.32 Hz, 1H), 8.49 (d, *J* = 1.60 Hz, 1H), 8.54 (d, *J* = 2.16 Hz, 1H), 8.82 (s, 1H), 10.22 (s, 1H), 13.44 (s, 1H).	**Example 850** methyl 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)pyridine-3-carboxylate

Example 852: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)-*N*-(methylsulfonyl)pyridine-3-carboxamide

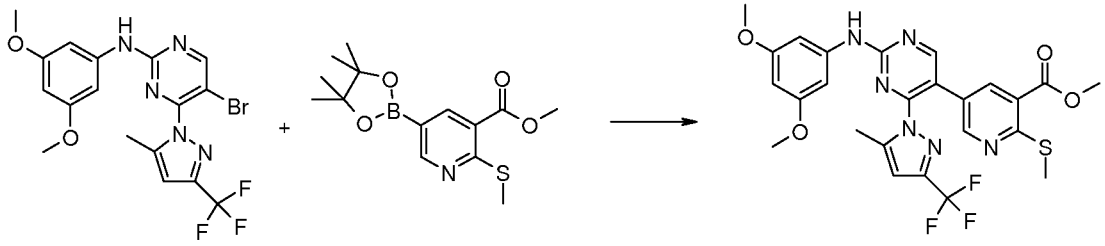


To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)pyridine-3-carboxylic acid (**Example 851**, 0.187 mmol, 0.1 g) in DCM was added TEA (0.56 mmol, 0.057 g), 2-chloro-1-methylpyridinium iodide (0.225 mmol, 0.0575 g), DMAP (0.037 mmol, 5 mg) and methanesulfonamide (0.28 mmol, 0.0268 g) stirred at RT for 2 h. The reaction mixture was diluted with DCM (20 mL), washed with water,

10% citric acid and brine, dried over Na_2SO_4, filtered and concentrated. The crude material was stirred with MeOH and hexane to give the pure title compound (0.1 g).

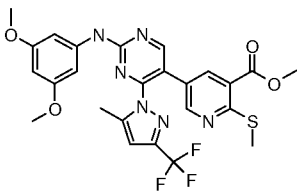
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 852	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)-*N*-(methylsulfonyl)pyridine-3-carboxamide	MS(ES): 610 (M+1) for $C_{24}H_{22}F_3N_7O_5S_2$. 400 MHz, DMSO-d_6: δ 2.41 (s, 3H), 3.27 (s, 3H), 3.74 (s, 6H), 6.20 (d, J = 1.92 Hz, 1H), 7.05 (d, J = 2.56 Hz, 1H), 7.11 (d, J = 2.04 Hz, 2H), 8.10 (d, J = 2.00 Hz, 1H), 8.25 (d, J = 2.04 Hz, 1H), 8.43 (s, 1H), 8.82 (s, 1H), 10.25 (s, 1H), 12.27 (s, 1H).	**Example 851** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)pyridine-3-carboxylic acid

Example 853: Methyl 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)pyridine-3-carboxylate

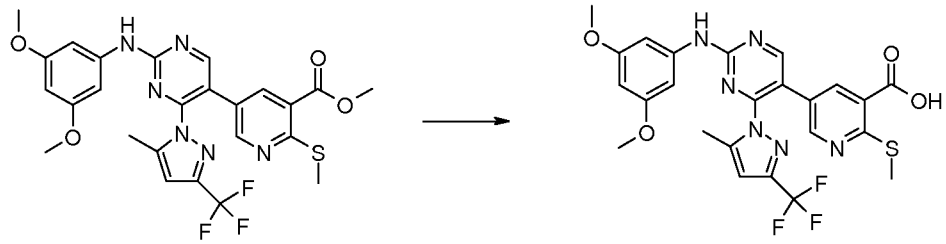


A suspension of 5-bromo-*N*-(3,5-dimethoxyphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 216**, 0.43 mmol, 0.2 g), a mixture of methyl 2-(methylsulfanyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carboxylate and [5-(methoxycarbonyl)-6-(methylsulfanyl)pyridin-3-yl]boronic acid (**Intermediate 359**, 0.56 mmol, 0.175 g), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (0.04 mmol, 0.036 g) and sodium carbonate (0.43 mmol, 0.0462 g) in acetonitrile/water (5 : 1) was degassed and heated to 90 °C for 30 min under an inert atmosphere.

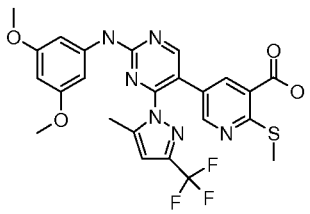
The reaction mass was passed through a diatomaceous earth bed and the solvent was concentrated *in vacuo*. The resultant residue taken in EtOAc (50 mL) was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude mass was further purified by silica gel column chromatography with (25% EtOAc/hexanes) to yield 0.180 g of the product.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 853	 Methyl 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)pyridine-3-carboxylate	MS(ES): 561 (M+1) for $C_{25}H_{23}F_3N_6O_4S$. 400 MHz, DMSO-d_6: δ 2.29 (s, 3H), 2.44 (s, 3H), 3.71 (s, 6H), 3.77 (s, 3H), 6.21 (s, 1H), 6.76 (s, 1H), 7.04 (s, 2H), 7.64 (d, J = 2.92 Hz, 1H), 8.53 (s, 1H), 8.98 (s, 1H), 10.24 (s, 1H).	**Intermediate 216** 5-Bromo-*N*-(3,5-dimethoxyphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

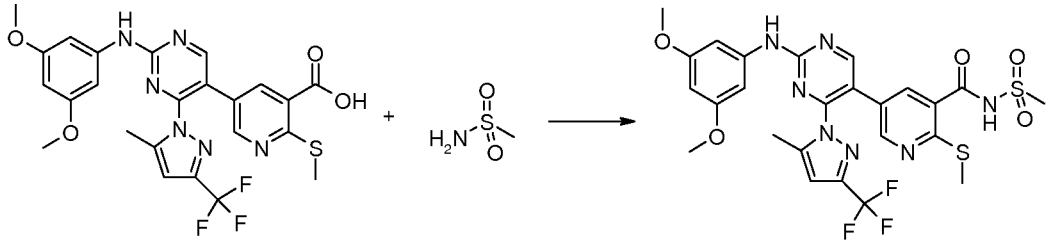
Example 854: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)pyridine-3-carboxylic acid



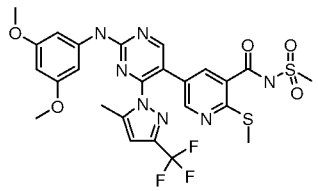
To 50 mg of methyl 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)pyridine-3-carboxylate (**Example 853**, 0.089 mmol) taken in a mixture of THF (5 mL) and water (5 mL), was added sodium hydroxide (0.22 mmol, 9 mg) and stirred at room temperature for 3 h. The mixture was carefully acidified with 1 N HCl and the solid obtained was filtered and then dried to yield the product (0.04 g).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 854	 5-{2-[(3,5-Dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)pyridine-3-carboxylic acid	MS(ES): 547 (M+1) for $C_{24}H_{21}F_3N_6O_4S$. 400 MHz, DMSO-d_6: δ 2.34 (s, 3H), 2.42 (s, 3H), 3.73 (s, 6H), 6.23 (s, 1H), 6.77 (s, 1H), 7.06 (s, 2H), 7.68 (s, 1H), 8.49 (s, 1H), 8.98 (s, 1H), 10.24 (s, 1H), 13.37 (s, 1H).	**Example 853** methyl 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)pyridine-3-carboxylate

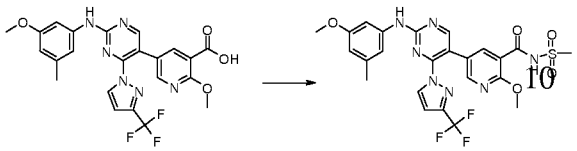
Example 855: 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)-*N*-(methylsulfonyl)pyridine-3-carboxamide



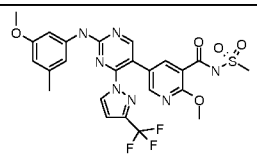
To a solution of 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)pyridine-3-carboxylic acid (**Example 854**, 0.219 mmol, 0.12 g) in DCM was added TEA (0.65 mmol, 0.066 g), 2-chloro-1-methylpyridinium iodide (0.263 mmol, 0.0673 g) (0.225 mmol, 0.0575 g), DMAP (0.0439 mmol, 6 mg) and Methanesulfonamide (0.329 mmol, 0.0313 g), and stirred at RT for 2 h. The reaction mixture was diluted with DCM (20 mL), washed with water, 10% citric acid and brine, dried over Na_2SO_4, filtered and concentrated. The crude mass was further purified by silica gel column chromatography with (2% MeOH / EtOAc). The material obtained from chromatography was stirred with DCM and hexane to yield 0.1 g of the pure product (100 mg).

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 855	 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)-*N*-(methylsulfonyl)pyridine-3-carboxamide	MS(ES): 624 (M+1) for $C_{25}H_{24}F_3N_7O_5S_2$. 400 MHz, DMSO-d_6: δ 2.34 (s, 3H), 2.40 (s, 3H), 3.35 (s, 3H), 3.72 (s, 6H), 6.21 (t, J = 2.08 Hz, 1H), 6.80 (s, 1H), 7.05 (d, J = 1.88 Hz, 2H), 7.97 (d, J = 2.00 Hz, 1H), 8.03 (d, J = 2.08 Hz, 1H), 9.01 (s, 1H), 10.29 (s, 1H), 12.31 (s, 1H).	**Example 854** 5-{2-[(3,5-dimethoxyphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-(methylsulfanyl)pyridine-3-carboxylic acid

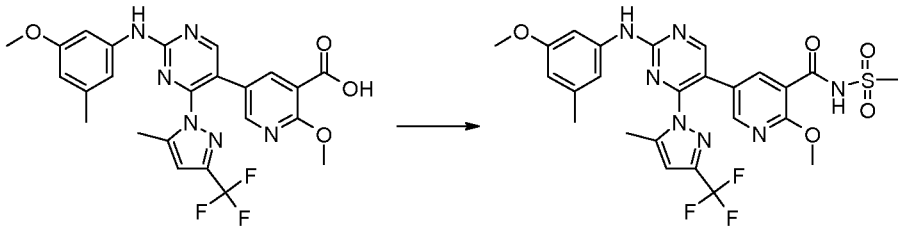
Example 856: 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(methylsulfonyl)pyridine-3-carboxamide



To a solution of 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid (**Example 760**, 0.33 mmol, 165 mg) in CH_2Cl_2 (10 mL), were added methanesulfonamide (0.82 mmol, 78 mg), triethylamine (0.99 mmol, 0.14 mL), 2-chloro-1-methylpyridinium iodide (0.41 mmol, 105 mg) and 4-(Dimethylamino)pyridine (0.066 mmol, 8 mg) and stirred at RT for 2 h. The reaction mixture was diluted with dichloromethane (20 mL) and further washed with 25% citric acid solution (2 x 15 mL), water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by 60-120 mesh silica (product eluted with 1-2% MeOH in $CHCl_3$) to afford 65 mg of the title compound as a white solid.

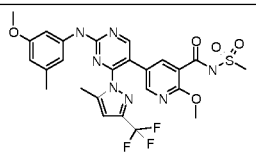
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 856	 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(methylsulfonyl)pyridine-3-carboxamide	MS (ES): 578 (M+1) for $C_{24}H_{22}F_3N_7O_5$. 400 MHz, MeOD: δ 2.33 (s, 3H), 3.36 (s, 3H), 3.80 (s, 3H), 4.14 (s, 3H), 6.49 (s, 1H), 6.83 (d, *J* = 2.68 Hz, 1H), 7.07 (s, 1H), 7.33 (s, 1H), 8.09 (d, *J* = 2.48 Hz, 1H), 8.24 (d, *J* = 2.48 Hz, 1H), 8.58 (s, 2H).	**Example 760** 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

Example 857: 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(methylsulfonyl)pyridine-3-carboxamide

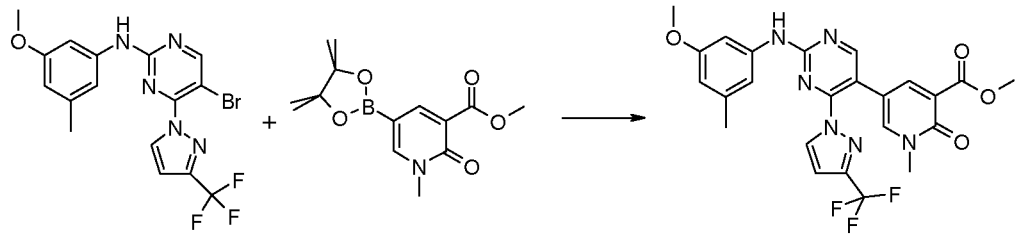


To a solution of 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid (**Example 761**, 0.36 mmol, 185 mg) in CH_2Cl_2 (10 mL), was added methanesulfonamide (0.90 mmol, 86 mg), triethylamine (1.08 mmol, 0.15 mL), 2-chloro-1-methylpyridinium iodide (0.45 mmol, 115 mg) and 4-(Dimethylamino)pyridine (0.072 mmol, 8.78 mg) and stirred at RT for 2 h. The reaction mixture was diluted with dichloromethane (20 mL) and further washed with 25% citric acid solution (2 x 15 mL), water (25 mL) and brine (25 mL). The organic layer was dried over

Na_2SO_4 and concentrated. The crude mass was purified by 230-400 mesh silica (product eluted with 1-2% MeOH in $CHCl_3$) to afford 130 mg of white solid of the title compound.

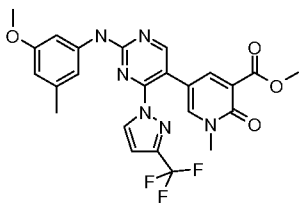
Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 857	 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(methylsulfonyl)pyridine-3-carboxamide	MS (ES): 592 (M+1) for $C_{25}H_{24}F_3N_7O_5S$. 400 MHz, $CDCl_3$: δ 2.36 (s, 3H), 2.48 (s, 3H), 3.40 (s, 3H), 3.82 (s, 3H), 4.18 (s, 3H), 6.44 (s, 1H), 6.52 (s, 1H), 6.93 (s, 1H), 7.19 (s, 1H), 7.35 (s, 1H), 8.07-8.09 (m, 2H), 8.63 (s, 1H), 10.10 (s, 1H).	**Example 761** 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carboxylic acid

Example 858: methyl 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate

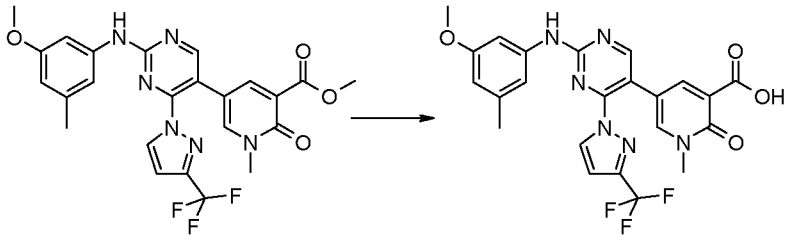


A solution of 5-bromo-*N*-(3-methoxy-5-methylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 293**, 0.93 mmol, 400 mg), a mixture of methyl 1-methyl-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate and [5-(methoxycarbonyl)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl]boronic acid (**Intermediate 323**, 1.1 mmol based on the boronic ester, 328 mg), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)complex with CH_2Cl_2 (0.18 mmol, 146

mg) and sodium carbonate (0.9 mmol, 95 mg) in acetonitrile (40 mL)/water (10 mL) was degassed and heated to 90 °C for 30 minutes under nitrogen. The reaction mixture was concentrated *in vacuo*. The residue obtained was taken in ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using 2% methanol/chloroform to obtain 300 mg of the title compound.

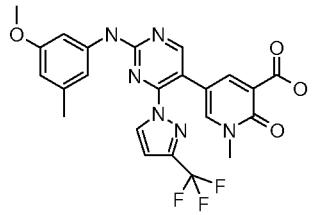
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 858	 methyl 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 515 (M+1) for $C_{24}H_{21}F_3N_6O_4$. 400 MHz, DMSO-d_6: δ 2.26 (s, 3H), 3.32 (s, 3H), 3.72 (s, 3H), 3.92 (s, 3H), 6.44 (s, 1H), 7.06 (d, J = 3.24 Hz, 1H), 7.12 (s, 1H), 7.32 (s, 1H), 7.62 (d, J = 3.48 Hz, 1H), 8.16 (d, J = 4.24 Hz, 1H), 8.54 (s, 1H), 8.70 (s, 1H), 10.09 (s, 1H).	**Intermediate 323** and **Intermediate 293** 5-bromo-*N*-(3-methoxy-5-methylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

Example 859: 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

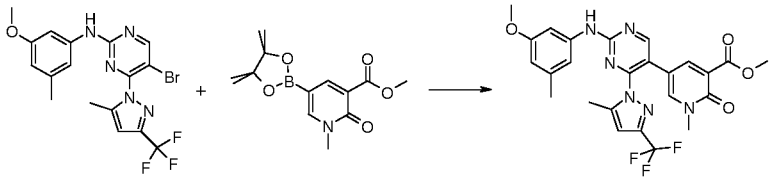


To 300 mg of methyl 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (**Example 858**, 0.58 mmol) taken in a mixture of THF (10 mL) /H_2O (10 mL), was added NaOH (1.1 mmol, 46 mg) and stirred at rt for 2 h. The solvent was removed *in vacuo* and the mixture was carefully

acidified with 1 N HCl and the solid that precipitated was filtered and dried to obtain 190 mg of the title compound.

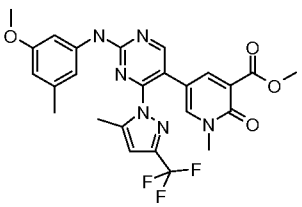
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 859	 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 501 (M+1) for $C_{23}H_{19}F_3N_6O_4$. 400 MHz, DMSO-d_6: δ 2.29 (s, 3H), 3.70 (s, 3H), 3.75 (s, 3H), 6.47 (s, 1H), 7.10 (s, 1H), 7.15 (s, 1H), 7.34 (s, 1H), 8.05 (d, J = 1.80 Hz, 1H), 8.44 (s, 1H), 8.60 (s, 1H), 8.72 (s, 1H), 10.17 (s, 1H), 14.53 (s, 1H).	**Example 858** methyl 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate

Example 860: methyl 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate

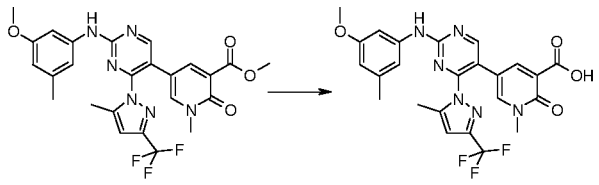


A solution 5-bromo-*N*-(3-methoxy-5-methylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 294**, 0.79 mmol, 350 mg), a mixture of methyl 1-methyl-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate and [5-(methoxycarbonyl)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl]boronic acid (**Intermediate 323**, 0.95 mmol based on the boronic ester, 279 mg), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)complex with CH_2Cl_2 (0.14 mmol, 112 mg) and sodium carbonate (0.7 mmol, 74 mg) in acetonitrile (40 mL)/water (10 mL) was

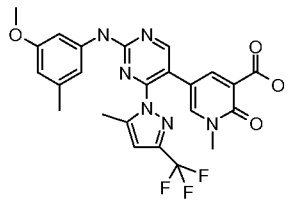
degassed and heated to 90 °C for 30 minutes under nitrogen. The reaction mixture was concentrated *in vacuo*. The residue obtained was taken in ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using 2% methanol/chloroform to afford 300 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 860	 Methyl 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 529 (M+1) for $C_{25}H_{23}F_3N_6O_4$. 300 MHz, $CDCl_3$: δ 2.35 (s, 3H), 2.38 (s, 3H), 3.56 (s, 3H), 3.81 (s, 3H), 3.88 (s, 3H), 6.45 (s, 1H), 6.51 (s, 1H), 6.90 (s, 1H), 7.18 (s, 1H), 7.52 (d, *J* = 2.76 Hz, 1H), 7.80 (d, *J* = 2.70 Hz, 1H), 8.58 (s, 1H).	**Intermediate 323** and **Intermediate 294** 5-bromo-*N*-(3-methoxy-5-methylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

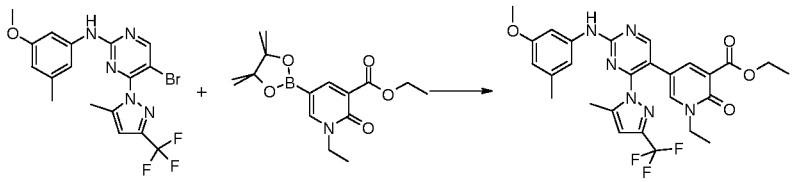
Example 861: 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid



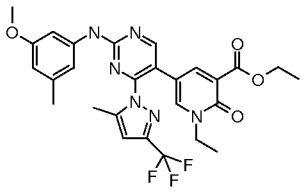
To 300 mg of methyl 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (**Example 860**, 0.57 mmol) dissolved in a mixture of THF (10 mL) /H_2O (10 mL), then NaOH (1.1 mmol, 46 mg) was added and the mixture was stirred at rt for 2 h. The solvent was removed *in vacuo* and the mixture was carefully acidified with 1 N HCl and the solid that precipitated was filtered and dried to obtain 200 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 861	 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 515 (M+1) for $C_{24}H_{21}F_3N_6O_4$. 400 MHz, DMSO-d_6: δ 2.27 (s, 3H), 2.50 (s, 3H), 3.68 (s, 3H), 3.73 (s, 3H), 6.48 (s, 1H), 6.82 (s, 1H), 7.13 (s, 1H), 7.26 (s, 1H), 7.64 (d, J = 2.40 Hz, 1H), 8.43 (d, J = 2.48 Hz, 1H), 8.86 (s, 1H), 10.16 (s, 1H), 14.41 (s, 1H).	**Example 860** methyl 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate

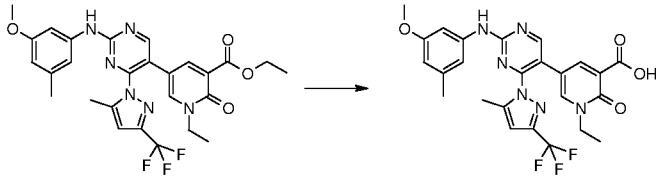
Example 862: ethyl 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-oxo-1,2-dihydropyridine-3-carboxylate



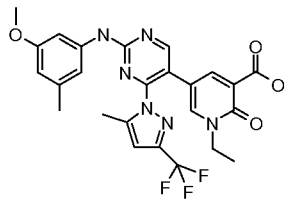
A solution 5-bromo-*N*-(3-methoxy-5-methylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 294**, 0.9 mmol, 400 mg), a mixture of ethyl 1-ethyl-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate and [5-(ethoxycarbonyl)-1-ethyl-6-oxo-1,6-dihydropyridin-3-yl]boronic acid (**Intermediate 361**, 1.1 mmol based on the boronic ester, 350 mg), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.2 mmol, 146 mg) and sodium carbonate (0.9 mmol, 95 mg) in acetonitrile (40 mL)/water (10 mL) was degassed and heated to 90 °C for 30 minutes under nitrogen. The reaction mixture was concentrated *in vacuo*. The residue obtained was taken in ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using 2% methanol/chloroform to yield 300 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 862	 ethyl 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 557 (M+1) for $C_{27}H_{27}F_3N_6O_4$. 400 MHz, $CDCl_3$: δ 1.27-1.37 (m, 6H), 2.34 (s, 6H), 3.80 (s, 3H), 3.97 (q, *J* = 7.16 Hz, 2H), 4.34 (q, *J* = 7.08 Hz, 2H), 6.44 (s, 1H), 6.50 (s, 1H), 6.89 (s, 1H), 7.19 (s, 1H), 7.39 (d, *J* = 2.48 Hz, 1H), 7.83 (d, *J* = 2.64 Hz, 1H), 8.59 (s, 1H) .	**Intermediate 361** and **Intermediate 294** 5-bromo-*N*-(3-methoxy-5-methylphenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

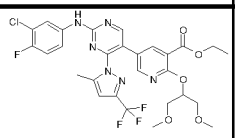
Example 863: 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-oxo-1,2-dihydropyridine-3-carboxylic acid

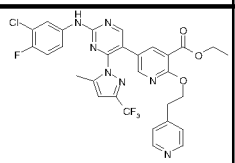


To 300 mg of ethyl 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-oxo-1,2-dihydropyridine-3-carboxylate (**Example 862**, 0.54 mmol) taken in a mixture of THF (10 mL) /H_2O (10 mL), was added NaOH (1.1 mmol, 43 mg) and stirred at rt for 2 h. The solvent was removed *in vacuo* and the mixture was then carefully acidified with 1 N HCl and the solid that precipitate was filtered and dried to obtain 180 mg of the title compound.

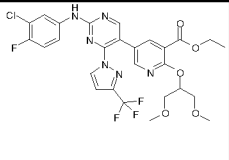
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 863	 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 529 (M+1) for $C_{25}H_{23}F_3N_6O_4$. 400 MHz, DMSO-d_6: δ 1.27 (t, *J* = 7.08 Hz, 3H), 2.26 (s, 3H), 2.49 (s, 3H), 3.71 (s, 3H), 4.11 (t, *J* = 7.12 Hz, 2H), 6.46 (s, 1H), 6.79 (s, 1H), 7.12 (s, 1H), 7.24 (s, 1H), 7.78 (d, *J* = 2.44 Hz, 1H), 8.30 (d, *J* = 1.60 Hz, 1H), 8.88 (s, 1H), 10.15 (s, 1H), 14.45 (s, 1H).	**Example 862** ethyl 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-oxo-1,2-dihydropyridine-3-carboxylate

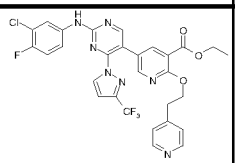
The compounds in the below table were prepared using the general method described above for Example **1** using **Intermediate 113** and the specified starting material.

Ex	Compound	Data	SM
Example 864	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(1,3-dimethoxypropan-2-yloxy)nicotinate	MS(ES): 639.21 (M+H) for C28H27ClF4N6O5 1H NMR (400 MHz, DMSO- *d*6) δ ppm 1.25 (t, *J*=7.06 Hz, 3 H) 3.26 (s, 6 H) 3.56 (d, *J*=5.09 Hz, 4 H) 3.92 (s, 3 H) 4.21 (q, *J*=7.16 Hz, 2 H) 5.49 (t, *J*=4.99 Hz, 1 H) 6.78 (s, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.61 (d, *J*=2.45 Hz, 1 H) 7.63 - 7.75 (m, 1 H) 8.06 (d, *J*=6.59 Hz, 1 H) 8.16 (d, *J*=2.45 Hz, 1 H) 8.96 (s, 1 H) 10.43 (s, 1 H)	ethyl 2-(1,3-dimethoxypropan-2-yloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 315**

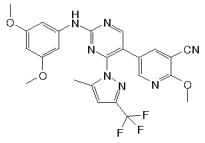
Ex	Compound	Data	SM
Example 865	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(pyridin-4-yl)ethoxy)nicotinate	MS(ES): 640.39 (M-H) for C30H24ClF4N7O3 1H NMR (400 MHz, DMSO- *d*6) δ ppm 1.19 (t, *J*=7.06 Hz, 3 H) 2.35 (s, 4 H) 3.06 (t, *J*=6.12 Hz, 2 H)4.18 (q, *J*=7.03 Hz, 2 H) 4.58 (t, *J*=6.22 Hz, 2 H) 6.77 (s, 1 H) 7.34 (d, *J*=5.84 Hz, 2 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.55 (d, *J*=2.45 Hz, 1 H) 7.61 - 7.70 (m, 1 H) 8.06 (br. s., 1 H) 8.22 (d, *J*=2.45 Hz, 1 H) 8.46 (d, *J*=5.84 Hz, 2 H) 8.96 (s, 1 H) 10.44 (s, 1 H)	ethyl 2-(2-(pyridin-4-yl)ethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) nicotinate **Intermediate 318**

The compounds in the below table were prepared using the general method described above for Example **1** using **Intermediate 115** and the specified starting material.

Ex	Compound	Data	SM
Example 866	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(1,3-dimethoxypropan-2-yloxy)nicotinate	MS(ES): 625.02 (M+H) for C27H25ClF4N6O5 1H NMR (400 MHz, DMSO- *d*6) δ ppm 1.25 (t, *J*=7.06 Hz, 3 H) 3.30 (d, *J*=9.42 Hz, 6 H) 3.59 (d, *J*=5.09 Hz, 4 H) 4.19 (q, 2 H) 5.52 (t, *J*=4.90 Hz, 1 H) 7.05 (d, *J*=2.45 Hz, 1 H) 7.42 (t, *J*=9.04 Hz, 1 H) 7.63 - 7.79 (m, 1 H) 7.84 (d, *J*=2.45 Hz,1 H) 8.09 (d, *J*=2.45 Hz, 1 H) 8.22 (d, *J*=2.45 Hz, 1 H) 8.52 (s, 1 H) 8.81 (s, 1 H) 10.40 (s, 1 H)	ethyl 2-(1,3-dimethoxypropan-2-yloxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 315**

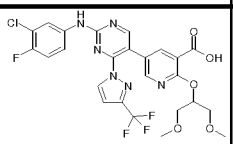
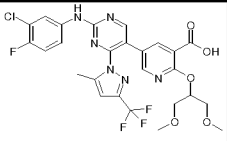
Ex	Compound	Data	SM
Example 867	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(pyridin-4-yl)ethoxy)nicotinate	MS(ES): 628.10 (M+H) for C29H22ClF4N7O3 1H NMR (400 MHz, DMSO- *d*6) δ ppm 1.12 - 1.28 (m, 6 H) 3.08 (br. s., 3 H) 3.93 (s, 3 H) 4.19 (q, *J*=7.10 Hz, 3 H) 4.27 (d, *J*=7.16 Hz, 1 H) 4.61 (s, 3 H) 7.05 (d, *J*=2.45 Hz, 1 H) 7.32 - 7.49 (m, 5 H) 7.52 (br. s., 2 H) 7.69 (d, *J*=2.64 Hz, 1 H) 7.80 (d, *J*=2.26 Hz, 1 H) 8.07 (d, *J*=6.59 Hz, 1 H) 8.27 (d, *J*=2.45 Hz, 1 H) 8.47 (br. s., 4 H) 8.80 (s, 1 H) 10.42 (s, 1 H)	ethyl 2-(2-(pyridin-4-yl)ethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 318**

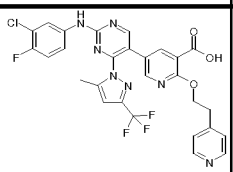
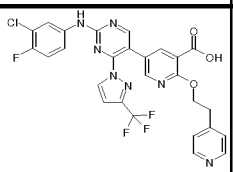
The compound in the below table was prepared using the general method described above for Example **1** using **Intermediate 216** and the specified starting material.

Ex	Compound	Data	SM
Example 868	 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinonitrile	MS(ES): 512.14 (M+H) for C24H20F3N7O3 1H NMR (400 MHz, DMSO- *d*6) δ ppm 2.46 (s, 3 H) 3.73 (s, 6 H) 3.99 (s, 3 H) 6.23 (s, 1 H) 6.81 (s, 1 H) 7.03 (d, *J*=1.70 Hz, 2 H) 7.93 (d, *J*=2.26Hz, 1 H) 8.20 (d, *J*=2.26 Hz, 1 H) 8.89 (s, 1 H) 10.21 (s, 1 H)	2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile **Intermediate 362**

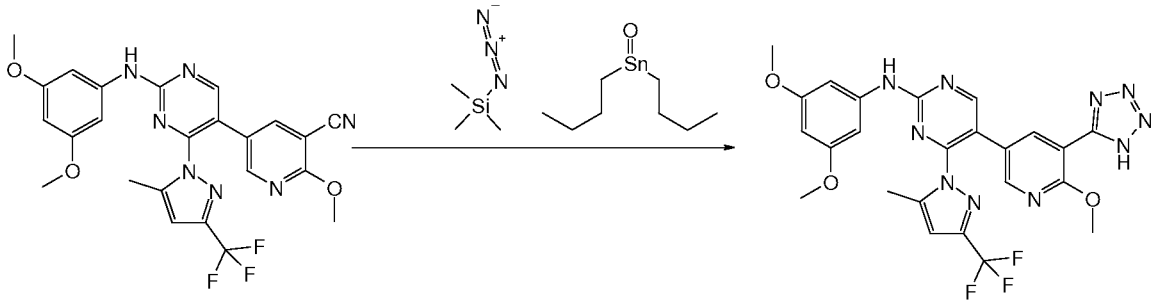
The compounds in the below table were prepared using the general method described above for Example **214** using 1N sodium hydroxide (2 equivalents), dioxane : THF (1:1) as solvent and the specified starting material.

5

Ex	Compound	Data	SM
Example 869	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(1,3-dimethoxypropan-2-yloxy)nicotinic acid	MS(ES): 597.09 (M+H) for C25H21ClF4N6O5 1H NMR (400 MHz, DMSO- *d*6) δ ppm 3.28 (s, 6 H) 3.58 (br. s., 2 H) 3.60 (d, *J*=1.70 Hz, 2 H) 5.52 (t, *J*=4.99 Hz, 1 H) 7.04 (d, *J*=2.45 Hz, 1 H) 7.42 (t, *J*=9.04 Hz, 1 H) 7.70 - 7.80 (m, 1 H) 7.86 (s, 1 H) 8.07 (dd, *J*=6.50, 2.54 Hz, 1 H) 8.17 (d, *J*=2.26 Hz, 1 H) 8.47 - 8.58 (m, 1H) 8.80 (s, 1 H) 10.40 (s, 1 H) 12.85 (br. s., 1 H)	ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(1,3-dimethoxypropan-2-yloxy)nicotinate **Example 866**
Example 870	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(1,3-dimethoxypropan-2-yloxy)nicotinic acid	MS(ES): 611.14 (M+H) for C26H23ClF4N6O5 1H NMR (400 MHz, DMSO- *d*6) δ ppm 2.37 (s, 3 H) 3.26 (s, 6 H) 3.43 - 3.60 (m, 4 H) 5.49 (t, *J*=4.99 Hz, 1 H) 6.76 (s, 1 H) 7.42(t, *J*=9.14 Hz, 1 H) 7.61 - 7.76 (m, 2 H) 8.05 (d, *J*=2.26 Hz, 1 H) 8.07 (d, *J*=2.45 Hz, 1 H) 8.95 (s, 1 H) 10.42 (s, 1 H) 12.88 (br. s., 1 H)	ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(1,3-dimethoxypropan-2-yloxy)nicotinate **Example 864**

Ex	Compound	Data	SM
Example 871	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(pyridin-4-yl)ethoxy)nicotinic acid	MS(ES): 612.44 (M-H) for C28H20ClF4N7O3 1H NMR (400 MHz, DMSO- *d*6) δ ppm 2.34 (s, 3 H) 3.14 (t, *J*=5.84 Hz, 2 H) 4.59 (t, *J*=6.03 Hz, 2 H) 6.76 (s, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.53 -7.69 (m, 4 H) 8.06 (br. s., 1 H) 8.13 (s, 1 H) 8.57 (d, *J*=4.71 Hz, 2 H) 8.94 (s, 1 H) 10.44 (s, 1 H)12.96 (br. s., 1 H)	ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(pyridin-4-yl)ethoxy)nicotinate **Example 865**
Example 872	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(pyridin-4-yl)ethoxy)nicotinic acid	MS(ES): 600.04 (M+H) for C27H18ClF4N7O3 1H NMR (400 MHz, DMSO- *d*6) δ ppm 3.07 (m, 2 H) 4.59 (m, 2 H) 7.03 (m, 1 H) 7.38 (m, 3 H) 7.71 m, 1 H) 7.84 (d, *J*=0.75 Hz, 1H) 8.08 (m., 1 H) 8.21 (m, 1 H) 8.47 (m, 3 H) 8.79 (m, 1 H) 10.35 - 10.51 (m, 1 H) 12.97 (m, 1 H)	ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(pyridin-4-yl)ethoxy)nicotinate **Example 867**

Example 873: N-(3,5-dimethoxyphenyl)-5-(6-methoxy-5-(1H-tetrazol-5-yl)pyridin-3-yl)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine

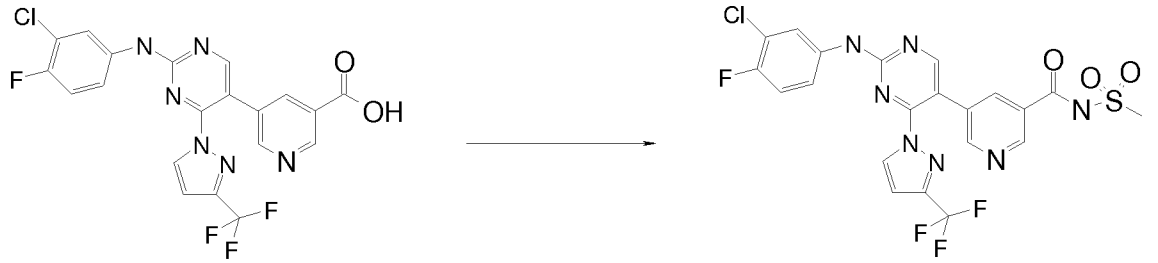


5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinonitrile (**Example 868**, 0.16 g, 0.31 mmol), dibutyltin oxide (0.023 g, 0.09 mmol), and TMS-N_3 (0.166 mL, 1.25 mmol) were suspended in 1,4-dioxane (1 mL) to give a yellow suspension. The mixture was heated in a microwave reactor at 140 °C for 1h. Concentrated *in vacuo*. Purified by flash chromatography: 25g silica gel column, 0-20% methanol in chloroform. Relevant fractions pooled and resulting material was dried under high vacuum to obtain the title compound as a tan foam in (0.1g).

MS(ES): 555.17 (M+H) for $C_{24}H_{21}F_3N_{10}O_3$

^{1}H-NMR (400 MHz, DMSO-d6): δ ppm 2.39 (m, 3 H) 3.73 (m., 6 H) 4.04 (m, 3 H) 6.22 (m, 1 H) 6.75 (m., 1 H) 7.06 (m, 2 H) 8.03 (m, 1 H) 8.18 (m., 1 H) 8.96 (m, 1 H) 10.22 (m, 1 H).

Example 874: 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(methylsulfonyl)nicotinamide



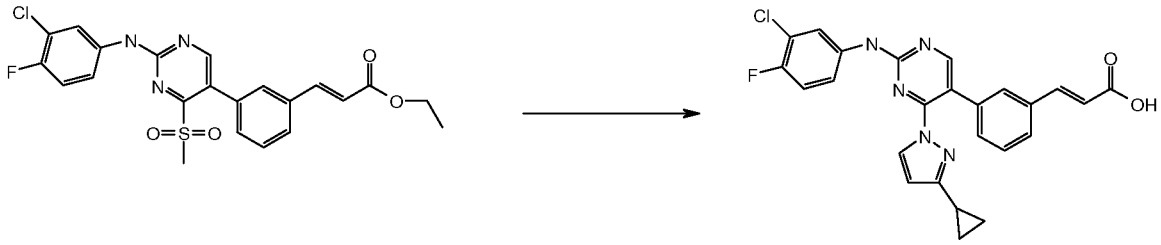
5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinic acid (**Example 320**, 57 mg, 0.12 mmol) and 1,1-carbonyldiimidazole (50 mg) were combined in DMF (1.5 mL) and stirred for 30 minutes. Methanesulfonamide (16.99 mg, 0.18

mmol) was added and the mixture was stirred at 90 °C overnight. Purification by reverse phase chromatography (05-95% ACN/ water NH4OH) gave the title compound (14 mg).

MS (Electrospray): 556.89, (MH^+) for $C_{21}H_{14}ClF_4N_7O_3S$

^{1}H NMR (300 MHz, DMSO-d_6) δ : 2.84 (s, 3 H) 7.00 (d, *J*=2.64 Hz, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.74 (ddd, *J*=9.09, 4.19, 2.73 Hz, 1 H) 8.00 - 8.13 (m, 2 H) 8.28 (d, *J*=2.07 Hz, 1 H) 8.45 (s, 1 H) 8.78 (s, 1 H) 8.95(d, *J*=1.70 Hz, 1 H) 10.43 (s, 1 H)

Example 875: (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-cyclopropyl-1H-pyrazol-1-yl)pyrimidin-5-yl)phenyl)acrylic acid



3-Cyclopropyl-1H-pyrazole (42.7 mg, 0.40 mmol) was dissolved in THF, then NaH (9.48 mg, 0.40 mmol) was added slowly and the mixture was stirred for 30 minutes. The mixture was added to a solution of (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(methylsulfonyl)pyrimidin-5-yl)phenyl)acrylate **Intermediate 125** (94 mg, 0.20 mmol) in THF (2 mL). The resulting mixture was allowed to stir overnight at room temperature. Methanol (0.25 ml) then water (0.25 ml) were added and the mixture was evaporated. Purification using reverse phase chromatography (C18, 20 to 95% CH_3CN / H2O / 0.1% Trifluoroacetic acid) yielded the title compound. (17 mg).

MS (Electrospray): 476.90(MH^+) for $C_{25}H_{19}ClFN_5O_2$

^{1}H NMR (300 MHz, DMSO-d_6) δ : 0.18 - 0.47 (m, 2 H) 0.57 - 0.76 (m, 2 H) 1.52 - 1.80 (m, 1 H) 6.35 (d,*J*=2.64 Hz, 1 H) 6.46 (s, 1 H) 6.52 (s, 1 H) 7.19 (d, *J*=7.54 Hz, 1 H) 7.32 - 7.46 (m, 2 H)

7.48 - 7.59 (m, 1 H)7.62 (d, *J*=8.10 Hz, 1 H) 7.72 (ddd, *J*=9.09, 4.19, 2.73 Hz, 1 H) 8.06 - 8.21 (m, 2 H) 8.58 (s, 1 H) 10.16 (s, 1H)

Example 876: N-(3-chloro-4-fluorophenyl)-5-(6-methoxypyridin-2-yl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine



5-bromo-N-(3-chloro-4-fluorophenyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine **Intermediate 115** (100 mg, 0.23 mmol), Pd(Ph3P)4 (79 mg, 0.07 mmol), and 0.5M (6-methoxypyridin-2-yl)zinc(II) bromide in THF (0.916 mL, 0.46 mmol) were combined in THF (6 mL) under argon. The reaction was heated at 65 °C for 45 minutes. Additional 0.5M (6-methoxypyridin-2-yl)zinc(II) bromide in THF (0.916 mL, 0.46 mmol) was added and the mixture was allowed to stir for an additional 1.5 hours. The reaction mixture was concentrated and purified by silica gel flash chromatography using 0-50% ethyl acetate in hexanes. The title compound was obtained as a solid. (7 mg)

MS (Electrospray): 467.80(MH^+) $C_{20}H_{13}ClF_4N_6O$

1H NMR (300 MHz, DMSO-*d*6) □ppm 3.55 (s, 3 H) 6.59 - 6.83 (m, 1 H) 6.93 - 7.14 (m, 2 H) 7.27 - 7.52 (m, 2 H) 7.63 - 7.82 (m, 1 H) 8.07 - 8.21 (m, 1 H) 8.37 - 8.52 (m, 1 H) 8.99 (s, 1 H) 10.32 - 10.54 (m, 1 H)

Example 877: 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)picolinic acid

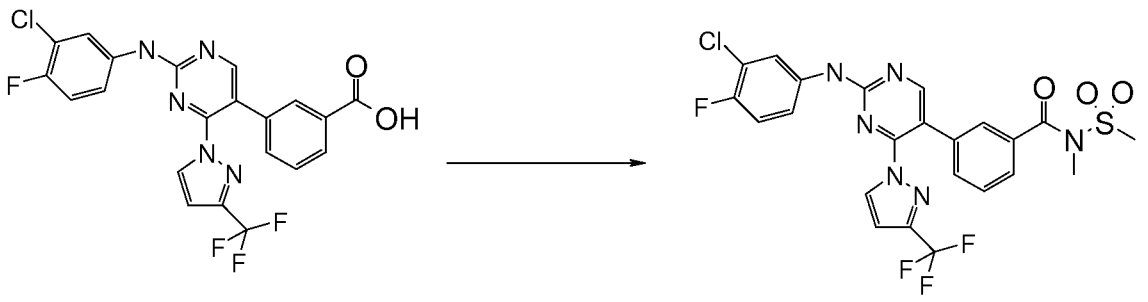


2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-ylboronic acid **Intermediate 364** (80 mg, 0.20 mmol), methyl 6-bromopicolinate (34.4 mg, 0.16 mmol), $Pd(Ph_3P)_4$ (46.0 mg, 0.04 mmol), and K_2CO_3 (41.3 mg, 0.30 mmol) were combined with Dioxane (4 mL) and water (1 mL). The mixture was heated in a microwave for 45 min. at 120 °C. Reverse phase chromatography (C18, 20-95% CH_3CN / H_2O/ 0.1% Trifluoroacetic acid) of the crude mixture gave the title compound. (19 mg)

MS (Electrospray): 479.79 (MH^+) C20H11ClF4N6O2

^{1}H NMR (300 MHz, DMSO-d6) δ ppm 7.04 (d, J=2.64 Hz, 1 H) 7.42 (d, J=7.91 Hz, 2 H) 7.70 - 7.83 (m, 1 H) 7.88 - 8.03 (m, 2 H) 8.06 - 8.15 (m, 1 H) 8.97 (s, 1 H) 10.50 (s, 1 H) 12.67 - 13.30 (m, 1 H)

Example 878: 3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-methyl-N-(methylsulfonyl)benzamide



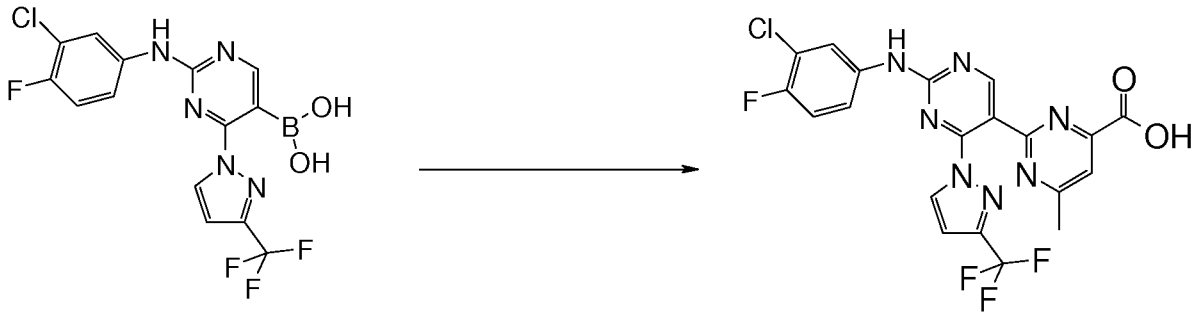
3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)benzoic acid **Example** (45 mg, 0,09 mmol) was dissolved in DMF (3ml). Triethylamine (

0.033 ml, 0.24 mmol) and HATU (35 mg, 0.09 mmol) was added and the mixture was allowed to stir for 10 min. N-methylmethanesulfonamide (10 mg, 0.09 mmol) was added to the reaction mixture and it was allowed to stir at RT overnight. Purification using reverse phase chromatography (C18, 5-95% CH_3CN / H_2O / 0.1% Trifluoroacetic acid) yielded the title compound. (12 mg).

MS (Electrospray): 569.93 (MH^+) $C_{23}H_{17}ClF_4N_6O_3S$

^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 3.25-3.35 (s, 3H), 3.55 (s, 3 H) 6.59 - 6.77 (m, 1 H) 6.92 - 7.11 (m, 2 H) 7.22 - 7.55 (m, 2 H) 7.65 - 7.85 (m, 2 H) 8.01 - 8.22 (m, 1 H) 8.34 - 8.53 (m, 1 H) 8.99 (s, 1 H) 10.40 - 10.54 (m, 1 H)

Example 879: 2'-(3-chloro-4-fluorophenylamino)-6-methyl-4'-(3-(trifluoromethyl)-1H-pyrazol-1-yl)-2,5'-bipyrimidine-4-carboxylic acid

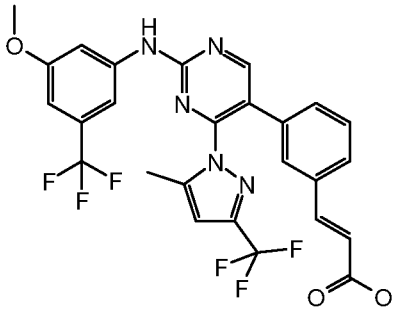
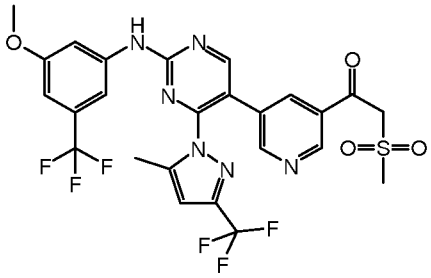


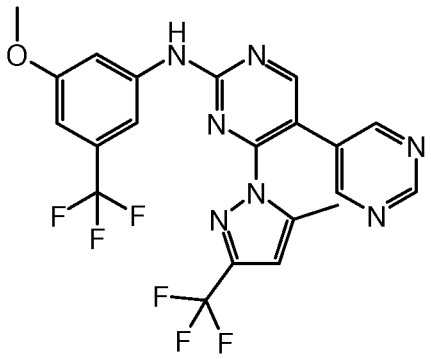
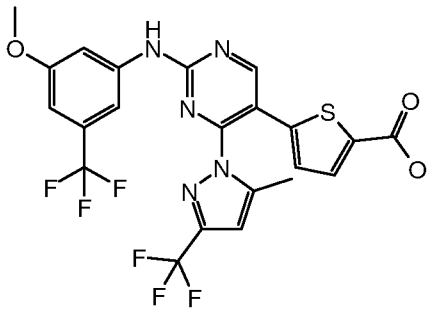
2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-ylboronic acid **Intermediate 364** (100 mg, 0.25 mmol), methyl 2-chloro-6-methylpyrimidine-4-carboxylate (93 mg, 0.50 mmol), $Pd(Ph_3P)_4$ (57.6 mg, 0.05 mmol), and K_2CO_3 (51.6 mg, 0.37 mmol) were combined with Dioxane (2 mL) and water (0.500 mL). The mixture was heated in a microwave for 45 min at 120 °C. The mixture was purified using reverse phase chromatography (C18, 5-95%.CH_3CN / H_2O / 0.1% Trifluoroacetic acid) to yield the title compound. (28 mg).

MS (Electrospray): 494.80 (MH^+) C20H12ClF4N7O2

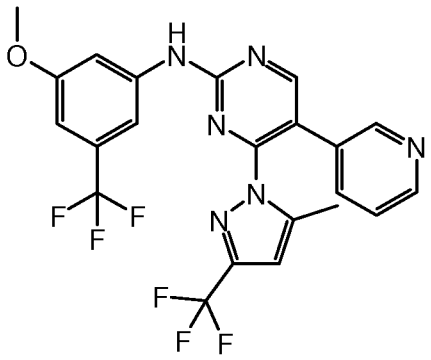
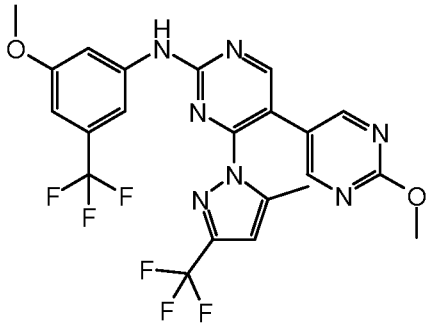
^{1}H NMR (300 MHz, DMSO-d6) δ ppm 2.46 (s, 3 H) 6.95 - 7.10 (m, 1 H) 7.38 - 7.49 (m, 1 H) 7.73 - 7.80 (m,1 H) 7.81 (s, 1 H) 8.05 - 8.13 (m, 1 H) 8.52 - 8.65 (m, 1 H) 9.10 (s, 1 H) 10.54 - 10.66 (m, 1 H) 13.49 - 13.84 (m, 1 H)

The compounds in the following table were prepared using the procedure for **Example 1** with the specified starting materials.

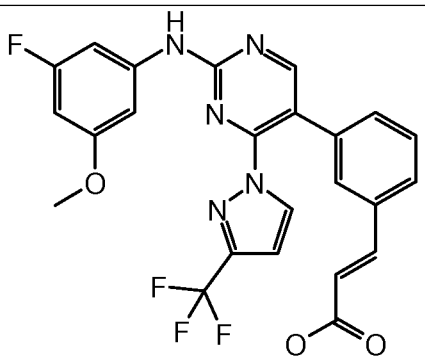
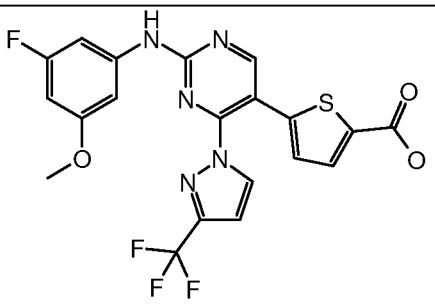
Example	Compound	Mass and NMR data	SM
Example 880	 (E)-3-(3-(2-(3-methoxy-5-(trifluoromethyl)phenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenyl)acrylic acid	MS: ES+ 564 for $C_{26}H_{19}F_6N_5O_3$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.21 (s, 3 H) 3.82 (s, 3 H) 6.45 (d, *J*=16.01 Hz, 1 H) 6.72 (s, 1 H) 6.90 (s, 1 H) 7.06 (d, *J*=7.91 Hz, 1 H) 7.31 - 7.43 (m, 2 H) 7.50 (d, *J*=16.01 Hz, 1 H) 7.61 (d, *J*=7.72 Hz, 1 H) 7.71 (s, 1 H) 7.82 (s, 1 H) 9.02 (s, 1 H) 10.56 (s, 1 H) 12.44 (br. s., 1 H)	**Intermediate 375** and [3-(trans-2-carboxy vinyl)phenyl]boronic acid
Example 881	 1-(5-(2-(3-methoxy-5-(trifluoromethyl)phenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)pyridin-3-yl)-2-(methylsulfonyl)ethanone	MS: ES+ 615 for $C_{25}H_{20}F_6N_6O_4S$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.45 (s, 3 H) 3.15 (s, 3 H) 3.83 (s, 3 H) 5.18 (br. s., 2 H) 6.79 (s, 1 H) 6.92 (s, 1 H) 7.68 (s, 1 H) 7.84 (s, 1 H) 8.21 (t, *J*=1.98 Hz, 1 H) 8.40 (d, *J*=2.07 Hz, 1 H) 9.06 (s, 1 H) 9.11 (d, *J*=1.88 Hz, 1 H) 10.60 (s, 1 H)	**Intermediate 375** and **Intermediate 415**

Example	Compound	Mass and NMR data	SM
Example 882	 N-(3-methoxy-5-(trifluoromethyl)phenyl)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-5,5'-bipyrimidin-2-amine	MS: ES+ 496 for $C_{21}H_{15}F_6N_7O$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.53 (s, 3 H) 3.83 (s, 3 H) 6.82 (s, 1 H) 6.93 (s, 1 H) 7.66 (s, 1 H) 7.82 (s, 1 H) 8.55 (s, 2 H) 9.01 (s, 1 H) 9.10 (s, 1 H) 10.57 (s, 1 H)	**Intermediate 375** and pyrimidin-5-yl boronic acid
Example 883	 5-(2-(3-methoxy-5-(trifluoromethyl)phenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)thiophene-2-carboxylic acid	MS: ES+ 544 for $C_{22}H_{15}F_6N_5O_3S$ ^{1}H NMR (300 MHz, DMSO-d_6) d ppm 2.18 (s, 3 H) 3.81 (s, 3 H) 6.82 (s, 1 H) 6.89 (s, 1 H) 6.97 (d, J=3.77 Hz, 1 H) 7.28 (d, J=3.58 Hz, 1 H) 7.66 - 7.80 (m, 2 H) 9.14 (s, 1 H) 10.61 (br. s., 1 H)	**Intermediate 375** and 5-boronothiophene-2-carboxylic acid

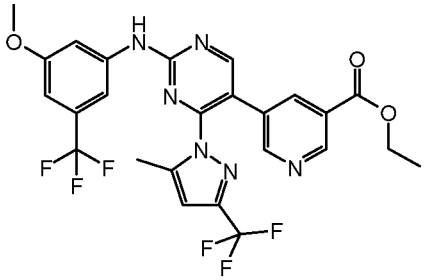
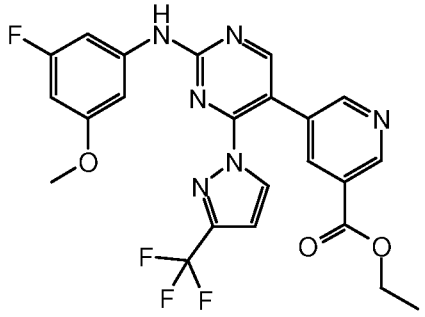
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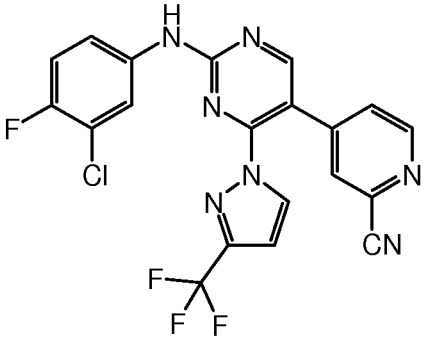
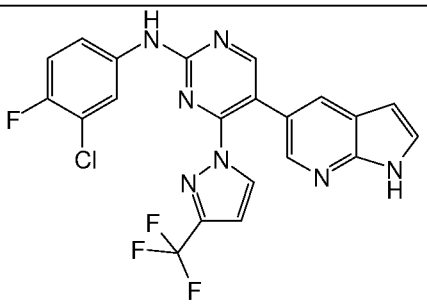
Example	Compound	Mass and NMR data	SM
Example 884	 N-(3-methoxy-5-(trifluoromethyl)phenyl)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-5-(pyridin-3-yl)pyrimidin-2-amine	MS: ES+ 495 for $C_{22}H_{16}F_6N_6O$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.46 (s, 3 H) 3.83 (s, 3 H) 6.79 (s, 1 H) 6.93 (s, 1 H) 7.61 (dd, *J*=7.91, 5.09 Hz, 1 H) 7.67 (s, 1 H) 7.75 - 7.86 (m, 2 H) 8.49 (d, *J*=1.70 Hz, 1 H) 8.64 (dd, *J*=5.09, 1.13 Hz, 1 H) 8.99 (s, 1 H) 10.58 (s, 1 H)	**Intermediate 375** and pyridin-3-ylboronic acid
Example 885	 2'-methoxy-N-(3-methoxy-5-(trifluoromethyl)phenyl)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-5,5'-bipyrimidin-2-amine	MS: ES+ 526 for $C_{22}H_{17}F_6N_7O_2$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.46 (s, 3 H) 3.83 (s, 3 H) 3.91 (s, 3 H) 6.80 (s, 1 H) 6.91 (s, 1 H) 7.66 (s, 1 H) 7.82 (s, 1 H) 8.33 (s, 2 H) 8.97 (s, 1 H) 10.53 (s, 1 H)	**Intermediate 375** and 2-methoxypyrimidin-5-ylboronic acid

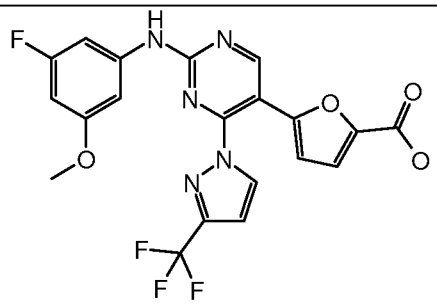
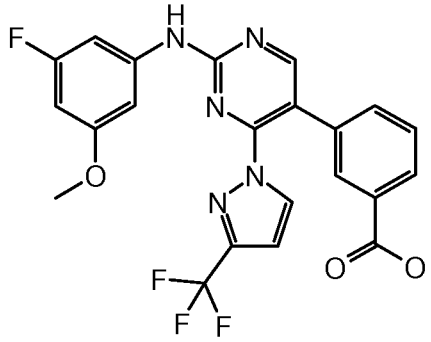
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Example	Compound	Mass and NMR data	SM
Example 886	 (E)-3-(3-(2-(3-fluoro-5-methoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenyl)acrylic acid	MS: ES+ 500 for $C_{24}H_{17}F_4N_5O_3$ 1H NMR (300 MHz, DMSO-d_6) d ppm 3.77 (s, 3 H) 6.44 - 6.48 (m, 1 H) 6.50 (s, 1 H) 6.99 (d, *J*=2.64 Hz, 1 H) 7.15 (d, *J*=7.72 Hz, 1 H) 7.29 - 7.43 (m, 3 H) 7.49 - 7.59 (m, 2 H) 7.64 (d, *J*=7.91 Hz, 1 H) 8.33 (d, *J*=1.70 Hz, 1 H) 8.84 (s, 1 H) 10.39 (s, 1 H) 12.38 (br. s., 1 H)	**Intermediate 376** and 3-(2-Carboxyvinyl) benzeneboronic acid
Example 887	 5-(2-(3-fluoro-5-methoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)thiophene-2-carboxylic acid	MS: ES+ 480 for $C_{20}H_{13}F_4N_5O_3S$ 1H NMR (300 MHz, DMSO-d_6) d ppm 3.77 (s, 3 H) 6.51 (dt, *J*=10.83, 2.21 Hz, 1 H) 7.07 (d, *J*=2.64 Hz, 1 H) 7.11 (d, *J*=3.77 Hz, 1 H) 7.26 - 7.34 (m, 2 H) 7.64 (d, *J*=3.77 Hz, 1 H) 8.43 (d, *J*=1.51 Hz, 1 H) 8.95 (s, 1 H) 10.52 (s, 1 H) 13.13 (br. s., 1 H)	**Intermediate 376** and 5-boronothiophene-2-carboxylic acid

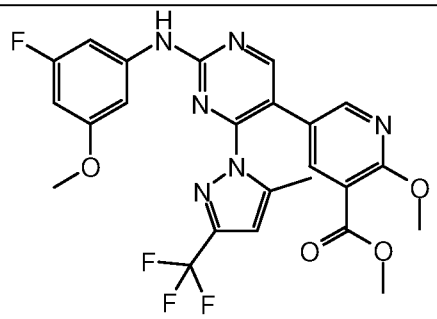
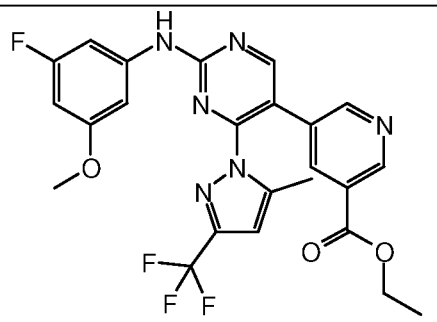
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Example	Compound	Mass and NMR data	SM
Example 888	 ethyl 5-(2-(3-methoxy-5-(trifluoromethyl)phenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinate	MS: ES+ 567 for $C_{25}H_{20}F_6N_6O_3$ 1H NMR (300 MHz, DMSO-d_6) d ppm 1.30 (t, 3 H) 2.42 (s, 3 H) 3.83 (s, 3 H) 4.32 (q, *J*=7.10 Hz, 2 H) 6.79 (s, 1 H) 6.92 (s, 1 H) 7.69 (s, 1 H) 7.79 - 7.85 (m, 2 H) 8.63 (d, *J*=2.26 Hz, 1 H) 8.99 (d, *J*=2.07 Hz, 1 H) 9.05 (s, 1 H) 10.59 (s, 1 H)	**Intermediate 375** and ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate
Example 889	 ethyl 5-(2-(3-fluoro-5-methoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinate	MS: ES+ 503 for $C_{23}H_{18}F_4N_6O_3$ 1H NMR (300 MHz, DMSO-d_6) d ppm 1.31 (t, *J*=7.16 Hz, 3 H) 3.78 (s, 3 H) 4.34 (q, *J*=7.16 Hz, 2 H) 6.51 (dt, *J*=10.93, 2.26 Hz, 1 H) 7.05 (d, *J*=2.64 Hz, 1 H) 7.27 - 7.37 (m, 2 H) 8.04 (t, *J*=2.17 Hz, 1 H) 8.54 (d, *J*=1.88 Hz, 1 H) 8.69 (d, *J*=2.26 Hz, 1 H) 8.86 (s, 1 H) 9.03 (d, *J*=2.07 Hz, 1 H) 10.43 (s, 1 H)	**Intermediate 376** and 3-(ethoxy-carbonyl) pyridine-5-boronic acid pinacol ester

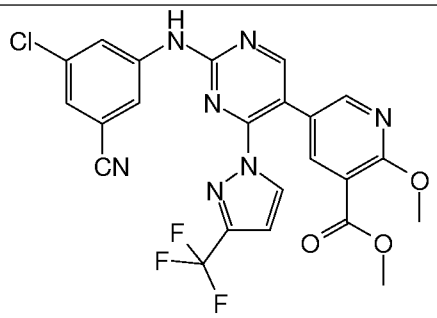
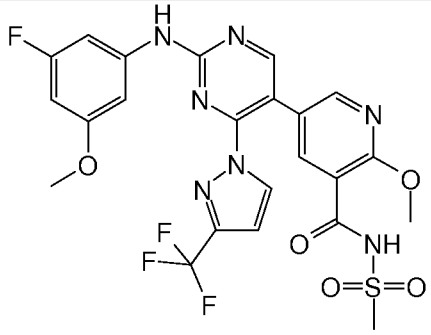
Example	Compound	Mass and NMR data	SM
Example 890	 4-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)picolinonitrile	MS: ES+ 460 for $C_{20}H_{10}ClF_4N_7$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 7.10 (d, *J*=2.64 Hz, 1 H) 7.44 (t, *J*=9.14 Hz, 1 H) 7.60 (dd, *J*=5.18, 1.79 Hz, 1 H) 7.74 (ddd, *J*=9.04, 4.24, 2.73 Hz, 1 H) 7.90 (d, *J*=0.94 Hz, 1 H) 8.05 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.59 (dd, *J*=2.54, 0.85 Hz, 1 H) 8.72 (d, *J*=5.09 Hz, 1 H) 8.83 (s, 1 H) 10.54 (s, 1 H)	**Intermediate 115** and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) Picolinonitrile
Example 891	 N-(3-chloro-4-fluorophenyl)-5-(1H-pyrrolo[2,3-b]pyridin-5-yl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine	MS: ES+ 474 for $C_{21}H_{12}ClF_4N_7$ 1H NMR (300 MHz, DMSO-d_6) d ppm 6.44 (dd, 1 H) 6.95 (d, *J*=2.45 Hz, 1 H) 7.41 (t, *J*=9.14 Hz, 1 H) 7.49 (t, 1 H) 7.72 (ddd, *J*=9.14, 4.05, 2.83 Hz, 1 H) 7.82 (d, *J*=1.88 Hz, 1 H) 7.93 (d, *J*=1.88 Hz, 1 H) 8.14 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.28 (s, 1 H) 8.82 (s, 1 H) 10.38 (s, 1 H) 11.71 (br. s., 1 H)	**Intermediate 115** and 5-(4,4,5,5-tetra methyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b] pyridine

Example	Compound	Mass and NMR data	SM
Example 892	 5-(2-(3-fluoro-5-methoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)furan-2-carboxylic acid	MS: ES+ 464 for $C_{20}H_{13}F_4N_5O_4$ 1H NMR (300 MHz, DMSO-d_6) d ppm 3.77 (s, 3 H) 6.50 (dt, *J*=10.93, 2.26 Hz, 1 H) 6.64 (s, 1 H) 7.09 (d, *J*=2.64 Hz, 1 H) 7.24 - 7.35 (m, 2 H) 8.15 (s, 1 H) 8.49 (d, *J*=1.70 Hz, 1 H) 8.95 (s, 1 H) 10.48 (br. s., 1 H)	**Intermediate 376** and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxylic acid
Example 893	 3-(2-(3-fluoro-5-methoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)benzoic acid	MS: ES+ 474 for $C_{22}H_{15}F_4N_5O_3$ 1H NMR (300 MHz, DMSO-d_6) d ppm 3.77 (s, 3 H) 6.49 (dt, *J*=10.93, 2.26 Hz, 1 H) 6.99 (d, *J*=2.64 Hz, 1 H) 7.28 - 7.38 (m, 2 H) 7.39 - 7.53 (m, 2 H) 7.68 (s, 1 H) 7.90 (dt, *J*=7.35, 1.60 Hz, 1 H) 8.37 (d, *J*=1.70 Hz, 1 H) 8.81 (s, 1 H) 10.39 (s, 1 H) 12.96 (br. s., 1 H)	**Intermediate 376** and 3-boronobenzoic acid

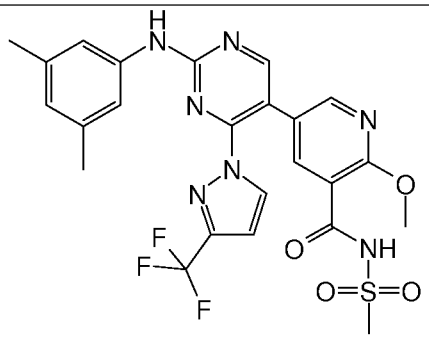
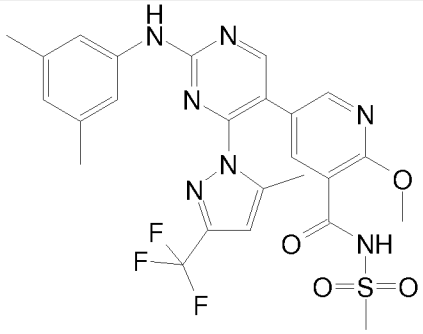
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Example	Compound	Mass and NMR data	SM
Example 894	 methyl 5-(2-(3-fluoro-5-methoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinate	MS: ES+ 533 for $C_{24}H_{20}F_4N_6O_4$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.31 (s, 3 H) 3.75 (s, 6 H) 3.92 (s, 3 H) 6.50 (dt, *J*=10.93, 2.26 Hz, 1 H) 6.76 (s, 1 H) 7.21 - 7.26 (m, 1 H) 7.31 (dt, *J*=11.59, 1.93 Hz, 1 H) 7.62 (d, *J*=2.45 Hz, 1 H) 8.23 (d, *J*=2.64 Hz, 1 H) 8.97 (s, 1 H) 10.41 (s, 1 H)	**Intermediate 377** and **Intermediate 175**
Example 895	 ethyl 5-(2-(3-fluoro-5-methoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinate	MS: ES+ 517 for $C_{24}H_{20}F_4N_6O_3$ 1H NMR (300 MHz, DMSO-d_6) d ppm 1.30 (t, *J*=7.06 Hz, 3 H) 2.41 (s, 3 H) 3.76 (s, 3 H) 4.32 (q, *J*=7.16 Hz, 2 H) 6.52 (dt, *J*=10.97, 2.33 Hz, 1 H) 6.77 (s, 1 H) 7.24 (s, 1 H) 7.28 - 7.37 (m, 1 H) 7.81 (t, *J*=2.17 Hz, 1 H) 8.62 (d, *J*=2.26 Hz, 1 H) 8.99 (d, *J*=2.07 Hz, 1 H) 9.02 (s, 1 H) 10.46 (s, 1 H)	**Intermediate 377** and ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate

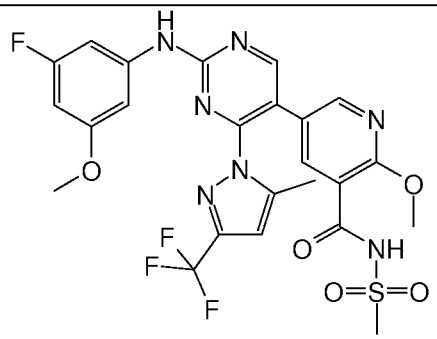
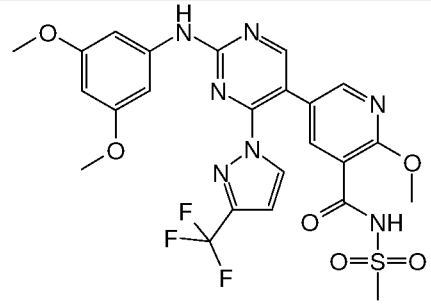
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Example	Compound	Mass and NMR data	SM
Example 896	 methyl 5-(2-(3-chloro-5-cyanophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinate	MS: ES+ 530 for $C_{23}H_{15}ClF_3N_7O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) d ppm 3.77 (s, 3 H) 3.95 (s, 3 H) 7.06 (d, *J*=2.64 Hz, 1 H) 7.64 (t, *J*=1.51 Hz, 1 H) 7.88 (d, *J*=2.45 Hz, 1 H) 8.20 (d, *J*=1.32 Hz, 1 H) 8.23 (t, *J*=1.88 Hz, 1 H) 8.29 (d, *J*=2.64 Hz, 1 H) 8.49 (d, *J*=1.70 Hz, 1 H) 8.88 (s, 1 H) 10.72 (s, 1 H)	**Intermediate 378** and **Intermediate 175**
Example 897	 5-(2-(3-fluoro-5-methoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxy-N-(methylsulfonyl)nicotinamide	MS: ES+ 582 for $C_{23}H_{19}F_4N_7O_5S$ 1H NMR (300 MHz, DMSO-d_6) d ppm 3.33 (s, 3 H) 3.78 (s, 3 H) 3.97 (s, 3 H) 6.50 (dt, *J*=10.93, 2.26 Hz, 1 H) 7.05 (d, *J*=2.64 Hz, 1 H) 7.23 - 7.40 (m, 2 H) 7.87 (d, *J*=2.45 Hz, 1 H) 8.18 (d, 1 H) 8.46 (d, *J*=1.70 Hz, 1 H) 8.80 (s, 1 H) 10.39 (s, 1 H) 11.69 (s, 1 H)	**Intermediate 376** and **Intermediate 368**

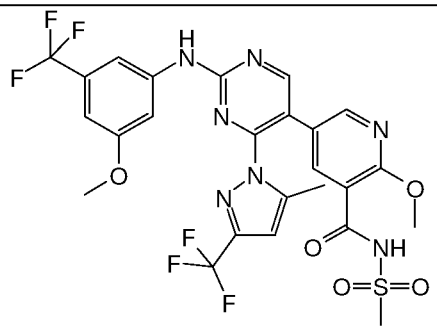
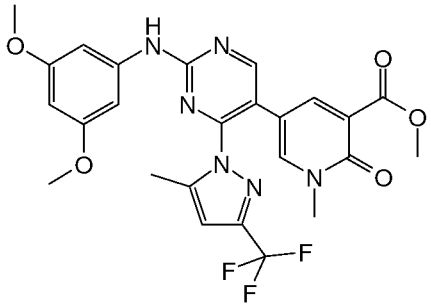
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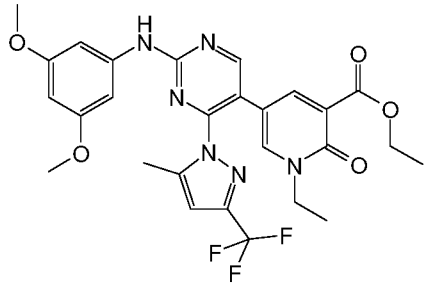
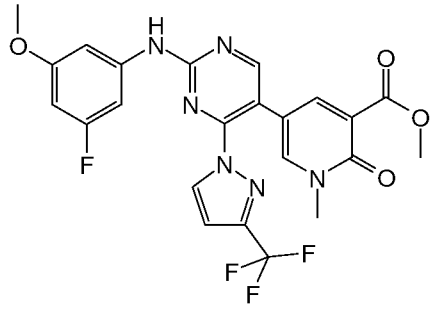
Example	Compound	Mass and NMR data	SM
Example 898	 5-(2-(3,5-dimethylphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxy-N-(methylsulfonyl)nicotinamide	MS: ES+ 562 for $C_{24}H_{22}F_3N_7O_4S$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.27 (s, 6 H) 3.38 (s, 3 H) 4.04 (s, 3 H) 6.76 (s, 1 H) 7.05 (d, *J*=2.64 Hz, 1 H) 7.44 (s, 2 H) 8.14 (d, *J*=2.45 Hz, 1 H) 8.27 (s, 1 H) 8.48 (d, *J*=2.45 Hz, 1 H) 8.65 (d, *J*=1.70 Hz, 1 H) 8.92 (s, 1 H) 11.77 (br. s., 1 H)	**Intermediate 217** and **Intermediate 368**
Example 899	 5-(2-(3,5-dimethylphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxy-N-(methylsulfonyl)nicotinamide	MS: ES+ 576 for $C_{25}H_{24}F_3N_7O_4S$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.25 (s, 6 H) 2.36 (s, 3 H) 3.32 (s, 3 H) 3.93 (s, 3 H) 6.70 (s, 1 H) 6.76 (s, 1 H) 7.37 (s, 2 H) 7.69 (d, *J*=2.45 Hz, 1 H) 8.00 (d, *J*=2.64 Hz, 1 H) 8.90 (s, 1 H) 10.09 (s, 1 H) 11.70 (br. s., 1 H)	**Intermediate 218** and **Intermediate 368**

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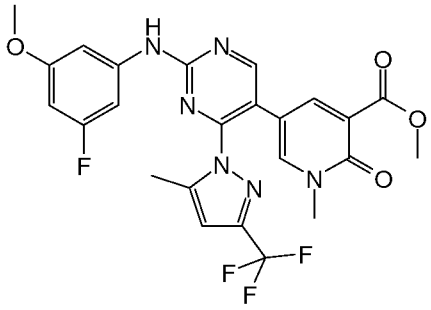
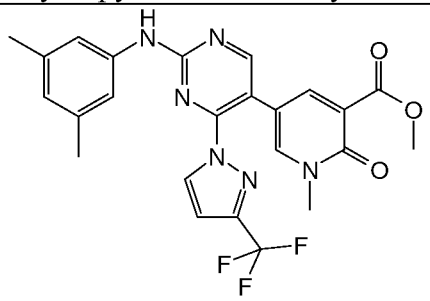
Example	Compound	Mass and NMR data	SM
Example 900	 5-(2-(3-fluoro-5-methoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxy-N-(methylsulfonyl)nicotinamide	MS: ES+ 596 for $C_{24}H_{21}F_4N_7O_5S$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.33 (s, 3 H) 3.32 (s, 3 H) 3.75 (s, 3 H) 3.94 (s, 3 H) 6.50 (dt, *J*=10.93, 2.26 Hz, 1 H) 6.77 (s, 1 H) 7.25 (s, 1 H) 7.30 (dt, *J*=11.54, 1.95 Hz, 1 H) 7.70 (d, *J*=2.45 Hz, 1 H) 8.01 (d, *J*=2.45 Hz, 1 H) 8.97 (s, 1 H) 10.42 (s, 1 H) 11.72 (s, 1 H)	**Intermediate 377** and **Intermediate 368**
Example 901	 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxy-N-(methylsulfonyl)nicotinamide	MS: ES+ 594 for $C_{24}H_{22}F_3N_7O_6S$ ^{1}H NMR (300 MHz, DMSO-d_6) d ppm 3.33 (s, 3 H) 3.75 (s, 6 H) 3.97 (s, 3 H) 6.21 (t, *J*=2.17 Hz, 1 H) 7.03 (d, *J*=2.64 Hz, 1 H) 7.10 (d, *J*=2.07 Hz, 2 H) 7.87 (d, *J*=2.45 Hz, 1 H) 8.17 (d, *J*=2.45 Hz, 1 H) 8.44 (d, *J*=1.70 Hz, 1 H) 8.77 (s, 1 H) 10.17 (s, 1 H) 11.69 (br. s., 1 H)	**Intermediate 215** and **Intermediate 368**

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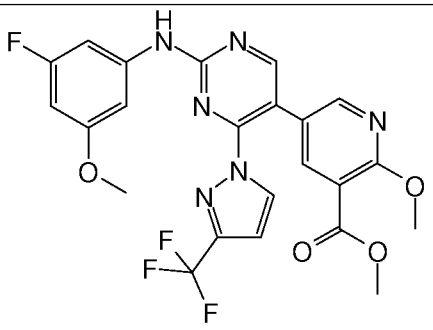
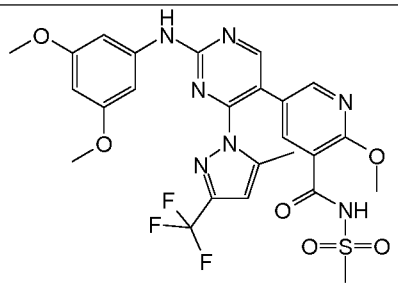
Example	Compound	Mass and NMR data	SM
Example 902	 2-methoxy-5-(2-(3-methoxy-5-(trifluoromethyl)phenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(methylsulfonyl)nicotinamide	MS: ES+ 646 for $C_{25}H_{21}F_6N_7O_5S$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.33 (s, 3 H) 3.33 (s, 3 H) 3.82 (s, 3 H) 3.94 (s, 3 H) 6.78 (s, 1 H) 6.90 (s, 1 H) 7.68 (s, 1 H) 7.73 (d, *J*=2.45 Hz, 1 H) 7.82 (s, 1 H) 8.01 (d, *J*=2.45 Hz, 1 H) 9.01 (s, 1 H) 10.55 (s, 1 H) 11.73 (s, 1 H)	**Intermediate 375** and **Intermediate 368**
Example 903	 methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate	MS: ES+ 545 for $C_{25}H_{23}F_3N_6O_5$ 1H NMR (300 MHz, ACETONITRILE-d_3) d ppm 2.35 (s, 3 H) 3.46 (s, 3 H) 3.70 (s, 3 H) 3.75 (s, 6 H) 6.21 (t, *J*=2.17 Hz, 1 H) 6.56 (s, 1 H) 6.93 (d, *J*=2.07 Hz, 2 H) 7.43 (d, *J*=2.83 Hz, 1 H) 7.64 (d, *J*=2.83 Hz, 1 H) 8.31 (s, 1 H) 8.62 (s, 1 H)	**Intermediate 216** and **Intermediate 369**

Example	Compound	Mass and NMR data	SM
Example 904	 ethyl 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-ethyl-2-oxo-1,2-dihydropyridine-3-carboxylate	MS: ES+ 573 for $C_{27}H_{27}F_3N_6O_5$ ^{1}H NMR (300 MHz, DMSO-d_6) d ppm 1.12 – 1.27 (m, 6 H) 2.38 (s, 3 H) 3.72 (s, 6 H) 3.94 (q, *J*=6.97 Hz, 2 H) 4.13 (q, *J*=7.16 Hz, 2 H) 6.21 (t, *J*=2.17 Hz, 1 H) 6.79 (s, 1 H) 7.04 (d, *J*=2.07 Hz, 2 H) 7.34 (d, *J*=2.64 Hz, 1 H) 8.05 (d, *J*=2.83 Hz, 1 H) 8.89 (s, 1 H) 10.15 (s, 1 H)	**Intermediate 216** and **Intermediate 370**
Example 905	 methyl 5-(2-(3-fluoro-5-methoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate	MS: ES+ 519 for $C_{23}H_{18}F_4N_6O_4$ 1H NMR (300 MHz, DMSO-d_6) d ppm 3.50 (s, 3 H) 3.67 (s, 3 H) 3.77 (s, 3 H) 6.49 (dt, *J*=10.93, 2.17 Hz, 1 H) 7.08 (d, *J*=2.64 Hz, 1 H) 7.22 – 7.36 (m, 2 H) 7.63 (d, *J*=2.83 Hz, 1 H) 8.17 (d, *J*=2.64 Hz, 1 H) 8.56 (d, *J*=1.51 Hz, 1 H) 8.76 (s, 1 H) 10.34 (s, 1 H)	**Intermediate 376** and **Intermediate 369**

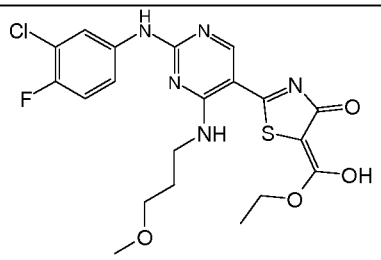
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Example	Compound	Mass and NMR data	SM
Example 906	 methyl 5-(2-(3-fluoro-5-ethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate	MS: ES+ 533 for $C_{24}H_{20}F_4N_6O_4$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.37 (s, 3 H) 3.48 (s, 3 H) 3.65 (s, 3 H) 3.75 (s, 3 H) 6.49 (dt, *J*=10.93, 2.26 Hz, 1 H) 6.80 (s, 1 H) 7.17 – 7.35 (m, 3 H) 8.18 (d, *J*=2.83 Hz, 1 H) 8.90 (s, 1 H) 10.37 (s, 1 H)	**Intermediate 377** and **Intermediate 369**
Example 907	 methyl 5-(2-(3,5-dimethylphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate	MS: ES+ 499 for $C_{24}H_{21}F_3N_6O_3$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.27 (s, 6 H) 3.50 (s, 3 H) 3.67 (s, 3 H) 6.69 (s, 1 H) 7.06 (d, *J*=2.64 Hz, 1 H) 7.40 (s, 2 H) 7.64 (d, *J*=2.64 Hz, 1 H) 8.15 (d, *J*=2.64 Hz, 1 H) 8.54 (d, *J*=1.70 Hz, 1 H) 8.69 (s, 1 H) 10.01 (s, 1 H)	**Intermediate 217** and **Intermediate 369**

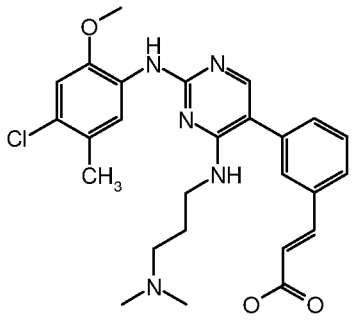
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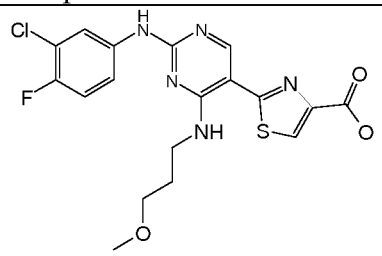
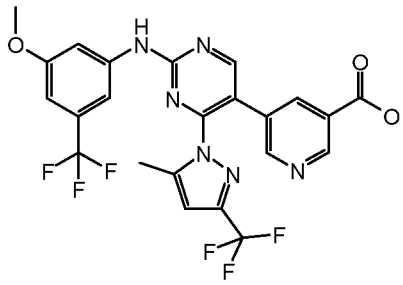
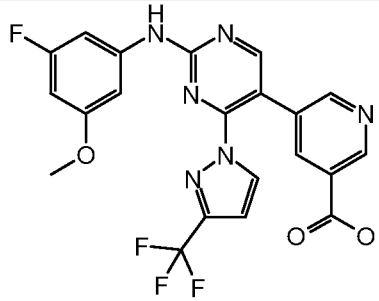
Example 908	 methyl 5-(2-(3-fluoro-5-methoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinate	MS: ES+ 519 for $C_{23}H_{18}F_4N_6O_4$ 1H NMR (300 MHz, DMSO-d_6) d ppm 3.77 (s, 3 H) 3.77 (s, 3 H) 3.95 (s, 3 H) 6.49 (dt, *J*=10.93, 2.26 Hz, 1 H) 7.04 (d, *J*=2.64 Hz, 1 H) 7.28 – 7.36 (m, 2 H) 7.86 (d, *J*=2.45 Hz, 1 H) 8.28 (d, *J*=2.45 Hz, 1 H) 8.49 (dd, *J*=2.64, 0.94 Hz, 1 H) 8.81 (s, 1 H) 10.37 (s, 1 H)	**Intermediate 376** and **Intermediate 175**
Example 909	 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxy-N-(methylsulfonyl)nicotinamide	MS: ES+ 608 for $C_{25}H_{24}F_3N_7O_6S$\ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.31 (s, 3 H) 3.32 (s, 3 H) 3.72 (s, 6 H) 3.93 (s, 3 H) 6.21 (t, *J*=2.17 Hz, 1 H) 6.76 (s, 1 H) 7.05 (d, *J*=2.26 Hz, 2 H) 7.71 (d, *J*=2.45 Hz, 1 H) 7.99 (d, *J*=2.45 Hz, 1 H) 8.93 (s, 1 H) 10.20 (s, 1 H) 11.72 (br. s., 1 H)	**Intermediate 216** and **Intermediate 368**

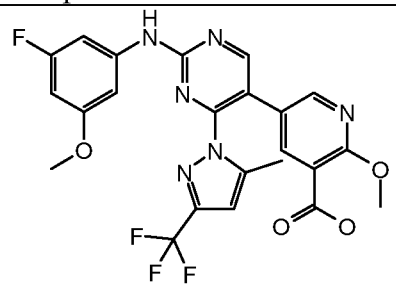
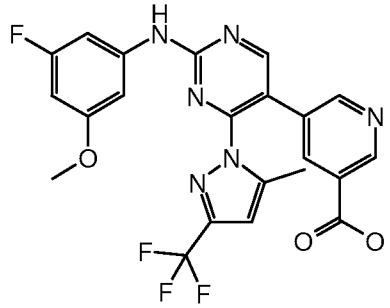
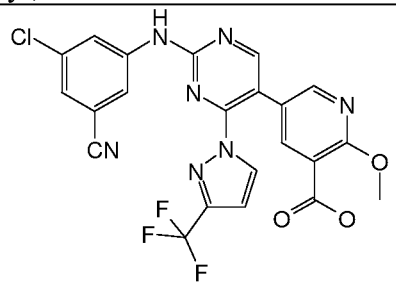
The following example was prepared using the general method described above for **Example 212** and the specified starting materials.

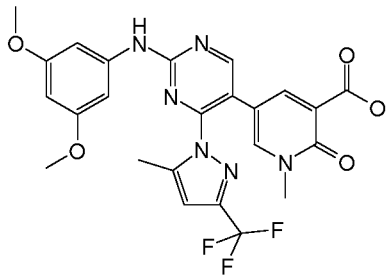
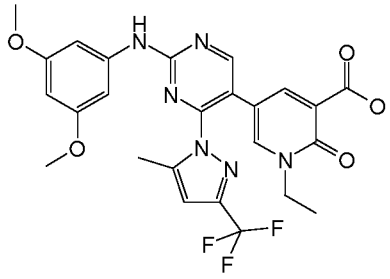
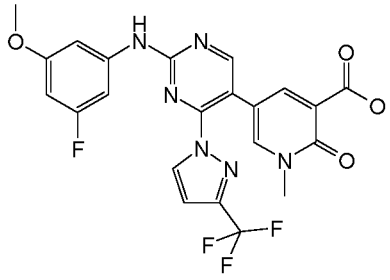
example	compound	mass and nmr data	sm
Example 910	 (Z)-2-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)-5-(ethoxy(hydroxy)methylene)thiazol-4(5H)-one	MS: ES+ 482 for $C_{20}H_{21}ClFN_5O_4S$ 1H NMR (300 MHz, DMSO-d_6) d ppm 1.26 (t, 3 H) 1.83 - 1.97 (m, *J*=6.66, 6.66, 6.55, 6.31 Hz, 2 H) 3.25 (s, 3H) 3.44 (t, *J*=6.12 Hz, 2 H) 3.60 (q, *J*=6.72 Hz, 2 H) 4.21 (q, *J*=6.97 Hz, 2 H) 7.35 (t, *J*=9.14 Hz, 1 H) 7.54 -7.69 (m, 1 H) 8.21 (dd, *J*=6.69, 2.35 Hz, 1 H) 8.58 (s, 1 H) 9.20 (t, *J*=4.90 Hz, 1 H) 10.01 (br. s., 1 H) 12.04 (br.s., 1 H)	**Intermediate 128** and diethyl chloro malonate

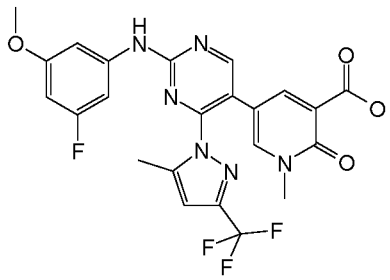
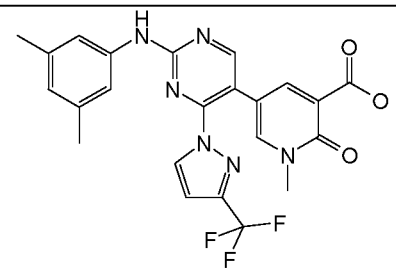
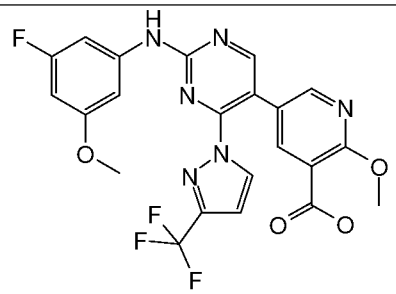
The compounds in the below table were prepared using the same procedure as **Example 214**, using the starting material and base specified.

example	compound	mass and nmr data	sm
Example 911	 (E)-3-(3-(2-(4-chloro-2-methoxy-5-methyl phenylamino)-4-(3-(dimethylamino)propyl amino)pyrimidin-5-yl)phenyl)acrylic acid	MS: ES+ 496 for $C_{26}H_{30}ClN_5O_3$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 1.93 (quin, *J*=7.02 Hz, 2 H) 2.31 (s, 3 H) 2.70 (d, *J*=4.71 Hz, 6 H) 2.92 - 3.06 (m, 2 H) 3.36 - 3.50 (m, 2 H) 3.86 (s, 3 H) 6.62 (d, *J*=16.01 Hz, 1 H) 7.22 (s, 1 H) 7.43 - 7.50 (m, 1 H) 7.56 (t, *J*=7.63 Hz, 1 H) 7.64 (d, *J*=16.01 Hz, 1 H) 7.73 - 7.82 (m, 2 H) 7.86 (s, 2 H) 8.07 (br. s., 1 H) 9.57 (br. s., 1 H) 10.10 (br. s., 1 H) 12.51 (br. s., 1 H)	**Example 343** and sodium hydroxide

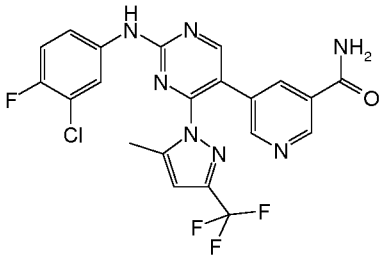
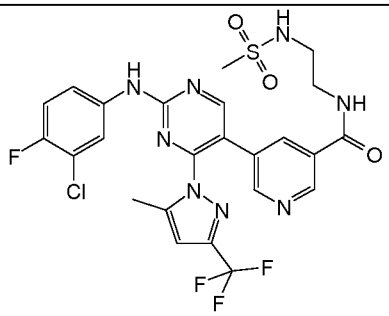
example	compound	mass and nmr data	sm
Example 912	 2-(2-(3-chloro-4-fluoro phenylamino)-4-(3-methoxypropylamino) pyrimidin-5-yl)thiazole-4-carboxylic acid	MS: ES+ 438 for $C_{18}H_{17}ClFN_5O_3S$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 1.88 (qd, *J*=6.59, 6.40 Hz, 2 H) 3.25 (s, 3 H) 3.47 (t, *J*=6.03 Hz, 2 H) 3.60 (q, *J*=6.34 Hz, 2 H) 7.30 (t, 1 H) 7.56 - 7.69 (m, 1 H) 7.83 (s, 1 H) 8.24 (dd, *J*=6.78, 1.88 Hz, 1 H) 8.47 (s, 1 H) 9.74 (br. s., 1 H) 9.85 (t, *J*=4.14 Hz, 1 H)	**Example 212** and barium hydroxide
Example 913	 5-(2-(3-methoxy-5-(trifluoromethyl)phenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinic acid	MS: ES+ 539 for $C_{23}H_{16}F6N_6O_3$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.43 (s, 3 H) 3.83 (s, 3 H) 6.78 (s, 1 H) 6.92 (s, 1 H) 7.69 (s, 1 H) 7.82 (s, 1 H) 7.86 (t, *J*=2.17 Hz, 1 H) 8.56 (d, *J*=2.26 Hz, 1 H) 8.97 (d, *J*=1.88 Hz, 1 H) 9.03 (s, 1 H) 10.57 (s, 1 H)	**Example 888** and sodium hydroxide
Example 914	 5-(2-(3-fluoro-5-methoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinic acid	MS: ES+ 475 for $C_{21}H_{14}F_4N_6O_3$ 1H NMR (300 MHz, DMSO-d_6) d ppm 3.78 (s, 3 H) 6.51 (dt, *J*=10.93, 2.17 Hz, 1 H) 7.04 (d, *J*=2.64 Hz, 1 H) 7.26 - 7.39 (m, 2 H) 8.03 (t, *J*=2.07 Hz, 1 H) 8.54 (d, *J*=1.51 Hz, 1 H) 8.65 (d, *J*=2.26 Hz, 1 H) 8.85 (s, 1 H) 9.01 (d, *J*=2.07 Hz, 1 H) 10.42 (s, 1 H) 13.37 (br. s., 1 H)	**Example 889** and sodium hydroxide

example	compound	mass and nmr data	sm
Example 915	 5-(2-(3-fluoro-5-methoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinic acid	MS: ES+ 519 for $C_{23}H_{18}F_4N_6O_4$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.33 (s, 3 H) 3.75 (s, 3 H) 3.91 (s, 3 H) 6.50 (dt, *J*=10.93, 2.26 Hz, 1 H) 6.75 (s, 1 H) 7.24 (s, 1 H) 7.31 (dt, *J*=11.49, 1.88 Hz, 1 H) 7.64 (d, *J*=2.64 Hz, 1 H) 8.16 (d, *J*=2.64 Hz, 1 H) 8.96 (s, 1 H) 10.39 (s, 1 H) 12.94 (br. s., 1 H)	**Example 894** and sodium hydroxide
Example 916	 5-(2-(3-fluoro-5-methoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinic acid	MS: ES+ 489 for $C_{22}H_{16}F_4N_6O_3$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.42 (s, 3 H) 3.76 (s, 3 H) 6.52 (dt, *J*=10.93, 2.17 Hz, 1 H) 6.77 (s, 1 H) 7.24 (s, 1 H) 7.32 (d, *J*=11.30 Hz, 1 H) 7.84 (t, *J*=2.07 Hz, 1 H) 8.55 (d, *J*=2.07 Hz, 1 H) 8.97 (d, *J*=1.88 Hz, 1 H) 9.01 (s, 1 H) 10.44 (s, 1 H) 13.42 (br. s., 1 H)	**Example 895** and sodium hydroxide
Example 917	 5-(2-(3-chloro-5-cyanophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinic acid	MS: ES+ 516 for $C_{22}H_{13}ClF_3N_7O_3$ 1H NMR (300 MHz, CHLOROFORM-*d*) d ppm 4.27 (s, 3 H) 6.72 (d, *J*=2.64 Hz, 1 H) 7.39 (d, *J*=1.32 Hz, 1 H) 7.86 (br. s., 1 H) 7.94 - 8.07 (m, 2 H) 8.25 - 8.31 (m, 1 H) 8.34 (d, *J*=2.45 Hz, 1 H) 8.47 (br. s., 1 H) 8.55 (br. s., 1 H)	**Example 896** and sodium hydroxide

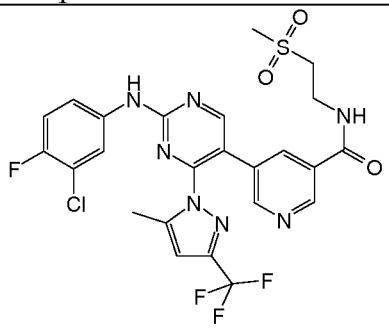
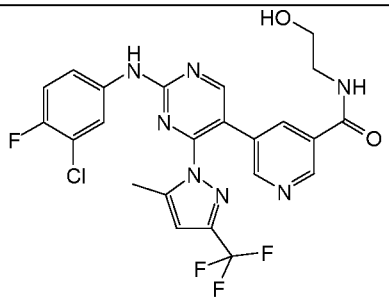
example	compound	mass and nmr data	sm
Example 918	 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS: ES+ 531 for $C_{24}H_{21}F_3N_6O_5$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.48 (s, 3 H) 3.67 (s, 3 H) 3.73 (s, 6 H) 6.22 (t, *J*=2.07 Hz, 1 H) 6.80 (s, 1 H) 7.03 (d, *J*=2.26 Hz, 2 H) 7.65 (d, *J*=2.64 Hz, 1 H) 8.41 (d, *J*=2.64 Hz, 1 H) 8.86 (s, 1 H) 10.17 (s, 1 H) 14.37 (br. s., 1 H)	**Example 903** and sodium hydroxide
Example 919	 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-ethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS: ES+ 545 for $C_{25}H_{23}F_3N_6O_5$ 1H NMR (300 MHz, DMSO-d_6) d ppm 1.28 (t, 3 H) 2.48 (s, 3 H) 3.73 (s, 6 H) 4.11 (q, *J*=7.16 Hz, 2 H) 6.22 (t, *J*=2.26 Hz, 1 H) 6.79 (s, 1 H) 7.03 (d, *J*=2.26 Hz, 2 H) 7.81 (d, *J*=2.64 Hz, 1 H) 8.29 (d, *J*=2.64 Hz, 1 H) 8.90 (s, 1 H) 10.17 (s, 1 H) 14.42 (br. s., 1 H)	**Example 904** and sodium hydroxide
Example 920	 5-(2-(3-fluoro-5-methoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS: ES+ 505 for $C_{22}H_{16}F_4N_6O_4$ 1H NMR (300 MHz, DMSO-d_6) d ppm 3.70 (s, 3 H) 3.78 (s, 3 H) 6.51 (dt, 1 H) 7.09 (d, *J*=2.64 Hz, 1 H) 7.23 - 7.36 (m, 2 H) 8.05 (d, *J*=2.64 Hz, 1 H) 8.43 (d, *J*=2.45 Hz, 1 H) 8.60 (d, *J*=1.70 Hz, 1 H) 8.76 (s, 1 H) 10.38 (s, 1 H) 14.48 (br. s., 1 H)	**Example 905** and sodium hydroxide

example	compound	mass and nmr data	sm
Example 921	 5-(2-(3-fluoro-5-methoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS: ES+ 519 for $C_{23}H_{18}F_4N_6O_4$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.49 (br. s., 3 H) 3.68 (s, 3 H) 3.76 (s, 3 H) 6.51 (dt, *J*=10.93, 2.07 Hz, 1 H) 6.82 (s, 1 H) 7.23 (s, 1 H) 7.30 (d, *J*=11.68 Hz, 1 H) 7.66 (d, *J*=2.64 Hz, 1 H) 8.42 (d, *J*=2.64 Hz, 1 H) 8.91 (s, 1 H) 10.39 (s, 1 H) 14.36 (br. s., 1 H)	**Example 906** and sodium hydroxide
Example 922	 5-(2-(3,5-dimethylphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS: ES+ 485 for $C_{23}H_{19}F_3N_6O_3$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.28 (s, 6 H) 3.70 (s, 3 H) 6.70 (s, 1 H) 7.07 (d, *J*=2.64 Hz, 1 H) 7.40 (s, 2 H) 8.06 (d, *J*=2.64 Hz, 1 H) 8.41 (d, *J*=2.64 Hz, 1 H) 8.58 (dd, *J*=2.64, 0.94 Hz, 1 H) 8.69 (s, 1 H) 10.06 (s, 1 H) 14.51 (s, 1	**Example 907** and sodium hydroxide
Example 923	 5-(2-(3-fluoro-5-methoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinic acid	MS: ES+ 505 for $C_{22}H_{16}F_4N_6O_4$ 1H NMR (300 MHz, DMSO-d_6) d ppm 3.77 (s, 3 H) 3.92 (s, 3 H) 6.49 (dt, *J*=10.93, 2.17 Hz, 1 H) 7.02 (d, *J*=2.83 Hz, 1 H) 7.31 (s, 1 H) 7.34 (t, *J*=1.98 Hz, 1 H) 7.79 (d, *J*=2.45 Hz, 1 H) 8.18 (d, *J*=2.45 Hz, 1 H) 8.45 (d, *J*=1.70 Hz, 1 H) 8.79 (s, 1 H) 10.36 (s, 1 H) 12.98 (br. s., 1 H)	**Example 908** and sodium hydroxide

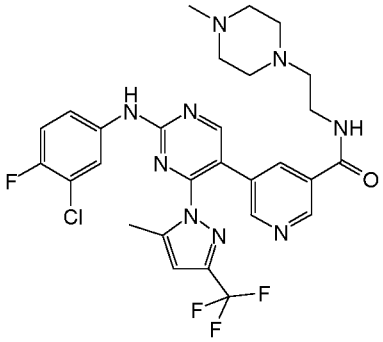
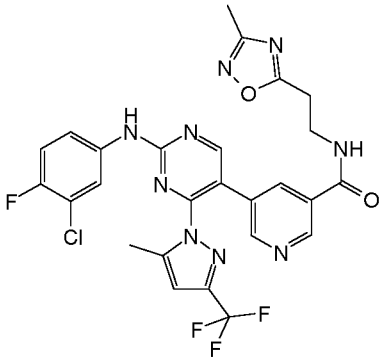
The compounds in the table below were prepared using the same procedure as **Example 360** with the specified starting materials.

example	compound	mass and NMR data	sm
Example 924	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinamide	MS: ES+ 492 for $C_{21}H_{14}ClF_4N_7O$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.43 (s, 3 H) 6.78 (s, 1 H) 7.43 (t, *J*=9.14 Hz, 1 H) 7.56 - 7.73 (m, 2 H) 7.98 (t, *J*=1.98 Hz, 1 H) 8.07 (dd, *J*=6.78, 2.26 Hz, 1 H) 8.13 (s, 1 H) 8.27 (d, *J*=2.07 Hz, 1 H) 8.91 (d, *J*=1.88 Hz, 1 H) 8.99 (s, 1 H) 10.49 (s, 1 H)	**Example 319** and ammonia
Example 925	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(2-(methylsulfonamido)ethyl)nicotinamide	MS: ES+ 613 for $C_{24}H_{21}ClF_4N_8O_3S$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.43 (s, 3 H) 2.91 (s, 3 H) 3.12 (q, *J*=6.22 Hz, 2 H) 3.39 (q, *J*=6.22 Hz, 2 H) 6.79 (s, 1 H) 7.20 (t, *J*=5.93 Hz, 1 H) 7.43 (t, *J*=9.04 Hz, 1 H) 7.66 (ddd, *J*=9.04, 4.14, 2.83 Hz, 1 H) 7.98 - 8.12 (m, 2 H) 8.23 (d, *J*=2.07 Hz, 1 H) 8.77 (t, *J*=5.56 Hz, 1 H) 8.90 (d, *J*=1.88 Hz, 1 H) 8.99 (s, 1 H) 10.51 (s, 1 H)	**Example 319** and N-(2-aminoethyl) methanesulfonamide

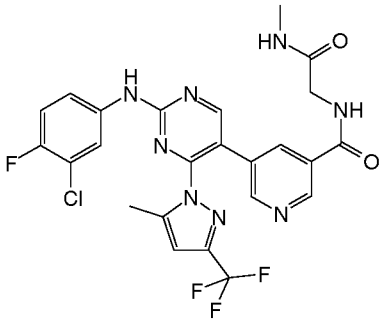
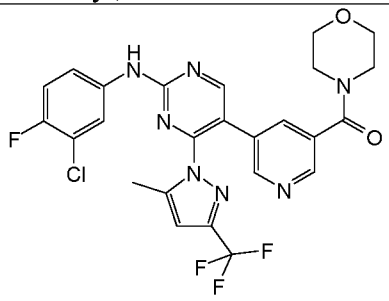
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example	compound	mass and NMR data	sm
Example 926	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(2-(methylsulfonyl)ethyl)nicotinamide	MS: ES+ 598 for $C_{24}H_{20}ClF_4N_7O_3S$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.44 (s, 3 H) 3.04 (s, 3 H) 3.37 - 3.43 (m, 2 H) 3.69 (q, *J*=6.53 Hz, 2 H) 6.79 (s, 1 H) 7.43 (t, *J*=9.14 Hz, 1 H) 7.66 (ddd, *J*=9.14, 4.14, 2.73 Hz, 1 H) 7.99 (t, *J*=2.07 Hz, 1 H) 8.07 (dd, *J*=6.78, 2.45 Hz, 1 H) 8.25 (d, *J*=2.07 Hz, 1 H) 8.88 (d, *J*=1.88 Hz, 1 H) 8.92 - 9.02 (m, 2 H) 10.50 (s, 1 H)	**Example 319** and 2-aminoethyl methyl sulfone hydro chloride
Example 927	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(2-hydroxyethyl)nicotinamide	MS: ES+ 536 for $C_{23}H_{18}ClF_4N_7O_2$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.43 (s, 3 H) 3.34 (q, *J*=5.90 Hz, 2 H) 3.47 - 3.55 (m, 2 H) 6.78 (s, 1 H) 7.43 (t, *J*=9.04 Hz, 1 H) 7.66 (ddd, *J*=8.90, 4.00, 2.73 Hz, 1 H) 8.01 - 8.13 (m, 2 H) 8.21 (d, *J*=2.07 Hz, 1 H) 8.67 (t, *J*=5.56 Hz, 1 H) 8.90 (d, 1 H) 9.00 (s, 1 H) 10.50 (s, 1 H)	**Example 319** and ethanolamine

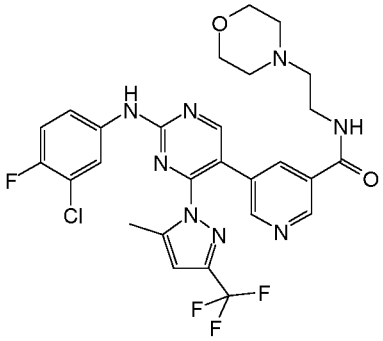
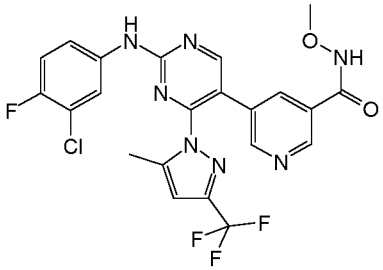
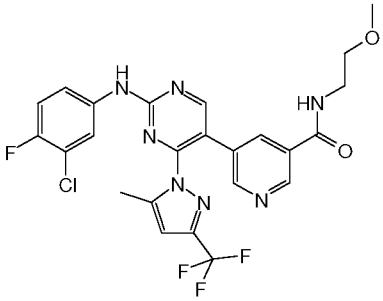
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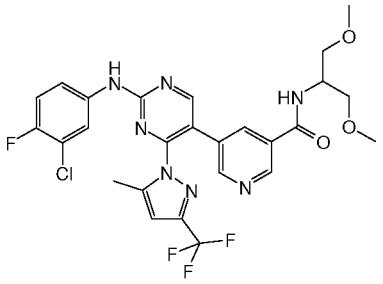
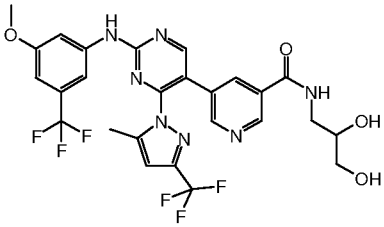
example	compound	mass and NMR data	sm
Example 928	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(2-(4-methylpiperazin-1-yl)ethyl)nicotinamide	MS: ES+ 618 for $C_{28}H_{28}ClF_4N_9O$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.45 (s, 3 H) 2.73 - 3.75 (m, 15 H) 6.79 (s, 1 H) 7.44 (t, *J*=9.04 Hz, 1 H) 7.65 (ddd, *J*=9.00, 4.10, 2.92 Hz, 1 H) 8.02 (t, *J*=1.98 Hz, 1 H) 8.08 (dd, *J*=6.69, 2.17 Hz, 1 H) 8.25 (d, *J*=2.07 Hz, 1 H) 8.86 (t, *J*=5.27 Hz, 1 H) 8.90 (d, *J*=1.88 Hz, 1 H) 8.97 (s, 1 H) 10.51 (s, 1 H)	**Example 319** and 2-(4-methyl-piperazin-1-yl)-ethyl amine
Example 929	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(2-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)nicotinamide	MS: ES+ 602 for $C_{26}H_{20}ClF_4N_9O_2$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.31 (s, 3 H) 2.43 (s, 3 H) 3.16 (t, *J*=6.78 Hz, 2 H) 3.67 (q, *J*=6.47 Hz, 2 H) 6.78 (s, 1 H) 7.43 (t, *J*=9.04 Hz, 1 H) 7.66 (ddd, *J*=9.04, 4.14, 2.83 Hz, 1 H) 7.96 (t, *J*=1.98 Hz, 1 H) 8.07 (dd, *J*=6.69, 2.35 Hz, 1 H) 8.25 (d, *J*=2.07 Hz, 1 H) 8.85 (d, *J*=1.88 Hz, 1 H) 8.91 (t, *J*=5.46 Hz, 1 H) 8.98 (s, 1 H) 10.50 (s, 1 H)	**Example 319** and 2-(3-methyl-1,2,4-oxadiazol-5-yl)ethan amine, HCl

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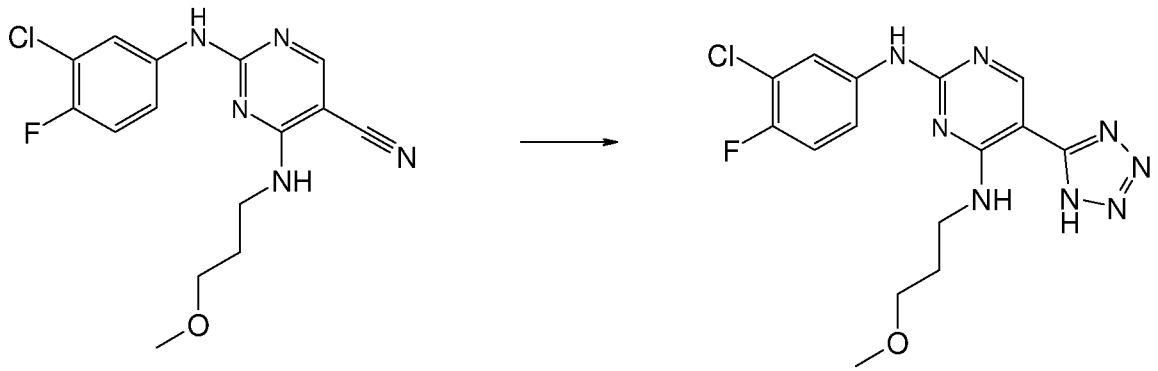
example	compound	mass and NMR data	sm
Example 930	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(2-(methylamino)-2-oxoethyl)nicotinamide	MS: ES+ 563 for $C_{24}H_{19}ClF_4N_8O_2$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.44 (s, 3 H) 2.61 (d, *J*=4.33 Hz, 3 H) 3.85 (d, *J*=5.65 Hz, 2 H) 6.79 (s, 1 H) 7.43 (t, *J*=9.14 Hz, 1 H) 7.60 - 7.71 (m, 1 H) 7.86 - 7.95 (m, 1 H) 8.07 (dd, 1 H) 8.11 - 8.15 (m, 1 H) 8.19 (d, *J*=1.88 Hz, 1 H) 8.93 (d, *J*=1.70 Hz, 1 H) 8.97 - 9.05 (m, 2 H) 10.51 (s, 1 H)	**Example 319** and 2-amino-N-methyl acetamide, HCl
Example 931	 (5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)pyridin-3-yl)(morpholino)methanone	MS: ES+ 562 for $C_{25}H_{20}ClF_4N_7O_2$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.42 (br. s., 2 H) 3.11 (br. s., 2 H) 3.27 (s, 3 H) 3.54 (br. s., 4 H) 6.73 (s, 1 H) 7.36 (t, *J*=9.04 Hz, 1 H) 7.44 - 7.51 (m, 1 H) 7.59 (dd, *J*=5.18, 3.11 Hz, 1 H) 8.00 (dd, *J*=6.59, 2.07 Hz, 1 H) 8.36 (d, *J*=1.88 Hz, 1 H) 8.48 (d, *J*=1.70 Hz, 1 H) 8.87 (s, 1 H) 10.40 (s, 1 H)	**Example 319** and morpholine

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example	compound	mass and NMR data	sm
Example 932	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(2-morpholinoethyl) nicotinamide	MS: ES+ 605 for $C_{27}H_{25}ClF_4N_8O_2$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.37 (s, 7 H) 3.29 - 3.42 (m, 4 H) 3.52 (t, *J*=3.96 Hz, 4 H) 6.71 (s, 1 H) 7.37 (t, *J*=9.14 Hz, 1 H) 7.59 (dt, *J*=8.85, 3.49 Hz, 1 H) 7.90 (s, 1 H) 8.01 (dd, *J*=6.59, 2.07 Hz, 1 H) 8.19 (d, *J*=1.88 Hz, 1 H) 8.58 (br. s., 1 H) 8.81 (d, *J*=1.51 Hz, 1 H) 8.93 (s, 1 H) 10.43 (s, 1 H)	**Example 319** and 2-morpholino ethylamine
Example 933	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-methoxynicotinamide	MS: ES+ 522 for $C_{22}H_{16}ClF_4N_7O_2$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.43 (s, 3 H) 3.71 (s, 3 H) 6.79 (s, 1 H) 7.43 (t, *J*=9.04 Hz, 1 H) 7.66 (dt, *J*=8.81, 3.41 Hz, 1 H) 7.84 (s, 1 H) 8.07 (dd, *J*=6.59, 2.26 Hz, 1 H) 8.32 (d, *J*=1.88 Hz, 1 H) 8.79 (d, *J*=1.70 Hz, 1 H) 8.99 (s, 1 H) 10.50 (s, 1 H) 11.91 (br. s., 1 H)	**Example 319** and methoxyl amine hydro chloride
Example 934	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(2-methoxyethyl)nicotinamide	MS: ES+ 550 for $C_{24}H_{20}ClF_4N_7O_2$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.43 (s, 3 H) 3.27 (s, 3 H) 3.40 - 3.50 (m, 4 H) 6.78 (s, 1 H) 7.43 (t, *J*=9.04 Hz, 1 H) 7.66 (dt, *J*=8.85, 3.48 Hz, 1 H) 8.00 (s, 1 H) 8.08 (dd, *J*=6.50, 1.98 Hz, 1 H) 8.23 (d, *J*=1.88 Hz, 1 H) 8.69 - 8.80 (m, 1 H) 8.89 (d, *J*=1.70 Hz, 1 H) 9.00 (s, 1 H) 10.50 (s, 1 H)	**Example 319** and 2-methoxy ethylamine

example	compound	mass and NMR data	sm
Example 935	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(1,3-dimethoxypropan-2-yl)nicotinamide	MS: ES+ 594 for $C_{26}H_{24}ClF_4N_7O_3$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.44 (s, 3 H) 3.27 (s, 6 H) 3.45 (dd, *J*=5.84, 2.26 Hz, 4 H) 4.30 (dt, 1 H) 6.78 (s, 1 H) 7.43 (t, *J*=9.14 Hz, 1 H) 7.66 (ddd, *J*=9.04, 4.24, 2.73 Hz, 1 H) 8.04 (t, *J*=2.07 Hz, 1 H) 8.08 (dd, *J*=6.59, 2.26 Hz, 1 H) 8.25 (d, *J*=2.07 Hz, 1 H) 8.53 (d, *J*=8.10 Hz, 1 H) 8.90 (d, *J*=2.07 Hz, 1 H) 9.02 (s, 1 H) 10.50 (s, 1 H)	**Example 319** and 1,3-dimethoxy propan-2-amine
Example 936	 N-(2,3-dihydroxypropyl)-5-(2-(3-methoxy-5-(trifluoromethyl)phenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinamide	MS: ES+ 612 for $C_{26}H_{23}F_6N_7O_4$ 1H NMR (300 MHz, DMSO-d_6) d ppm 2.41 (s, 3 H) 3.14 - 3.26 (m, 1 H) 3.33 - 3.48 (m, 3 H) 3.58 - 3.70 (m, 1 H) 3.83 (s, 3 H) 4.55 (t, *J*=5.75 Hz, 1 H) 4.81 (d, *J*=4.90 Hz, 1 H) 6.78 (s, 1 H) 6.92 (s, 1 H) 7.68 (s, 1 H) 7.84 (s, 1 H) 8.08 (t, *J*=2.07 Hz, 1 H) 8.20 (d, *J*=2.07 Hz, 1 H) 8.60 (t, *J*=5.56 Hz, 1 H) 8.90 (d, *J*=2.07 Hz, 1 H) 9.04 (s, 1 H) 10.59 (s, 1 H)	**Example 913** and 3-amino-1,2-propanediol

Example 937: N2-(3-chloro-4-fluorophenyl)-N4-(3-methoxypropyl)-5-(1H-tetrazol-5-yl)pyrimidine-2,4-diamine

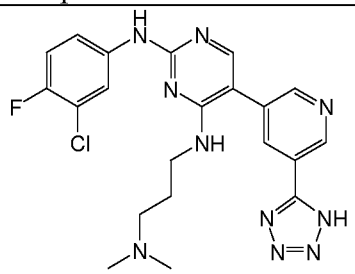


Intermediate 127 (100 mg, 0.30 mmol), sodium azide (77 mg, 1.2 mmol), and ammonium chloride (64 mg, 1.2 mmol) were combined in N,N-dimethylformamide (2 mL) and heated at 100 degrees C for 3 hours. The reaction mixture was allowed to cool, then it was filtered. Reverse-phase chromatography (C18: water, acetonitrile, formic acid additive) was used to isolate the desired product (59 mg).

MS: ES+ 379 for $C_{15}H_{16}ClFN_8O$.

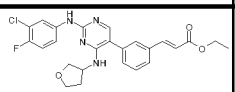
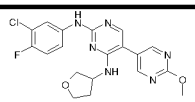
1H NMR (300 MHz, DMSO-d_6) δ ppm 1.90 (quin, *J*=6.45 Hz, 2 H) 3.25 (s, 3 H) 3.46 (t, *J*=6.03 Hz, 2 H) 3.64 (q, *J*=6.53 Hz, 2 H) 7.34 (t, *J*=9.14 Hz, 1 H) 7.58 - 7.73 (m, 1 H) 8.20 (dd, *J*=6.78, 2.45 Hz, 1 H) 8.48 (t, *J*=4.80 Hz, 1 H) 8.63 (s, 1 H) 9.88 (s, 1 H).

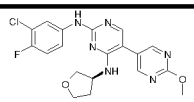
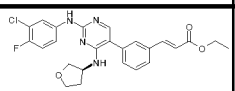
The compound in the table below was made using the method above for **Example 937** with the specified starting material.

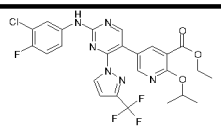
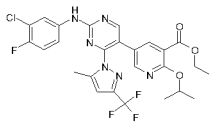
example	compound	mass and nmr data	sm
Example 938	 5-(5-(1H-tetrazol-5-yl)pyridin-3-yl)-N2-(3-chloro-4-fluorophenyl)-N4-(3-(dimethylamino)propyl)pyrimidine-2,4-diamine	MS: ES+ 469 for $C_{21}H_{22}ClF_4N_7O$ 1H NMR (300 MHz, DMSO-d_6) d ppm 1.59 - 1.73 (m, 2 H) 1.92 (s, 6 H) 2.27 (t, *J*=6.31 Hz, 2 H) 3.38 - 3.50 (m, 2 H) 7.30 (t, *J*=9.14 Hz, 1 H) 7.48 (t, *J*=4.71 Hz, 1 H) 7.65 (ddd, *J*=9.09, 4.10, 2.83 Hz, 1 H) 7.84 (s, 1 H) 8.20 (t, *J*=2.07 Hz, 1 H) 8.26 (dd, *J*=6.88, 2.54 Hz, 1 H) 8.43 (d, *J*=2.26 Hz, 1 H) 9.12 (d, *J*=2.07 Hz, 1 H) 9.44 (s, 1 H)	**Example 15**

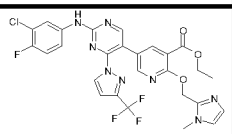
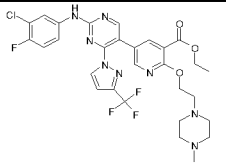
The compounds in the below table were prepared using the general method described above for **Example 1** and the starting materials (SM) indicated.

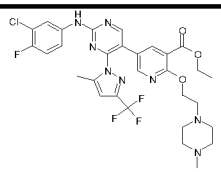
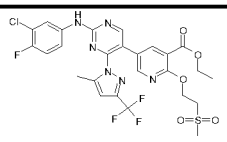
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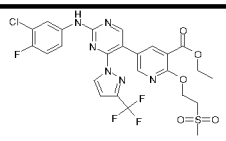
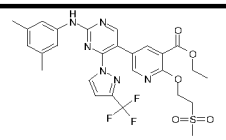
Ex	Compound	Data	SM
Example 939	 (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(tetrahydrofuran-3-ylamino)pyrimidin-5-yl)phenyl)acrylate	MS(ES): 483.2 (M+H) for C25H24ClFN4O3 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.20 - 1.27 (m, 3 H) 1.53 - 1.74 (m, 2 H) 3.54 - 3.62 (m, 2 H) 3.72 - 3.82 (m, 2 H) 3.91 - 3.97 (m, 1 H) 4.48 - 4.58 (m, 2 H) 6.61 (d, *J*=16.01 Hz, 1 H) 7.30 - 7.41 (m, 1 H) 7.42 - 7.50 (m, 1 H) 7.58 - 7.68 (m, 2 H) 7.71 - 7.78 (m, 1 H) 8.01 - 8.07 (m, 1 H) 8.12 - 8.21 (m, 1 H) 8.42 (d, *J*=3.77 Hz, 1 H) 8.49 (s, 1 H) 9.87 - 9.98 (m, 1 H)	5-bromo-N2-(3-chloro-4-fluorophenyl)-N4-(tetrahydrofuran-3-yl)pyrimidine-2,4-diamine **Intermediate 381** And (E)-4-(3-ethoxy-3-oxoprop-1-enyl)phenylboronic acid
Example 940	 N2-(3-chloro-4-fluorophenyl)-2'-methoxy-N4-(tetrahydrofuran-3-yl)-5,5'-bipyrimidine-2,4-diamine	MS(ES): 417.1 (M+H) for C19H18ClFN6O2 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.84 - 1.98 (m, 1 H) 2.10 - 2.24 (m, 1 H) 3.52 - 3.62 (m, 1 H) 3.77 (s, 2 H) 3.89 - 3.97 (m, 4 H) 4.58 (s, 1 H) 6.91 (s, 1 H) 7.31 (t, *J*=9.14 Hz, 1 H) 7.53 - 7.60 (m, 1 H) 7.79 (s, 1 H) 8.24 (dd, *J*=6.97, 2.45 Hz, 1 H) 8.53 (s, 2 H) 9.47 (s, 1 H)	5-bromo-N2-(3-chloro-4-fluorophenyl)-N4-(tetrahydrofuran-3-yl)pyrimidine-2,4-diamine **Intermediate 381** and 2-methoxypyrimidin-5-ylboronic acid

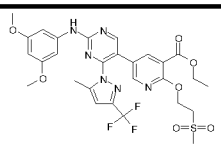
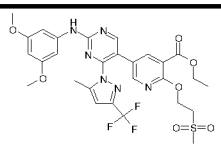
Ex	Compound	Data	SM
Example 941	 (S)-N2-(3-chloro-4-fluorophenyl)-2'-methoxy-N4-(tetrahydrofuran-3-yl)-5,5'-bipyrimidine-2,4-diamine	MS(ES): 417.2 (M+H) for C19H18ClFN6O2 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.83 - 1.98 (m, 1 H) 2.12 - 2.25 (m, 1 H) 3.65 - 3.84 (m, 2 H) 3.90 - 3.95 (m, 1 H) 3.96 (s, 3 H) 4.53 - 4.66 (m, 1 H) 6.93 (d, *J*=6.22 Hz, 1 H) 7.31 (t, *J*=9.14 Hz, 1 H) 7.58 (ddd, *J*=6.83, 4.38, 1.98 Hz, 1 H) 7.80 (s, 1 H) 8.24 (dd, *J*=6.97, 2.64 Hz, 1 H) 8.54 (s, 2 H) 9.47 (s, 1 H)	(S)-5-bromo-N2-(3-chloro-4-fluorophenyl)-N4-(tetrahydrofuran-3-yl)pyrimidine-2,4-diamine **Intermediate 382** and 2-methoxypyrimidin-5-ylboronic acid
Example 942	 (S, E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(tetrahydrofuran-3-ylamino)-pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 455.0 (M+H) for C23H20ClFN4O3 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.87 - 2.01 (m, *J*=12.48, 6.19, 6.19, 5.84 Hz, 1 H) 2.13 - 2.31 (m, 1 H) 3.66 - 3.86 (m, 3 H) 3.91 - 4.01 (m, 1 H) 4.57 - 4.69 (m, 1 H) 6.51 - 6.62 (m, 1 H) 7.27 - 7.36 (m, 1 H) 7.38 - 7.52 (m, 2 H) 7.53 - 7.62 (m, 2 H) 7.63 - 7.68 (m, 2 H) 7.85 (s, 1 H) 8.22 - 8.29 (m, 1 H) 9.45 (s, 1 H)	(S)-5-bromo-N2-(3-chloro-4-fluorophenyl)-N4-(tetrahydrofuran-3-yl)-pyrimidin-2,4-diamine **Intermediate 382** And (E)-4-(3-ethoxy-3-oxoprop-1-enyl)phenylboronic acid

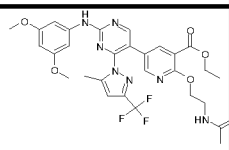
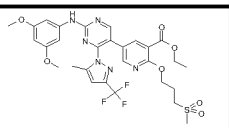
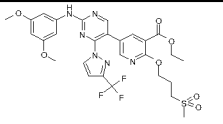
Ex	Compound	Data	SM
Example 943	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-isopropoxynicotinate	MS(ES): 565.0 (M+H) for C25H21ClF4N6O3 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.25 (t, *J*=7.06 Hz, 4 H) 1.31 (d, *J*=6.03 Hz, 5 H) 4.22 (q, *J*=7.16 Hz, 2 H) 5.35 (spt, *J*=6.19 Hz, 1 H) 7.04 (d, *J*=2.64 Hz, 1 H) 7.40 (d, *J*=9.04 Hz, 1 H) 7.75 - 7.84 (m, 2 H) 8.07(dd, *J*=6.78, 2.64 Hz, 1 H) 8.21 (d, *J*=2.45 Hz, 1 H) 8.51 (d, *J*=1.70 Hz, 1 H) 8.80 (s, 1 H) 10.39 (s, 1 H)	Ethyl 2-isopropoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 317** And **Intermediate 115**
Example 944	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-isopropoxynicotinate	MS(ES): 579.0 (M+H) for C26H23ClF4N6O3 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.17 - 1.35 (m, 9 H) 2.36 (s, 3 H) 4.20 (q, *J*=7.10 Hz, 2 H) 5.32 (spt, *J*=6.15 Hz, 1 H) 6.77 (s, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.57 (d, *J*=2.64 Hz, 1 H) 7.66 (ddd, *J*=9.00, 4.19, 2.83 Hz, 1 H) 8.06 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.14 (d, *J*=2.64 Hz, 1 H) 8.96 (s, 1 H) 10.42 (s, 1 H)	Ethyl 2-isopropoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 317** And **Intermediate 113**

Ex	Compound	Data	SM
Example 945	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-((1-methyl-1H-imidazol-2-yl)methoxy)nicotinate	MS(ES): 617.1 (M+H) for C27H21ClF4N8O3 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.16 (t, *J*=7.06 Hz, 3 H) 3.73 (s, 3 H) 4.18 (q, *J*=6.97 Hz, 2 H) 5.38 - 5.50 (m, 2 H) 6.86 (s, 1 H) 7.05 (d, *J*=2.07 Hz, 1 H) 7.21 (s, 1 H) 7.42 (t, *J*=9.04 Hz, 1 H) 7.72 (dd, *J*=4.90, 4.14 Hz, 1 H) 7.84 (d, *J*=1.88 Hz, 1 H) 8.08 (d, *J*=8.85 Hz, 1 H) 8.35 (s, 1 H) 8.52 (br. s., 1 H) 8.82 (s, 1 H) 10.41 (s, 1 H)	ethyl 2-((1-methyl-1H-imidazol-2-yl)methoxy)-5-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)nicotinate **Intermediate 320** And **Intermediate 115**
Example 946	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(4-methylpiperizin-1-yl)ethoxy)nicotinate	MS(ES): 649.1 (M+H) for C29H29ClF4N8O3 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.25 (t, *J*=7.06 Hz, 3 H) 1.75 (s, 3 H) 2.13 - 2.29 (m, 4 H) 2.65 - 2.77 (m, 4 H) 3.35 - 3.42 (m, 2 H) 4.22 (q, *J*=7.03 Hz, 2 H) 4.47 (t, *J*=5.37 Hz, 2 H) 7.05 (d, *J*=2.45 Hz, 1 H) 7.42(t, *J*=9.14 Hz, 1 H) 7.66-7.77 (m ,1H) 7.81 (d, *J*=2.45 Hz, 1 H) 8.25 (d,*J*=2.45 Hz, 1 H) 8.51 (d, *J*=1.32 Hz, 1 H) 8.81 (s, 1 H) 10.42 (s, 1 H)	ethyl 2-(2-(4-methylpiperizin-1-yl)ethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 316** And **Intermediate 115**

Ex	Compound	Data	SM
Example 947	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(4-methylpiperizin-1-yl)ethoxy)nicotinate	MS(ES): 663.1 (M+H) for $C_{30}H_{31}ClF_4N_8O_3$ 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.24 (t, *J*=7.06 Hz, 4 H) 2.14 (s, 4 H) 2.22 - 2.40 (m, 8 H) 2.67 (t, *J*=5.46 Hz, 2 H) 3.16 (d, *J*=5.27 Hz, 1 H) 4.20 (q, *J*=7.28 Hz, 2 H) 4.43 (t, *J*=5.65 Hz, 2 H) 6.77 (s, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.56 (d, *J*=2.45 Hz, 1 H) 7.65 (td, *J*=6.45, 3.48 Hz, 1 H) 8.06 (dd, *J*=6.59, 2.64 Hz, 1 H) 8.19 (d, *J*=2.45 Hz, 1 H) 8.96 (s, 1 H) 10.44 (s, 1 H)	Ethyl 2-(2-(4-methylpiperizin-1-yl)ethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 316** And **Intermediate 113**
Example 948	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(methylsulfonyl)ethoxy)nicotinate	MS(ES): 643.0 (M+H) for $C_{26}H_{23}ClF_4N_6O_5S$ 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.25 (t, *J*=7.06 Hz, 3 H) 2.38 (s, 2 H) 3.03 - 3.10 (m, 4 H) 3.53 - 3.65 (m, 2 H) 4.21 (q, *J*=7.16 Hz, 1 H) 4.35 (dt, *J*=13.85, 6.83 Hz, 2 H) 6.82 (s, 1 H) 7.16 (d, *J*=2.64 Hz, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.58 - 7.69 (m, 1 H) 7.98 - 8.09 (m, 2 H) 8.28 (d, *J*=2.45 Hz, 1 H) 8.88 (s, 1 H) 10.44 (s, 1H)	Ethyl 2-(2-(methylsulfonyl)ethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 321** And **Intermediate 113**

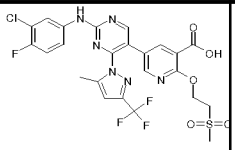
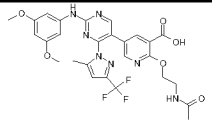
Ex	Compound	Data	SM
Example 949	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(methylsulfonyl)ethoxy)nicotinate	MS(ES): 629.0 (M+H) for $C_{25}H_{21}ClF_4N_6O_5S$ 1H NMR (300 MHz, DMSO-d6) δ ppm 1.21 - 1.30 (m, 2 H) 3.03 - 3.11 (m, 8 H) 3.55 - 3.65 (m, 4 H) 4.13 (q,J=6.59 Hz, 3 H) 4.33 - 4.42 (m, 3 H) 7.09 (d, J=2.26 Hz, 1 H) 7.41 (t, J=9.23 Hz, 1 H) 7.60 (d, J=2.64 Hz, 1H) 7.65 - 7.73 (m, 1 H) 8.06 (dd, J=6.78, 2.45 Hz, 1 H) 8.20 (d, J=2.64 Hz, 1 H) 8.57 (s, 1 H) 8.71 (s, 1 H)10.40 (s, 1 H)	Ethyl 2-(2-(methylsulfonyl)ethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 321** And **Intermediate 115**
Example 950	 ethyl 5-(2-(3,5-dimethylphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(methylsulfonyl)ethoxy)nicotinate	MS(ES): 605.2 (M+H) for $C_{27}H_{27}F_3N_6O_5S$ 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.18 (t, *J*=6.97 Hz, 3 H) 2.27 (s, 6 H) 3.07 (s, 3 H) 3.54 - 3.66 (m, 2H) 4.14 (q, *J*=7.10 Hz, 2 H) 4.38 (t, *J*=7.16 Hz, 2 H) 6.69 (s, 1 H) 7.08 (d, *J*=2.83 Hz, 1 H) 7.40 (s, 2 H) 7.60(d, *J*=2.64 Hz, 1 H) 8.21 (d, *J*=2.45 Hz, 1 H) 8.54 (s, 1 H) 8.68 (s, 1 H) 10.07 (s, 1 H)	Ethyl 2-(2-(methylsulfonyl)ethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 321** And **Intermediate 217**

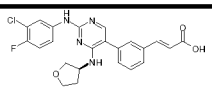
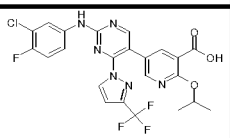
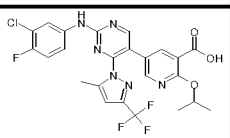
Ex	Compound	Data	SM
Example 951	 ethyl 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(methylsulfonyl)ethoxy)nicotinate	MS(ES): 651.3 (M+H) for C28H29F3N6O7S 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.25 (t, *J*=7.06 Hz, 3 H) 2.36 (s, 3 H) 3.06 (d, *J*=5.27 Hz, 3 H) 3.57 (t,*J*=6.97 Hz, 2 H) 3.72 (s, 6 H) 4.21 (q, *J*=7.16 Hz, 2 H) 4.33 (t, *J*=6.88 Hz, 2 H) 6.17 - 6.24 (m, 1 H) 6.34 (t,*J*=6.97 Hz, 1 H) 7.04 (d, *J*=1.70 Hz, 2 H) 7.96 - 8.06 (m, 2 H) 8.85 (s, 1 H) 10.20 (s, 1 H)	Ethyl 2-(2-(methylsulfonyl)ethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 321** And **Intermediate 216**
Example 952	 ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(methylsulfonyl)ethoxy)nicotinate	MS(ES): 629.1 (M+H) for C25H21F4N6O5S 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.21 - 1.30 (m, 3 H) 3.03 - 3.11 (m, 3 H) 3.55 - 3.65 (m, 2 H) 4.13 (q,*J*=6.59 Hz, 2 H) 4.33 - 4.42 (m, 2 H) 7.09 (d, *J*=2.26 Hz, 1 H) 7.41 (t, *J*=9.23 Hz, 1 H) 7.60 (d, *J*=2.64 Hz, 1H) 7.65 - 7.73 (m, 1 H) 8.06 (dd, *J*=6.78, 2.45 Hz, 1 H) 8.20 (d, *J*=2.64 Hz, 1 H) 8.57 (s, 1 H) 8.71 (s, 1 H)10.40 (s, 1 H)	ethyl 2-(2-(methylsulfonyl)ethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 321** And **Intermediate 216**

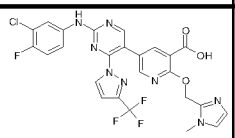
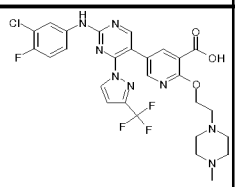
Ex	Compound	Data	SM
Example 953	 ethyl 2-(2-acetamidoethoxy)-5-(2-(3,5-dimethoxyphenylamino-4-(5-methyl-3-(trifluromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinate	MS(ES): 630.3 (M+H) for C29H30F3N7O6 80 % purity, taken on to next step crude	ethyl 2-(2-acetamidoethoxy)-5(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 324** And **Intermediate 216**
Example 954	 ethyl 5-(2-(3,5-dimethoxyphenylamino-4-(5-methyl-3-(trifluromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(3-(methylsulfonyl)propoxy)nicotinate	MS(ES): 665.3 (M+H) for C29H31F3N6O7S 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.26 (t, *J*=7.16 Hz, 3 H) 2.08 - 2.22 (m, 2 H) 2.32 (s, 3 H) 2.96 - 3.03(m, 3 H) 3.24 - 3.33 (m, 2 H) 3.72 (s, 6 H) 4.17 - 4.26 (m, 2 H) 4.44 (t, *J*=6.12 Hz, 2 H) 6.21 (t, *J*=2.17 Hz, 1 H) 6.76 (s, 1 H) 7.05 (d, *J*=2.26 Hz, 2 H)7.59 (d, *J*=2.64 Hz, 1 H) 8.24 (d, *J*=2.45 Hz, 1 H) 8.94 (s, 1 H) 10.20 (s, 1 H)	ethyl 2-(3-(methylsulfonyl)propoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 321-B** And **Intermediate 216**
Example 955	 ethyl 5-(2-(3,5-dimethoxyphenylamino-4-(3-(trifluromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(3-(methylsulfonyl)propoxy)nicotinate	MS(ES): 651.2 (M+H) for C28H29F3N6O7S 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.26 (t, *J*=7.08 Hz, 3 H) 2.10 - 2.27 (m, 2 H) 2.97 - 3.04 (m, 3 H) 3.75(s, 6 H) 3.90 (s, 2 H) 4.25 (q, *J*=7.11 Hz, 2 H) 4.43 - 4.54 (m, 2 H) 6.21 (t, *J*=2.27 Hz, 1 H) 7.03 (d, *J*=2.46 Hz,1 H) 7.10 (d, *J*=2.08 Hz, 2 H) 7.84 (d, *J*=2.64 Hz, 1 H) 8.28 (d, *J*=2.46 Hz, 1 H) 8.48 (dd, *J*=2.64, 0.94 Hz, 1H) 8.78 (s, 1 H)10.15 (s, 1 H)	ethyl 2-(3-(methylsulfonyl)propoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 321-B** And **Intermediate 215**

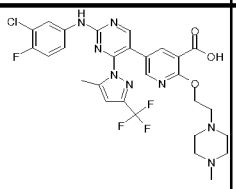
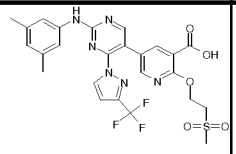
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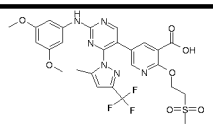
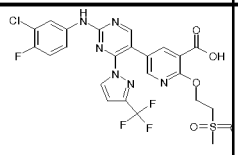
The compounds in the below table were prepared using the general method described above for **Example 214** using 1N sodium hydroxide and the starting material (SM) indicated.

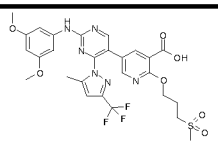
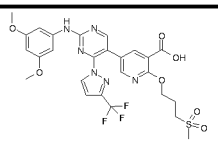
Ex	Compound	Data	SM
Example 956	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(methylsulfonyl)ethoxy)nicotinic acid	MS(ES): 615.2 (M+H) for C24H19ClF4N6O5S 1H NMR (300 MHz, DMSO- *d*6) δ ppm 2.44 (s, 5 H) 3.09 (s, 3 H) 3.67 (t, *J*=6.78 Hz, 2 H) 4.48 (t, *J*=6.50 Hz,2 H) 6.82 (s, 1 H) 7.37 - 7.48 (m, 2 H) 7.59 - 7.70 (m, 1 H) 8.06 (dd, *J*=6.59, 2.26 Hz, 1 H) 8.30 (d, *J*=2.07 Hz,1 H) 8.87 (s, 1 H) 10.45 (s, 1 H)	ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(methylsulfonyl)ethoxy)nicotinate **Example 948**
Example 957	 2-(2-acetamidoethoxy)-5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinic acid	MS(ES): 602.3 (M+H) for C27H26F3N7O6 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.78 (s, 3 H) 2.22 (s, 3 H) 3.72 (s, 7 H) 4.26 (t, *J*=4.90 Hz, 2 H) 6.19 (s, 1 H) 6.71 (s, 1 H) 7.05 (s, 2 H) 7.51 (d, *J*=1.70 Hz, 1 H) 7.57 - 7.68 (m, 1 H) 8.86 (s, 1 H) 10.16 (s, 1 H)	Ethyl 2-(2-acetamidoethoxy)-5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinate **Example 953**

Ex	Compound	Data	SM
Example 958	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(tetrahydrofuran-3-ylamino)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 455.0 (M+H) for C23H20ClF4N4O3 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.84 - 2.30 (m, 2 H) 3.52 - 4.00 (m, 4 H) 4.53 - 4.70 (m, 1 H) 6.49 - 6.65 (m, 1 H) 7.25 - 7.37 (m, 1 H) 7.39 - 7.53 (m, 3 H) 7.55 - 7.62 (m, 1 H) 7.64 - 7.72 (m, 2 H) 7.81 - 7.89 (m, 1 H) 8.20 - 8.31 (m, 1 H) 9.46 (s, 1 H)	(E)-ethyl-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(tetrahydrofuran-3-ylamino)pyrimidin-5-yl)phenyl)acrylate **Example 939**
Example 959	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-isopropoxynicotinic acid	MS(ES): 537.0 (M+H) for C23H17ClF4N6O3 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.30 (d, *J*=6.03 Hz, 6 H) 5.20 - 5.42 (m, 1 H) 7.03 (d, *J*=2.45 Hz, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.66 - 7.79 (m, 2 H) 8.08 (dd, *J*=6.69, 2.35 Hz, 2 H) 8.47 (br. s., 1 H) 8.78 (s, 1 H) 10.40 (s, 1 H)	Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-isopropoxynicotinate **Example 943**
Example 960	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-isopropoxynicotinic acid	MS(ES): 551.0 (M+H) for C24H19ClF4N6O3 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.28 (d, *J*=6.22 Hz, 6 H) 2.35 (s, 3 H) 5.31 (quin, *J*=6.08 Hz, 1 H) 6.75 (s, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.59 - 7.70 (m, 2 H) 7.98 - 8.10 (m, 2 H) 8.94 (s, 1 H) 10.41 (s, 1 H) 12.82 (s,1 H)	Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-isopropoxynicotinate **Example 944**

Ex	Compound	Data	SM
Example 961	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-((1-methyl-1H-imidazol-2-yl)methoxy)-nicotinic acid	MS(ES): 589.0 (M+H) for C25H17ClF4N8O3 1H NMR (300 MHz, DMSO- *d*6) δ ppm 3.94 (s, 4 H) 5.71 (s, 2 H) 7.05 (d, J=2.83 Hz, 1 H) 7.43 (t, J=9.14 Hz,1 H) 7.59 - 7.65 (m, 1 H) 7.65 - 7.77 (m, 2 H) 7.96 (d, J=2.45 Hz, 1 H) 8.08 (dd, J=6.50, 2.54 Hz, 1 H) 8.27 (d,J=2.45 Hz, 1 H) 8.54 (d, J=1.51 Hz, 1 H) 8.79 (s, 1 H) 10.43 (s, 1 H)	Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-((1-methyl-1H-imidazol-2-yl)methoxy)-nicotinate **Example 945**
Example 962	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(4-methylpiperazin-1-yl)ethoxy)nicotinic acid	MS(ES): 621.0 (M+H) for C27H25ClF4N8O3 1H NMR (300 MHz, DMSO- *d*6) δ ppm 2.83 (br. s., 3 H) 3.38 (s, 2 H) 3.40 - 3.53 (m, 2 H) 3.63 (d, *J*=5.65 Hz, 5 H) 4.77 (br. s., 3 H) 7.05 (d, *J*=2.45 Hz, 1 H) 7.42 (t, *J*=9.14 Hz, 2 H) 7.67 - 7.77 (m, 1 H) 7.90 (d, *J*=2.45 Hz, 1 H) 8.09 (dd, *J*=6.50, 2.35 Hz, 1 H) 8.30 (d, *J*=2.26 Hz, 1 H) 8.51 (s, 1 H) 8.80 (s, 1 H) 10.44 (s, 1 H)	Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(4-methylpiperazin-1-yl)ethoxy)nicotinate **Example 946**

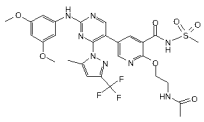
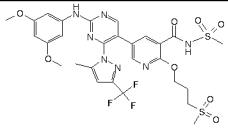
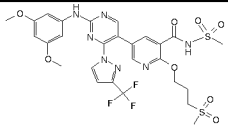
Ex	Compound	Data	SM
Example 963	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(4-methylpiperazin-1-yl)ethoxy)nicotinic acid	MS(ES): 635.0 (M+H) for C28H27ClF4N8O3 1H NMR (300 MHz, DMSO- *d*6) δ ppm 2.37 (s, 3 H) 2.48-2.52 (s, 8H) 2.70 - 2.80 (m, 5 H) 4.41 - 4.53 (m, 2 H) 6.78 (s, 1 H)7.43 (t, *J*=9.04 Hz, 1 H) 7.66 (d, *J*=2.64 Hz, 2 H) 8.08 (dd, *J*=7.06, 2.35 Hz, 1 H) 8.15 (d, *J*=2.45 Hz, 1 H) 8.95 (s, 1 H) 10.45 (s, 1 H)	Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(4-methylpiperazin-1-yl)ethoxy)nicotinate **Example 947**
Example 964	 5-(2-(3,5-dimethylphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(methylsulfonyl)ethoxy)nicotinic acid	MS(ES): 577.2 (M+H) for C25H23F3N6O5S 1H NMR (300 MHz, DMSO- *d*6) δ ppm 2.28 (s, 5 H) 3.10 (s, 4 H) 3.71 (t, J=6.69 Hz, 3 H) 4.49 - 4.61 (m, 1H) 6.70 (s, 1 H) 7.08 (d, 2 H) 7.40 (s, 2 H) 8.05 (d, 1 H) 8.44 (s, 1 H) 8.58 (d, 1 H) 8.67 (s, 1 H) 10.12 (s, 1 H)	Ethyl 5-(2-(3,5-dimethylphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(methylsulfonyl)ethoxy)nicotinate **Example 950**

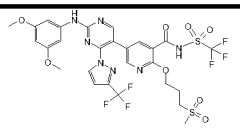
Ex	Compound	Data	SM
Example 965	 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(methylsulfonyl)ethoxy)nicotinic acid	MS(ES): 623.2 (M+H) for C26H25F3N6O7S 1H NMR (300 MHz, DMSO- *d*6) δ ppm 2.42 (s, 4 H) 3.09 (s, 3 H) 3.67 (t, *J*=6.69 Hz, 2 H) 3.73 (s, 6 H) 4.48 (t, *J*=6.31 Hz, 2 H) 6.22 (t, *J*=1.98 Hz, 1 H) 6.80 (s, 1 H) 7.04 (d, *J*=1.88 Hz, 2 H) 7.46 (d, 1 H) 8.33 (d, 1 H) 8.85 (s, 1 H) 10.21 (s, 1 H)	Ethyl 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(methylsulfonyl)ethoxy)nicotinate **Example 951**
Example 966	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(methylsulfonyl)ethoxy)nicotinic acid	MS(ES): 601.1 (M+H) for C23H17ClF4N6O5S 1H NMR (300 MHz, DMSO- *d*6) δ ppm 3.09 (s, 3 H) 3.70 (t, J=6.78 Hz, 2 H) 4.53 (t, J=6.59 Hz, 2 H) 7.10 (d,J=2.64 Hz, 1 H) 7.43 (t, J=9.14 Hz, 1 H) 7.67 - 7.76 (m, 1 H) 7.97 (s, 1 H) 8.07 (dd, J=6.59, 2.26 Hz, 1 H) 8.38 (br. s., 1 H) 8.59 (s, 1 H) 8.72 (s, 1 H) 10.44 (s, 1 H)	Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-(methylsulfonyl)ethoxy)nicotinic acid **Example 952**

Ex	Compound	Data	SM
Example 967	 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(3-(methylsulfonyl)propoxy)nicotinic acid	MS(ES): 637.2 (M+H) for C27H27F3N6O7S 1H NMR (300 MHz, DMSO- *d*6) δ ppm 2.09 - 2.20 (m, 2 H) 2.31 (s, 3 H) 2.99 (s, 3 H) 3.25 (br. s., 1 H) 3.72(s, 6 H) 4.42 (t, *J*=6.22 Hz, 2 H) 6.21 (t, *J*=2.17 Hz, 1 H) 6.74 (s, 1 H) 7.05 (d, *J*=2.26 Hz, 2 H) 7.64 (d, *J*=2.45 Hz, 1 H) 8.11 (br. s., 1 H) 8.92 (s, 1 H) 10.18 (s, 1 H) 12.96 (br. s., 1 H)	ethyl 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(3-(methylsulfonyl)propoxy)nicotinate **Example 954**
Example 968	 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(3-(methylsulfonyl)propoxy)nicotinic acid	MS(ES): 623.1 (M+H) for C26H25F3N6O7S 1H NMR (300 MHz, DMSO- *d*6) δ ppm 2.01 - 2.15 (m, 2 H) 2.97 (s, 3 H) 3.25 - 3.34 (m, 20 H) 3.74 (s, 6 H) 4.32 (t, *J*=6.23 Hz, 2 H) 6.18 (t, *J*=2.17 Hz, 1 H) 6.95 (d, *J*=2.64 Hz, 1 H) 7.13 (d, *J*=2.08 Hz, 2 H) 7.40 (d,*J*=2.08 Hz, 1 H) 7.70 (d, *J*=2.27 Hz, 1 H) 8.22 (d, *J*=1.51 Hz, 1 H) 8.69 (s, 1 H) 10.10 (s, 1 H)	Ethyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(3-(methylsulfonyl)propoxy)nicotinate **Example 955**

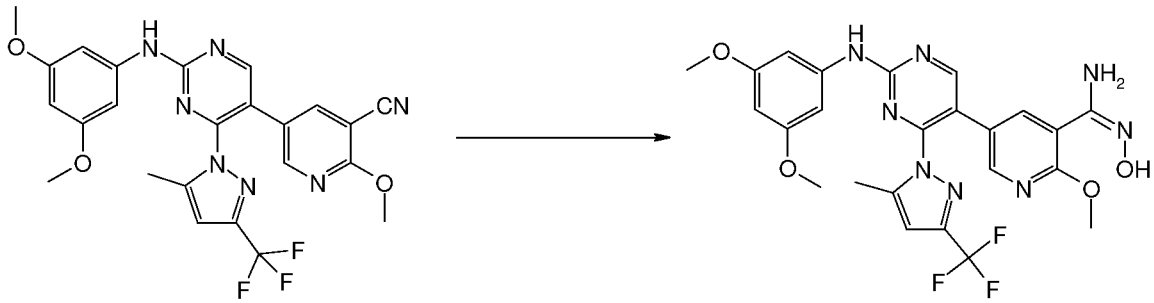
The compounds in the below table were prepared using the general method described above for **Example 824** and the starting material (SM) indicated.

5

Ex	Compound	Data	SM
Example 969	 2-(2-acetamidoethoxy)-5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(methylsulfonyl)nicotinamide	MS(ES): 679.3 (M+H) for C28H29F3N8O7S 1H NMR (300 MHz, DMSO- *d*6) δ ppm 1.81 (s, 2 H) 2.33 (s, 2 H) 3.33 (br. s., 5 H) 3.38 - 3.46 (m, 2 H) 3.67 -3.75 (m, 6 H) 4.37 (t, *J*=5.75 Hz, 2 H) 6.22 (t, *J*=2.17 Hz, 1 H) 6.77 (s, 1 H) 7.05 (d, *J*=2.07 Hz, 2 H) 7.71 (d,*J*=2.45 Hz, 1 H) 7.99 - 8.03 (m, 1 H) 8.94 (s, 1 H) 10.21 (s, 1 H) 11.50 (s, 1 H)	2-(2-acetamidoethoxy)-5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinic acid **Example 957**
Example 970	 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(methylsulfonyl)-2-(3-(methylsulfonyl)propoxy) nicotinamide	MS(ES): 714.3 (M+H) for C28H30F3N7O8S2 1H NMR (300 MHz, DMSO- *d*6) δ ppm 2.11 - 2.23 (m, 2 H) 2.32 (s, 3 H) 2.99 (s, 3 H) 3.27 (br. s., 2 H) 3.33(d, *J*=3.77 Hz, 3 H) 3.72 (s, 6 H) 4.41 (t, *J*=6.22 Hz, 2 H) 6.21 (t, *J*=2.07 Hz, 1 H) 6.77 (s, 1 H) 7.05 (d, *J*=2.07 Hz, 2 H) 7.68 (d, *J*=2.26 Hz, 1 H) 7.99 (d, *J*=2.45 Hz, 1 H) 8.94 (s, 1 H) 10.21 (s, 1 H) 11.80 (br. s., 1 H)	5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(3-(methylsulfonyl)propoxy) nicotinic acid **Example 967**
Example 971	 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(methylsulfonyl)-2-(3-(methylsulfonyl)propoxy)nicotinamide	MS(ES): 700.2 (M+H) for C27H28F3N7O8S2 1H NMR (300 MHz, DMSO- *d*6) δ ppm 2.15 – 2.24 (m, 2 H) 3.00 (s, 3 H) 3.25 – 3.37 (m, 5 H) 3.75 (s, 6 H)4.46 (t, *J*=6.33 Hz, 2 H) 6.22 (t, *J*=2.17 Hz, 1 H) 7.04 (d, *J*=2.45 Hz, 1 H) 7.11 (d, *J*=2.27 Hz, 2 H) 7.86 (d, *J*=2.45 Hz, 1 H) 8.17 (d, *J*=2.45 Hz, 1 H) 8.45 (d, *J*=1.70 Hz, 1 H) 8.77 (s, 1 H) 10.17 (s, 1 H)	5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(3-(methylsulfonyl)propoxy)nicotinic acid **Example 968**

Ex	Compound	Data	SM
Example 972	 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(3-(methylsulfonyl)propoxy)-N-(trifluoromethylsulfonyl)nicotinamide	MS(ES): 754.2 (M+H) for $C_{27}H_{25}F_6N_7O_8S_2$ 1H NMR (300 MHz, DMSO- *d*6) δ ppm 2.03 - 2.19 (m, 2 H) 2.97 (s, 3 H) 3.36 (s, 2 H) 3.74 (s, 6 H) 3.83 (s, 1H) 4.38 (t, J=6.14 Hz, 2 H) 6.19 (t, 1 H) 6.95 (d, J=2.64 Hz, 1 H) 7.12 (d, J=2.27 Hz, 2 H) 7.63 (d, J=2.45 Hz, 1 H) 7.99 (d, J=2.46 Hz, 1 H) 8.34 (d, J=0.94 Hz, 1 H) 8.73 (s, 1 H) 10.12 (s, 1 H)	5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(3-(methylsulfonyl)propoxy)-nicotinic acid **Example 968**

Example 973: (E)-5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N'-hydroxy-2-methoxynicotinimidamide



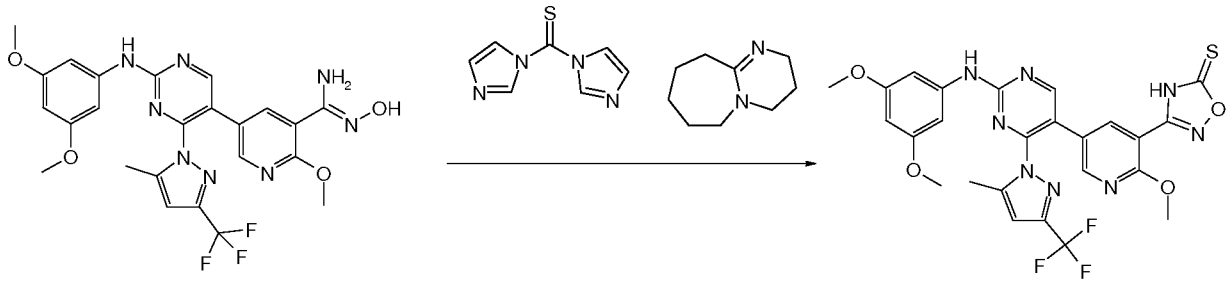
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5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinonitrile **Example 868** (0.10 g, 0.20 mmol), and hydroxylamine (0.018 ml, 0.30 mmol) were suspended in ethanol (4.6 mL) to give a white suspension. The mixture was heated at 80 °C for 2 hours then concentrated *in vacuo*. The residue was triturated with acetonitrile and dried under high vacuum to obtain the title compound as an off-white solid (0.095g).

MS(ES): 545.2 (M+H) for $C_{24}H_{23}F_3N_8O_4$

^{1}H-NMR (400 MHz, DMSO-d6): δ ppm 2.27 (s, 3 H) 3.72 (s, 7 H) 3.87 (s, 3 H) 5.69 (s, 2 H) 6.21 (s, 1 H) 6.73 (s, 1 H) 7.04 (d, *J*=1.88 Hz, 2 H) 7.57 (d, *J*=2.26 Hz, 1 H) 7.81 (d, *J*=2.45 Hz, 1 H) 8.88 (s, 1 H) 9.58 (s, 1 H)10.19 (s, 1 H)

Example 974: 3-(5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxypyridin-3-yl)-1,2,4-oxadiazol-5(4H)-thione

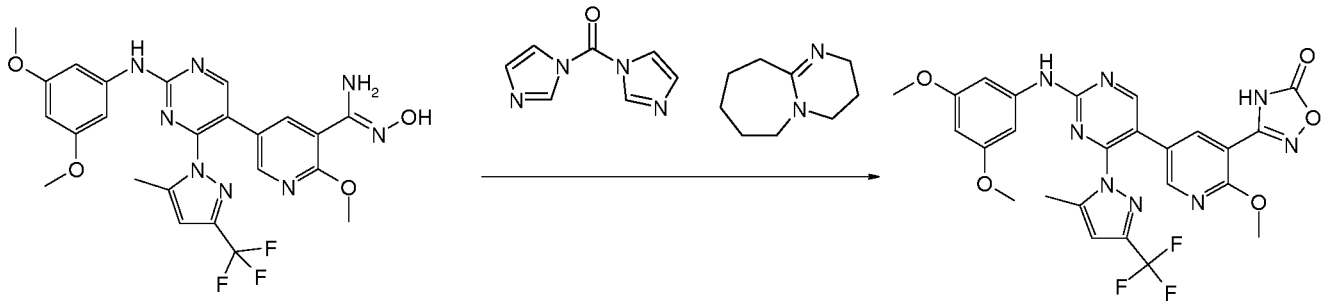


(E)-5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N'-hydroxy-2-methoxynicotinimidamide **Example 973** (0.20 g, 0.37 mmol), di(1H-imidazol-1-yl)methanethione (0.099 g, 0.55 mmol) and DBU (0.222 ml, 1.47 mmol) were suspended in acetonitrile (8.16 mL). The mixture was stirred at room temperature for 1.5 hours then concentrated *in vacuo*. The residue was purified by flash chromatography : 4 g silica column, 3-30 % methanol in chloroform over 25 min. The relevant fractions were pooled and resulting material was dried and purified by reverse phase HPLC: 65-95% methanol in 0.1% formic acid-water (pH 3) using a 19mm x100mm 5μm waters T3 C18 column. Evaporation of fractions gave the title compound as an off-white solid (0.05g).

MS(ES): 587.2 (M+H) for $C_{25}H_{21}F_3N_8O_4S$

^{1}H-NMR (300 MHz, DMSO-d6): δ ppm 2.37 (s, 3 H) 3.72 (s, 7 H) 3.95 (s, 3 H) 6.22 (t, *J*=2.07 Hz, 1 H) 6.77 (s, 1 H) 7.05 (d, *J*=2.07 Hz, 2 H) 7.82 (d, *J*=2.45 Hz, 1 H) 8.09 (d, *J*=1.88 Hz, 1 H) 8.93 (s, 1 H) 10.22 (s, 1 H)

Example 975: 3-(5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxypyridin-3-yl)-1,2,4-oxadiazol-5(4H)-one



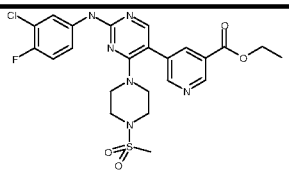
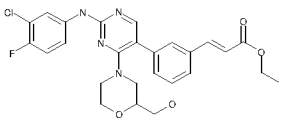
(E)-5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N'-hydroxy-2-methoxynicotinimidamide **Example 973** (0.0951 g, 0.17 mmol), CDI (0.042 g, 0.26 mmol) and DBU (0.053 ml, 0.35 mmol) were suspended in 1,4-dioxane (3.5 mL). The mixture was stirred at room temperature overnight then concentrated *in vacuo*. The residue was purified by reverse phase flash chromatography: 50 g C18 column, 5-75% acetonitrile in water over 25 min. Relevant fractions pooled and evaporated to give the title compound as a white solid (0.029g).

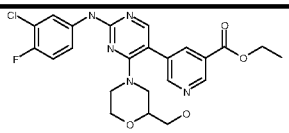
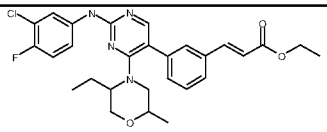
MS(ES): 571.2 (M+H) for $C_{25}H_{21}F_3N_8O_5$

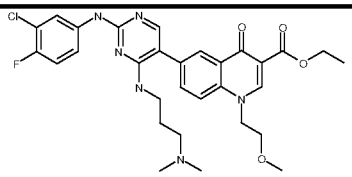
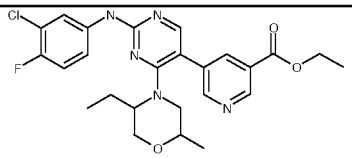
^{1}H-NMR (300 MHz, DMSO-d6): δ ppm 2.38 (s, 4 H) 3.72 (s, 6 H) 3.95 (s, 3 H) 6.22 (br. s., 1 H) 6.77 (s, 1 H) 7.04 (s, 2 H) 7.72 (s, 1 H) 8.15 (s, 1 H) 8.93 (s, 1 H) 10.22 (s, 1 H)

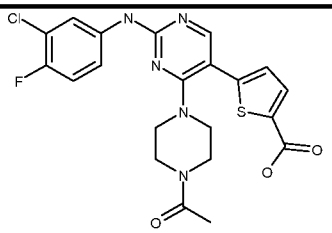
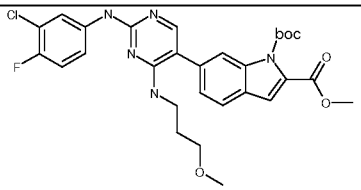
The following compounds were prepared using the general method described for **Example 1** using tris(dibenzyledeneacetone)-dipalladium(0), 2-dicyclohexyl phosphino-2',4',6'-triiso-propyl-1,1'-biphenyl, sodium carbonate and the starting materials (SM) indicated.

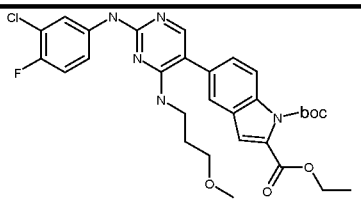
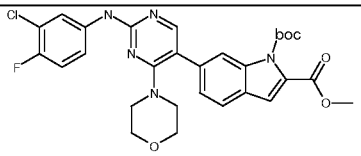
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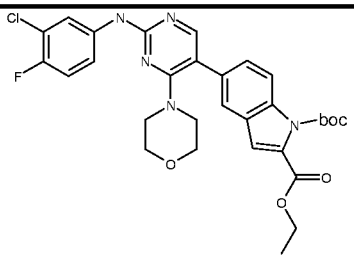
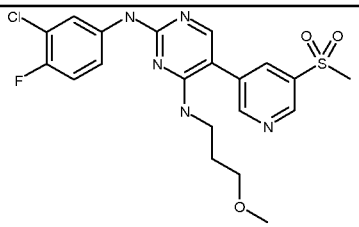
Ex	Compound	Data	SM
Example 976	 Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-5-yl)nicotinate	MS(ES): 535 (M+1) for $C_{23}H_{24}ClFN_6O_4S$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.34 (t, *J*=7.06 Hz, 3 H) 2.87 (s, 3 H) 3.02 - 3.14 (m, 4 H) 3.24 - 3.48 (m, 4 H) 4.37 (q, *J*=7.10 Hz, 2 H) 7.36 (t, *J*=9.14 Hz, 1 H) 7.56 - 7.75 (m, 1 H) 8.10 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.20 (s, 1 H) 8.37 (t, *J*=2.07 Hz, 1 H) 8.93 (d, *J*=2.07 Hz, 1 H) 9.03 (d, *J*=1.88 Hz, 1 H) 9.83 (s, 1 H)	5-bromo-N-(3-chloro-4-fluorophenyl)-4-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-2-amine **(Intermediate 130)** and 3-(ethoxycarbonyl) pyridine-5-boronic acid pinacol ester
Example 977	 (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(2-(hydroxymethyl)morpholino)pyrimidin-5-yl)phenyl)acrylate	MS(ES): 514 (M+1) for $C_{26}H_{26}ClFN_4O_4$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.27 (t, *J*=7.06 Hz, 3 H) 2.63 - 3.02 (m, 2 H) 3.13 - 3.63 (m, 5 H) 3.63 - 3.99 (m, 2 H) 4.20 (q, *J*=7.16 Hz, 2 H) 6.74 (d, *J*=16.01 Hz, 1 H) 7.36 (t, *J*=9.14 Hz, 1 H) 7.43 - 7.58 (m, 2 H) 7.58 - 7.79 (m, 3 H) 7.76 - 7.91 (m, 1 H) 7.98 - 8.22 (m, 2 H) 9.83 (s, 1 H)	(4-(5-bromo-2-(3-chloro-4-fluorophenylamino)pyrimidin-4-yl)morpholin-2-yl)methanol **Intermediate 383** and Ethyl 3-boronocinnamate

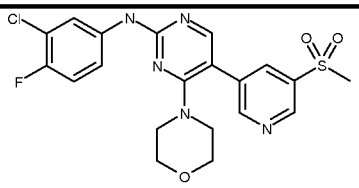
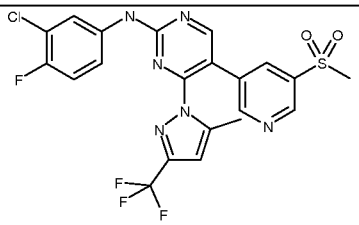
Ex	Compound	Data	SM
Example 978	 Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(2-(hydroxymethyl)morpholino)pyrimidin-5-yl)nicotinate	MS(ES): 488 (M+1) for $C_{23}H_{23}ClFN_5O_4$. ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.34 (t, *J*=7.06 Hz, 3 H) 2.60 - 2.80 (m, 1 H) 2.79 - 2.99 (m, 1 H) 3.06 - 3.58 (m, 5 H) 3.75 (d, *J*=14.69 Hz, 2 H) 4.37 (q, *J*=6.97 Hz, 2 H) 7.35 (t, *J*=9.14 Hz, 1 H) 7.52 - 7.73 (m, 1 H) 7.97 - 8.14 (m, 1 H) 8.17 (s, 1 H) 8.37 (t, *J*=2.07 Hz, 1 H) 8.91 (d, *J*=2.26 Hz, 1 H) 9.02 (d, *J*=1.88 Hz, 1 H) 9.88 (s, 1 H)	(4-(5-bromo-2-(3-chloro-4-fluorophenylamino)pyrimidin-4-yl)morpholin-2-yl)methanol **Intermediate 383** and 3-(ethoxycarbonyl) pyridine-5-boronic acid pinacol ester
Example 979	 (E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(5-ethyl-2-methylmorpholino)pyrimidin-5-yl)phenyl)acrylate	MS(ES): 525 (M+1) for $C_{28}H_{30}ClFN_4O_3$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 0.39 - 0.73 (m, 3 H) 0.98 (d, *J*=5.65 Hz, 3 H) 1.25 (t, *J*=7.16 Hz, 3 H) 1.39 - 1.79 (m, 2 H) 2.61 - 2.90 (m, 1 H) 3.39 - 3.71 (m, 5 H) 4.19 (q, *J*=7.03 Hz, 2 H) 6.72 (d, *J*=16.01 Hz, 1 H) 7.38 (t, *J*=9.14 Hz, 1 H) 7.42 - 7.60 (m, 3 H) 7.58 - 7.90 (m, 3 H) 7.98 (d, *J*=0.94 Hz, 1 H) 8.02 - 8.18 (m, 1 H) 9.88 (s, 1 H)	5-bromo-N-(3-chloro-4-fluorophenyl)-4-(5-ethyl-2-methylmorpholino)pyrimidin-2-amine **Intermediate 384** and Ethyl 3-boronocinnamate

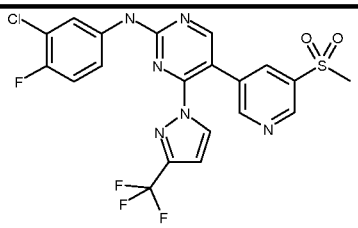
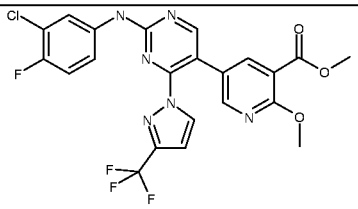
Ex	Compound	Data	SM
Example 980	 Ethyl 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino)propylamino)pyrimidin-5-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate	MS(ES): 597 (M+1) for $C_{30}H_{34}ClFN_6O_4$	5-Bromo-N^2-(3-chloro-4-fluoro-phenyl)-N^4-(3-dimethylamino-propyl)-pyrimidine-2,4-diamine **Intermediate 26** and ethyl 1-(2-methoxyethyl)-4-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydroquinoline-3-carboxylate **Intermediate 134**
Example 981	 Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-ethyl-2-methylmorpholino)pyrimidin-5-yl)nicotinate	MS(ES): 500 (M+1) for $C_{25}H_{27}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 0.60 (t, *J*=7.44 Hz, 3 H) 1.01 (d, *J*=6.03 Hz, 3 H) 1.34 (t, *J*=7.06 Hz, 3 H) 1.45 - 1.89 (m, 2 H) 2.63 - 2.96 (m, 1 H) 3.33 - 3.76 (m, 5 H) 4.37 (q, *J*=7.10 Hz, 2 H) 7.36 (t, *J*=9.14 Hz, 1 H) 7.46 - 7.68 (m, 1 H) 8.04 - 8.20 (m, 2 H) 8.32 (t, *J*=2.17 Hz, 1 H) 8.90 (d, *J*=2.26 Hz, 1 H) 9.04 (d, *J*=1.88 Hz, 1 H) 9.84 (s, 1 H)	5-Bromo-N-(3-chloro-4-fluorophenyl)-4-(5-ethyl-2-methylmorpholino)pyrimidin-2-amine **Intermediate 384** and 3-(ethoxycarbonyl)pyridine-5-boronic acid pinacol ester

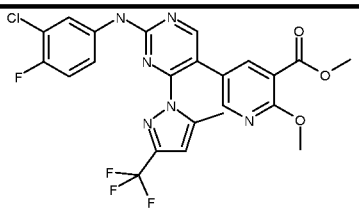
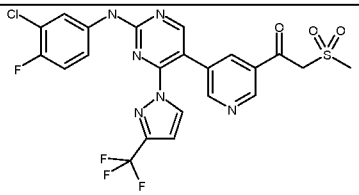
Ex	Compound	Data	SM
Example 982	 5-(4-(4-Acetylpiperazin-1-yl)-2-(3-chloro-4-fluorophenylamino)pyrimidin-5-yl)thiophene-2-carboxylic acid	MS(ES): 476 (M+1) for $C_{21}H_{19}ClFN_5O_3S$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.98 (s, 3 H) 3.22 - 3.41 (m, 4 H) 3.40 - 3.66 (m, 4 H) 7.27 (d, *J*=3.77 Hz, 1 H) 7.35 (t, *J*=9.14 Hz, 1 H) 7.53 - 7.68 (m, 1 H) 7.70 (d, *J*=3.77 Hz, 1 H) 7.96 - 8.17 (m, 1 H) 8.22 (s, 1 H) 9.84 (s, 1 H)	1-(4-(5-bromo-2-(3-chloro-4-fluorophenylamino)pyrimidin-4-yl)piperazin-1-yl)ethanone **Intermediate 98** and 2-carboxythiophene-5-boronic acid
Example 983	 1-tert-butyl 2-methyl 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)-1H-indole-1,2-dicarboxylate	MS(ES): 584 (M+1) for $C_{29}H_{31}ClFN_5O_5$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.55 (s, 9 H) 1.69 - 2.00 (m, 2 H) 3.15 (s, 3 H) 3.35 - 3.61 (m, 4 H) 3.87 (s, 3 H) 6.82 (t, *J*=5.27 Hz, 1 H) 7.20 - 7.39 (m, 3 H) 7.53 - 7.71 (m, 1 H) 7.74 - 7.90 (m, 2 H) 7.99 (s, 1 H) 8.25 (dd, *J*=6.88, 2.54 Hz, 1 H) 9.40 (s, 1 H)	5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)pyrimidine-2,4-diamine **Intermediate 119** and 1-tert-butyl 2-methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-1,2-dicarboxylate **Intermediate 408**

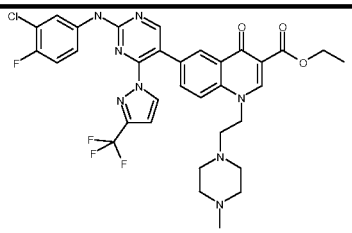
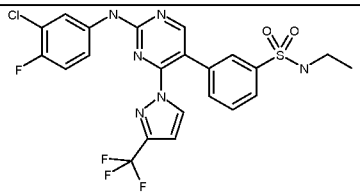
Ex	Compound	Data	SM
Example 984	 1-tert-butyl 2-ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)-1H-indole-1,2-dicarboxylate	MS(ES): 598 (M+1) for $C_{30}H_{33}ClFN_5O_5$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.32 (t, *J*=7.06 Hz, 3 H) 1.58 (s, 9 H) 1.79 (t, *J*=6.41 Hz, 2 H) 3.15 (s, 3 H) 3.32 - 3.54 (m, 4 H) 4.33 (q, *J*=7.16 Hz, 2 H) 6.60 (t, *J*=5.27 Hz, 1 H) 7.16 - 7.38 (m, 2 H) 7.44 (dd, *J*=8.67, 1.70 Hz, 1 H) 7.56 - 7.75 (m, 2 H) 7.79 (s, 1 H) 8.02 (d, *J*=8.67 Hz, 1 H) 8.24 (dd, *J*=6.97, 2.45 Hz, 1 H) 9.37 (s, 1 H)	5-bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)pyrimidine-2,4-diamine **Intermediate 119** and 1-tert-butyl 2-ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-1,2-dicarboxylate **Intermediate 409**
Example 985	 1-tert-butyl 2-methyl 6-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)-1H-indole-1,2-dicarboxylate	MS(ES): 582 (M+1) for $C_{29}H_{29}ClFN_5O_5$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.56 (s, 9 H) 3.11 - 3.27 (m, 4 H) 3.43 - 3.62 (m, 4 H) 3.87 (s, 3 H) 7.19 - 7.38 (m, 2 H) 7.44 (dd, *J*=8.29, 1.32 Hz, 1 H) 7.54 - 7.72 (m, 1 H) 7.77 (d, *J*=8.10 Hz, 1 H) 8.03 - 8.23 (m, 3 H) 9.65 (s, 1 H)	5-Bromo-N-(3-chloro-4-fluorophenyl)-4-morpholin-4-ylpyrimidin-2-amine **Intermediate 111** and 1-tert-butyl 2-methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-1,2-dicarboxylate **Intermediate 408**

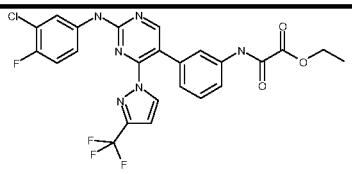
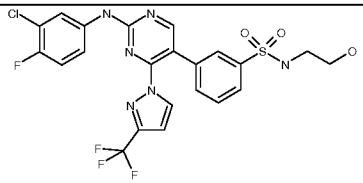
Ex	Compound	Data	SM
Example 986	 1-tert-butyl 2-ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)-1H-indole-1,2-dicarboxylate	MS(ES): 596 (M+1) for $C_{30}H_{31}ClFN_5O_5$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.32 (t, *J*=7.06 Hz, 3 H) 1.58 (s, 9 H) 3.14 - 3.27 (m, 4 H) 3.43 - 3.69 (m, 4 H) 4.32 (q, *J*=7.10 Hz, 2 H) 7.17 - 7.42 (m, 2 H) 7.47 - 7.71 (m, 2 H) 7.78 (d, *J*=1.32 Hz, 1 H) 7.95 - 8.10 (m, 2 H) 8.15 (dd, *J*=6.78, 2.64 Hz, 1 H) 9.60 (s, 1 H)	5-Bromo-N-(3-chloro-4-fluorophenyl)-4-morpholin-4-ylpyrimidin-2-amine **Intermediate 111** and 1-tert-butyl 2-ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-1,2-dicarboxylate **Intermediate 409**
Example 987	 N2-(3-chloro-4-fluorophenyl)-N4-(3-methoxypropyl)-5-(5-(methylsulfonyl)pyridin-3-yl)pyrimidine-2,4-diamine	MS(ES): 466 (M+1) for $C_{20}H_{21}ClFN_5O_3S$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.71 - 1.93 (m, 2 H) 3.20 (s, 3 H) 3.33 - 3.55 (m, 7 H) 7.09 (t, *J*=5.56 Hz, 1 H) 7.30 (t, *J*=9.14 Hz, 1 H) 7.53 - 7.74 (m, 1 H) 7.91 (s, 1 H) 8.16 - 8.35 (m, 2 H) 8.88 (d, *J*=2.07 Hz, 1 H) 9.01 (d, *J*=2.07 Hz, 1 H) 9.53 (s, 1 H)	5-Bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)pyrimidine-2,4-diamine **Intermediate 119** and 3-(methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine **Intermediate 410**

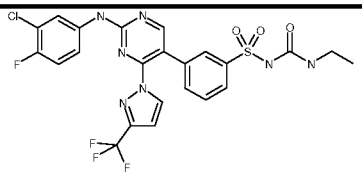
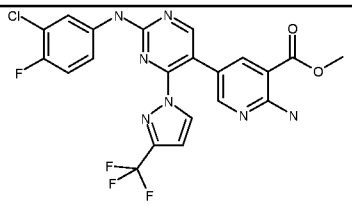
Ex	Compound	Data	SM
Example 988	 N-(3-chloro-4-fluorophenyl)-5-(5-(methylsulfonyl)pyridin-3-yl)-4-morpholinopyrimidin-2-amine	MS(ES): 464 (M+1) for $C_{20}H_{19}ClFN_5O_3S$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 3.10 - 3.28 (m, 4 H) 3.37 (s, 3 H) 3.49 - 3.73 (m, 4 H) 7.34 (t, *J*=9.14 Hz, 1 H) 7.52 - 7.78 (m, 1 H) 8.04 - 8.20 (m, 1 H) 8.25 (s, 1 H) 8.41 (s, 1 H) 9.00 (dd, *J*=16.48, 1.41 Hz, 2 H) 9.79 (s, 1 H)	5-Bromo-N-(3-chloro-4-fluorophenyl)-4-morpholin-4-ylpyrimidin-2-amine **Intermediate 111** and 3-(methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine **Intermediate 410**
Example 989	 N-(3-chloro-4-fluorophenyl)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-5-(5-(methylsulfonyl)pyridin-3-yl)pyrimidin-2-amine	MS(ES): 527 (M+1) for $C_{21}H_{15}ClF_4N_6O_2S$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 3.24 (s, 3 H) 3.30 (s, 3 H) 6.80 (s, 1 H) 7.43 (t, *J*=9.14 Hz, 1 H) 7.58 - 7.75 (m, 1 H) 7.94 (t, *J*=2.17 Hz, 1 H) 8.07 (dd, *J*=6.59, 2.26 Hz, 1 H) 8.62 (d, *J*=2.07 Hz, 1 H) 8.92 - 9.09 (m, 2 H) 10.51 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 113** and 3-(methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine **Intermediate 410**

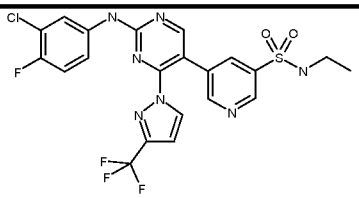
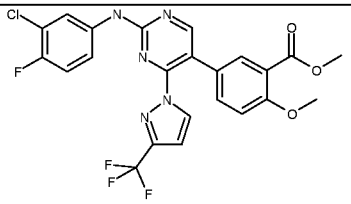
Ex	Compound	Data	SM
Example 990	 N-(3-chloro-4-fluorophenyl)-5-(5-(methylsulfonyl)pyridin-3-yl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine	MS(ES): 513 (M+1) for $C_{20}H_{13}ClF_4N_6O_2S$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 3.27 (s, 3 H) 7.07 (d, *J*=2.64 Hz, 1 H) 7.43 (t, *J*=9.04 Hz, 1 H) 7.63 - 7.80 (m, 1 H) 8.06 (dd, *J*=6.78, 2.45 Hz, 1 H) 8.15 (t, *J*=2.07 Hz, 1 H) 8.59 (d, *J*=1.70 Hz, 1 H) 8.76 (d, *J*=2.07 Hz, 1 H) 8.85 (s, 1 H) 9.02 (d, *J*=2.26 Hz, 1 H) 10.50 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoro-methyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and 3-(methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine **Intermediate 410**
Example 991	 Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinate	MS(ES): 523 (M+1) for $C_{22}H_{15}ClF_4N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.77 (s, 3 H) 3.95 (s, 3 H) 7.05 (d, *J*=2.64 Hz, 1 H) 7.43 (t, *J*=9.14 Hz, 1 H) 7.72 (ddd, *J*=9.04, 4.24, 2.73 Hz, 1 H) 7.86 (d, *J*=2.45 Hz, 1 H) 8.08 (dd, *J*=6.69, 2.54 Hz, 1 H) 8.28 (d, *J*=2.45 Hz, 1 H) 8.51 (d, *J*=1.51 Hz, 1 H) 8.81 (s, 1 H) 10.42 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoro-methyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 411**

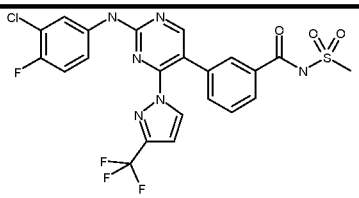
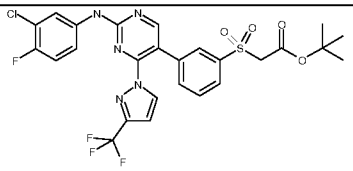
Ex	Compound	Data	SM
Example 992	 Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinate	MS(ES): 537 (M+1) for $C_{23}H_{17}ClF_4N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.33 (s, 3 H) 3.75 (s, 3 H) 3.92 (s, 3 H) 6.77 (s, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.54 - 7.76 (m, 2 H) 8.07 (d, *J*=6.97 Hz, 1 H) 8.23 (d, *J*=2.45 Hz, 1 H) 8.97 (s, 1 H) 10.46 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 113** and methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 411**
Example 993	 1-(5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)pyridin-3-yl)-2-(methylsulfonyl)ethanone	MS(ES): 555 (M+1) for $C_{22}H_{15}ClF_4N_6O_3S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.16 (s, 3 H) 5.19 (s, 2 H) 7.07 (d, *J*=2.64 Hz, 1 H) 7.44 (t, *J*=9.14 Hz, 1 H) 7.74 (ddd, *J*=9.14, 4.24, 2.83 Hz, 1 H) 8.08 (dd, *J*=6.69, 2.54 Hz, 1 H) 8.31 (t, *J*=2.17 Hz, 1 H) 8.49 - 8.70 (m, 2 H) 8.85 (s, 1 H) 9.15 (d, *J*=2.07 Hz, 1 H) 10.50 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and 2-(Methylsulfonyl)-1-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)ethanone **Intermediate 415**

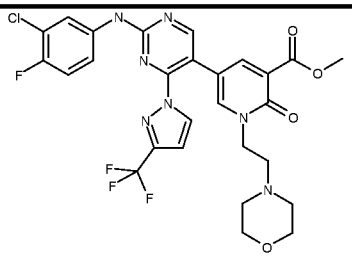
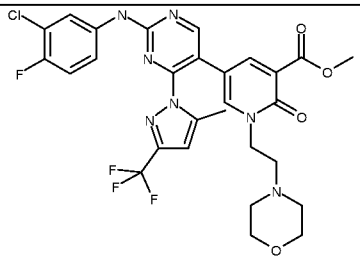
Ex	Compound	Data	SM
Example 994	 Ethyl 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(4-methylpiperazin-1-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate	MS(ES): 699 (M+1) for $C_{33}H_{31}ClF_4N_8O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.30 (t, *J*=7.06 Hz, 3 H) 2.01 - 2.46 (m, 11 H) 2.60 (t, *J*=4.80 Hz, 2 H) 4.23 (q, *J*=7.10 Hz, 2 H) 4.47 (t, *J*=4.24 Hz, 2 H) 7.00 (d, *J*=2.64 Hz, 1 H) 7.33 - 7.56 (m, 2 H) 7.60 - 7.88 (m, 2 H) 8.00 - 8.19 (m, 2 H) 8.44 (d, *J*=1.51 Hz, 1 H) 8.58 (s, 1 H) 8.83 (s, 1 H) 10.44 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and Ethyl 1-(2-(4-methylpiperazin-1-yl)ethyl)-4-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydroquinoline-3-carboxylate **Intermediate 416**
Example 995	 3-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-ethylbenzenesulfonamide	MS(ES): 541 (M+1) for $C_{22}H_{17}ClF_4N_6O_2S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.91 - 1.01 (m, 3 H) 2.56 - 2.81 (m, 2 H) 7.00 (d, *J*=2.64 Hz, 1 H) 7.29 - 7.66 (m, 5 H) 7.65 - 7.90 (m, 2 H) 8.09 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.45 (d, *J*=1.51 Hz, 1 H) 8.77 (s, 1 H) 10.42 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and ethyl 3-boronobenzenesulfonamide

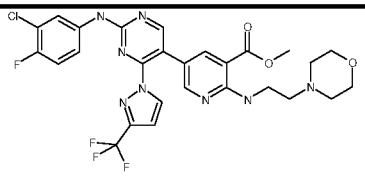
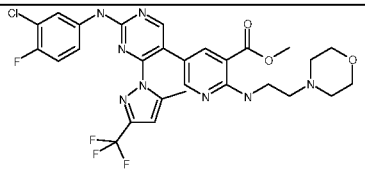
Ex	Compound	Data	SM
Example 996	 Ethyl 2-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenylamino)-2-oxoacetate	MS(ES): 549 (M+1) for $C_{24}H_{17}ClF_4N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.31 (t, *J*=7.06 Hz, 3 H) 4.30 (q, *J*=7.16 Hz, 2 H) 6.81 - 7.07 (m, 2 H) 7.21 - 7.48 (m, 2 H) 7.63 (s, 1 H) 7.66 - 7.81 (m, 2 H) 8.12 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.29 (s, 1 H) 8.73 (s, 1 H) 10.40 (s, 1 H) 10.77 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoro-methyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and ethyl 2-oxo-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylamino)acetate **Intermediate 418**
Example 997	 3-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(2-hydroxyethyl)benzenesulfonamide	MS(ES): 557 (M+1) for $C_{22}H_{17}ClF_4N_6O_3S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.71 (q, 2 H) 3.36 (q, *J*=6.03 Hz, 2 H) 4.66 (t, *J*=5.56 Hz, 1 H) 6.99 (d, *J*=2.83 Hz, 1 H) 7.30 - 7.49 (m, 2 H) 7.49 - 7.67 (m, 3 H) 7.67 - 7.90 (m, 2 H) 8.10 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.43 (d, *J*=1.70 Hz, 1 H) 8.78 (s, 1 H) 10.43 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoro-methyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and 3-(N-(2-hydroxyethyl)sulfamoyl)phenylboronic acid

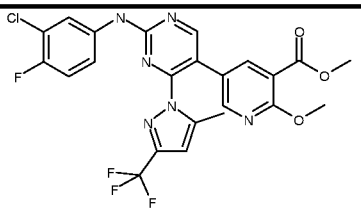
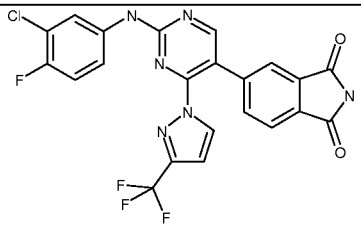
Ex	Compound	Data	SM
Example 998	 3-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(ethylcarbamoyl)benzenesulfonamide	MS(ES): 584 (M+1) for $C_{23}H_{18}ClF_4N_7O_3S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.92 (t, 3 H) 2.85 - 3.04 (m, 2 H) 6.41 (t, *J*=5.93 Hz, 1 H) 6.99 (d, *J*=2.45 Hz, 1 H) 7.26 - 7.67 (m, 5 H) 7.73 (ddd, *J*=9.09, 4.29, 2.64 Hz, 1 H) 7.79 - 7.97 (m, 1 H) 8.10 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.43 (s, 1 H) 8.76 (s, 1 H) 10.46 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and N-(ethylcarbamoyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide **Intermediate 419**
Example 999	 Methyl 2-amino-5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinate	MS(ES): 508 (M+1) for $C_{21}H_{14}ClF_4N_7O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.77 (s, 3 H) 7.02 (d, *J*=2.64 Hz, 1 H) 7.28 (s, 2 H) 7.40 (t, *J*=9.04 Hz, 1 H) 7.62 - 7.82 (m, 2 H) 7.98 - 8.18 (m, 2 H) 8.43 (d, *J*=1.70 Hz, 1 H) 8.78 (s, 1 H) 10.35 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and methyl 2-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 420**

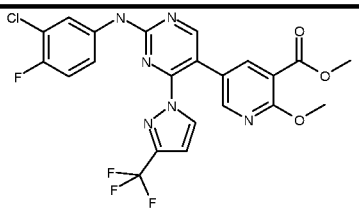
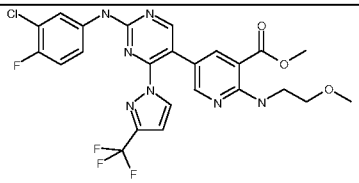
Ex	Compound	Data	SM
Example 1000	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-ethylpyridine-3-sulfonamide	MS(ES): 542 (M+1) for $C_{21}H_{16}ClF_4N_7O_2S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.97 (t, 3 H) 2.63 - 2.86 (m, 2 H) 7.05 (d, *J*=2.83 Hz, 1 H) 7.43 (t, *J*=9.14 Hz, 1 H) 7.65 - 7.86 (m, 2 H) 7.97 (t, *J*=2.07 Hz, 1 H) 8.06 (dd, *J*=6.69, 2.54 Hz, 1 H) 8.58 (dd, *J*=2.54, 0.85 Hz, 1 H) 8.67 (d, *J*=2.07 Hz, 1 H) 8.81 (s, 1 H) 8.89 (d, *J*=2.07 Hz, 1 H) 10.46 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and N-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide **Intermediate 421**
Example 1001	 Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxybenzoate	MS(ES): 522 (M+1) for $C_{23}H_{16}ClF_4N_5O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.74 (s, 3 H) 3.83 (s, 3 H) 6.98 (d, *J*=2.64 Hz, 1 H) 7.07 - 7.19 (m, 1 H) 7.31 - 7.38 (m, 2 H) 7.70 (ddd, *J*=9.14, 4.14, 2.73 Hz, 1 H) 7.77 - 7.94 (m, 1 H) 8.11 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.32 (d, *J*=1.70 Hz, 1 H) 8.77 (s, 1 H) 10.37 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate **Intermediate 422**

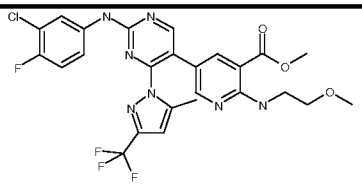
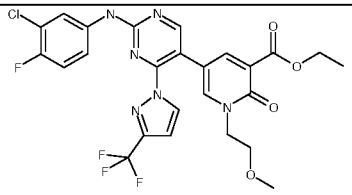
Ex	Compound	Data	SM
Example 1002	 3-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(methylsulfonyl)benzamide	MS(ES): 555 (M+1) for $C_{22}H_{15}ClF_4N_6O_3S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.38 (s, 3 H) 7.01 (d, *J*=2.64 Hz, 1 H) 7.20 - 7.35 (m, 1 H) 7.35 - 7.61 (m, 2 H) 7.62 - 7.81 (m, 1 H) 7.81 - 8.04 (m, 2 H) 8.13 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.39 (s, 1 H) 8.85 (s, 1 H) 10.44 (s, 1 H) 12.13 (br. s., 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and N-(methylsulfonyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide **Intermediate 423**
Example 1003	 tert-Butyl 2-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenylsulfonyl)acetate	MS(ES): 612 (M+1) for $C_{26}H_{22}ClF_4N_5O_4S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.27 (s, 9 H) 4.44 (s, 2 H) 7.02 (d, *J*=2.64 Hz, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.48 - 7.58 (m, 1 H) 7.60 - 7.81 (m, 3 H) 7.79 - 7.96 (m, 1 H) 8.10 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.46 (d, *J*=1.51 Hz, 1 H) 8.81 (s, 1 H) 10.46 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and tert-butyl 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylsulfonyl)acetate **Intermediate 424**

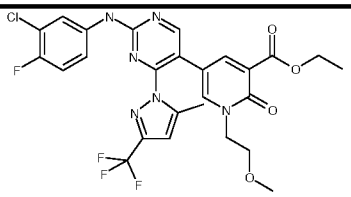
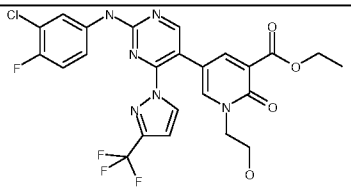
Ex	Compound	Data	SM
Example 1004	 Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-morpholinoethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 622 (M+1) for $C_{27}H_{24}ClF_4N_7O_4$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.34 - 2.45 (m, 4 H) 2.56 (t, *J*=6.40 Hz, 2 H) 3.41 - 3.59 (m, 4 H) 3.68 (s, 3 H) 3.97 - 4.11 (m, 2 H) 7.08 (d, *J*=2.83 Hz, 1 H) 7.42 (t, *J*=9.04 Hz, 1 H) 7.59 - 7.80 (m, 2 H) 7.94 - 8.16 (m, 2 H) 8.48 - 8.63 (m, 1 H) 8.71 (s, 1 H) 10.36 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and methyl 1-(2-morpholinoethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate **Intermediate 425**
Example 1005	 Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-morpholinoethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 636 (M+1) for $C_{28}H_{26}ClF_4N_7O_4$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.31 - 2.46 (m, 7 H) 2.51 - 2.63 (m, 2 H) 3.40 - 3.60 (m, 4 H) 3.65 (s, 3 H) 3.94 - 4.13 (m, 2 H) 6.79 (s, 1 H) 7.27 (d, *J*=2.64 Hz, 1 H) 7.41 (t, *J*=9.14 Hz, 1 H) 7.64 (ddd, *J*=9.09, 4.19, 2.73 Hz, 1 H) 7.95 - 8.16 (m, 2 H) 8.86 (s, 1 H) 10.40 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 113** and Methyl 1-(2-morpholinoethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate **Intermediate 425**

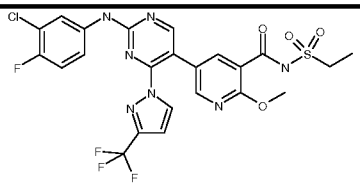
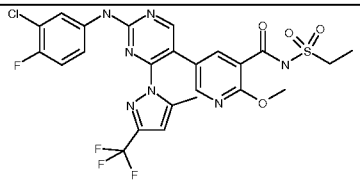
Ex	Compound	Data	SM
Example 1006	 Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-morpholinoethylamino)nicotinate	MS(ES): 621 (M+1) for $C_{27}H_{25}ClF_4N_8O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.32 - 2.46 (m, 4 H) 2.45 - 2.63 (m, 2 H) 3.45 - 3.68 (m, 6 H) 3.77 (s, 3 H) 7.02 (d, *J*=2.64 Hz, 1 H) 7.40 (t, *J*=9.14 Hz, 1 H) 7.57 - 7.83 (m, 2 H) 8.09 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.10 - 8.26 (m, 2 H) 8.43 (d, *J*=1.32 Hz, 1 H) 8.72 - 8.89 (m, 1 H) 10.35 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and methyl 2-(2-morpholinoethylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 426**
Example 1007	 Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-morpholinoethylamino)nicotinate	MS(ES): (M+1) for $C_{28}H_{27}ClF_4N_8O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.18 (s, 3 H) 2.32 - 2.46 (m, 4 H) 2.47 - 2.60 (m, 2 H) 3.55 - 3.68 (m, 6 H) 3.75 (s, 3 H) 7.18 - 7.54 (m, 2 H) 7.65 (ddd, *J*=9.14, 4.24, 2.64 Hz, 1 H) 8.06 (dd, *J*=6.69, 2.54 Hz, 1 H) 8.12 - 8.27 (m, 3 H) 8.95 (s, 1 H) 10.39 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 113** and methyl 2-(2-morpholinoethylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 426**

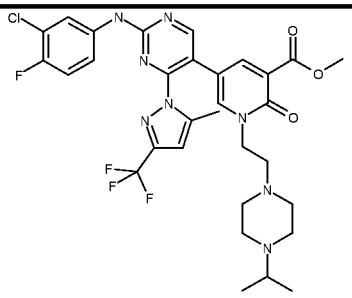
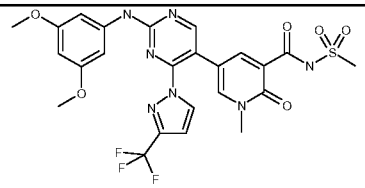
Ex	Compound	Data	SM
Example 1008	 Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinate	MS(ES): 537 (M+1) for $C_{23}H_{17}ClF_4N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.33 (s, 3 H) 3.75 (s, 3 H) 3.92 (s, 3 H) 6.76 (s, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.53 - 7.75 (m, 2 H) 8.06 (dd, *J*=6.69, 2.54 Hz, 1 H) 8.22 (d, *J*=2.64 Hz, 1 H) 8.96 (s, 1 H) 10.43 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 113** and methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 411**
Example 1009	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)isoindoline-1,3-dione	MS(ES): 503 (M+1) for $C_{22}H_{11}ClF_4N_6O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.03 (d, 1 H) 7.43 (t, *J*=9.04 Hz, 1 H) 7.54 - 7.69 (m, 2 H) 7.69 - 7.91 (m, 2 H) 8.09 (dd, *J*=6.78, 2.45 Hz, 1 H) 8.49 (d, *J*=1.70 Hz, 1 H) 8.83 (s, 1 H) 10.46 (s, 1 H) 11.37 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoro-methyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindoline-1,3-dione **Intermediate 427**

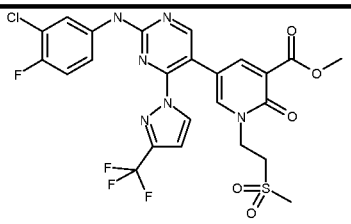
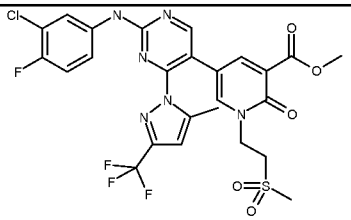
Ex	Compound	Data	SM
Example 1010	 Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinate	MS(ES): 523 (M+1) for $C_{22}H_{15}ClF_4N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.77 (s, 3 H) 3.95 (s, 3 H) 7.04 (d, *J*=2.64 Hz, 1 H) 7.42 (t, *J*=9.04 Hz, 1 H) 7.62 - 7.81 (m, 1 H) 7.86 (d, *J*=2.45 Hz, 1 H) 8.07 (dd, *J*=6.69, 2.54 Hz, 1 H) 8.28 (d, *J*=2.45 Hz, 1 H) 8.51 (s, 1 H) 8.80 (s, 1 H) 10.39 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoro-methyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 411**
Example 1011	 Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-methoxyethylamino)nicotinate	MS(ES): 566 (M+1) for $C_{24}H_{20}ClF_4N_7O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.30 (s, 3 H) 3.43 - 3.57 (m, 2 H) 3.65 (q, *J*=5.27 Hz, 2 H) 3.77 (s, 3 H) 7.02 (d, *J*=2.64 Hz, 1 H) 7.40 (t, *J*=9.14 Hz, 1 H) 7.63 - 7.83 (m, 2 H) 8.02 - 8.14 (m, 2 H) 8.17 (d, *J*=2.45 Hz, 1 H) 8.44 (d, *J*=1.70 Hz, 1 H) 8.79 (s, 1 H) 10.35 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoro-methyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and methyl 2-(2-methoxyethylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 428**

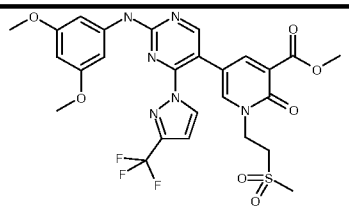
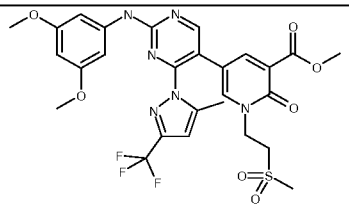
Ex	Compound	Data	SM
Example 1012	 Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-methoxyethylamino)nicotinate	MS(ES): 580 (M+1) for $C_{25}H_{22}ClF_4N_7O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.20 (s, 3 H) 3.28 (s, 3 H) 3.42 - 3.56 (m, 2 H) 3.62 (q, *J*=5.21 Hz, 2 H) 3.75 (s, 3 H) 6.74 (s, 1 H) 7.40 (t, *J*=9.14 Hz, 1 H) 7.50 (d, *J*=2.45 Hz, 1 H) 7.65 (ddd, *J*=9.04, 4.24, 2.73 Hz, 1 H) 7.99 - 8.15 (m, 2 H) 8.19 (d, *J*=2.45 Hz, 1 H) 8.96 (s, 1 H) 10.39 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 113** and methyl 2-(2-methoxyethylamino)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 428**
Example 1013	 Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 581 (M+1) for $C_{25}H_{21}ClF_4N_6O_4$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.19 (t, *J*=7.16 Hz, 3 H) 3.23 (s, 3 H) 3.50 - 3.67 (m, 2 H) 3.96 - 4.21 (m, 4 H) 7.07 (d, *J*=2.83 Hz, 1 H) 7.41 (t, *J*=9.14 Hz, 1 H) 7.56 - 7.79 (m, 2 H) 7.97 - 8.12 (m, 2 H) 8.55 (d, *J*=1.70 Hz, 1 H) 8.71 (s, 1 H) 10.36 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and ethyl 1-(2-methoxyethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate **Intermediate 429**

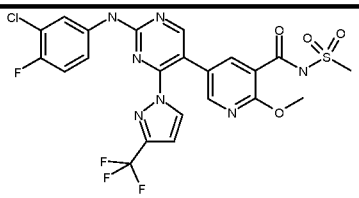
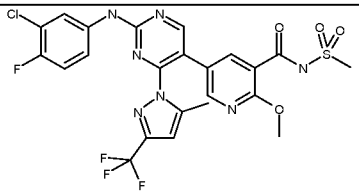
Ex	Compound	Data	SM
Example 1014	 Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 595 (M+1) for $C_{26}H_{23}ClF_4N_6O_4$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.19 (t, *J*=7.06 Hz, 3 H) 2.37 (s, 3 H) 3.22 (s, 3 H) 3.57 (t, *J*=5.37 Hz, 2 H) 3.96 - 4.24 (m, 4 H) 6.79 (s, 1 H) 7.21 - 7.54 (m, 2 H) 7.64 (ddd, *J*=9.04, 4.14, 2.64 Hz, 1 H) 8.03 (ddd, *J*=11.63, 6.55, 2.54 Hz, 2 H) 8.84 (s, 1 H) 10.40 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 113** and ethyl 1-(2-methoxyethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate **Intermediate 429**
Example 1015	 Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 567 (M+1) for $C_{24}H_{19}ClF_4N_6O_4$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.19 (t, *J*=7.16 Hz, 3 H) 3.55 - 3.76 (m, 2 H) 3.89 - 4.27 (m, 4 H) 4.92 (t, *J*=5.56 Hz, 1 H) 7.07 (d, *J*=2.45 Hz, 1 H) 7.41 (t, *J*=9.14 Hz, 1 H) 7.52 - 7.81 (m, 2 H) 7.91 - 8.16 (m, 2 H) 8.54 (d, *J*=1.88 Hz, 1 H) 8.72 (s, 1 H) 10.37 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoro-methyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and ethyl 1-(2-hydroxyethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate **Intermediate 430**

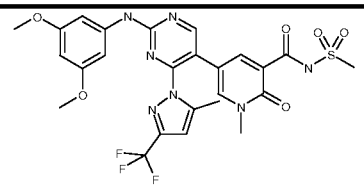
Ex	Compound	Data	SM
Example 1016	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(ethylsulfonyl)-2-methoxynicotinamide	MS(ES): 600 (M+1) for $C_{23}H_{18}ClF_4N_7O_4S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.26 (t, *J*=7.35 Hz, 3 H) 3.36 - 3.57 (m, 2 H) 3.96 (s, 3 H) 7.04 (d, *J*=2.64 Hz, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.61 - 7.87 (m, 2 H) 8.09 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.19 (d, *J*=2.07 Hz, 1 H) 8.47 (s, 1 H) 8.79 (s, 1 H) 10.41 (s, 1 H) 11.65 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and N-(ethylsulfonyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinamide **Intermediate 431**
Example 1017	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(ethylsulfonyl)-2-methoxynicotinamide	MS(ES): 614 (M+1) for $C_{24}H_{20}ClF_4N_7O_4S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.26 (t, 3 H) 2.33 (s, 3 H) 3.36 - 3.55 (m, 2 H) 3.93 (s, 3 H) 6.76 (s, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.53 - 7.77 (m, 2 H) 7.93 - 8.21 (m, 2 H) 8.96 (s, 1 H) 10.44 (s, 1 H) 11.67 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 113** and N-(ethylsulfonyl)-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinamide **Intermediate 431**

Ex	Compound	Data	SM
Example 1018	 Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(4-isopropylpiperazin-1-yl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 677 (M+1) for $C_{31}H_{33}ClF_4N_8O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.94 (d, *J*=6.40 Hz, 6 H) 2.25 - 2.47 (m, 14 H) 3.65 (s, 3 H) 4.02 (t, *J*=6.12 Hz, 2 H) 6.80 (s, 1 H) 7.26 (d, *J*=2.64 Hz, 1 H) 7.41 (t, *J*=9.04 Hz, 1 H) 7.63 (ddd, *J*=9.09, 4.19, 2.73 Hz, 1 H) 8.01 - 8.19 (m, 2 H) 8.87 (s, 1 H) 10.41 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 113** and methyl 1-(2-(4-isopropylpiperazin-1-yl)ethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate **Intermediate 433**
Example 1019	 5-(2-(3,5-Dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-N-(methylsulfonyl)-2-oxo-1,2-dihydropyridine-3-carboxamide	MS(ES): 594 (M+1) for $C_{24}H_{22}F_3N_7O_6S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.35 (s, 3 H) 3.65 (s, 3 H) 3.75 (s, 6 H) 6.22 (t, *J*=2.17 Hz, 1 H) 6.95 - 7.23 (m, 3 H) 8.09 (d, *J*=2.64 Hz, 1 H) 8.44 (d, *J*=2.83 Hz, 1 H) 8.52 - 8.65 (m, 1 H) 8.74 (s, 1 H) 10.17 (s, 1 H) 12.79 (s, 1 H)	5-Bromo-N-(3,5-dimethoxyphenyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine **Intermediate 215** and 1-methyl-N-(methylsulfonyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxamide **Intermediate 432**

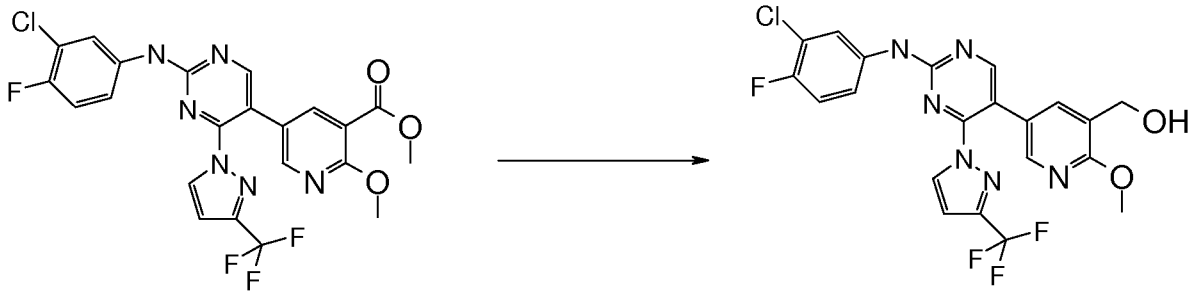
Ex	Compound	Data	SM
Example 1020	 Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 615 (M+1) for $C_{24}H_{19}ClF_4N_6O_5S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.06 (s, 3 H) 3.61 (t, *J*=6.88 Hz, 2 H) 3.68 (s, 3 H) 4.38 (t, *J*=6.88 Hz, 2 H) 7.09 (d, *J*=2.64 Hz, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.60 - 7.79 (m, 2 H) 8.06 (dd, *J*=6.69, 2.54 Hz, 1 H) 8.20 (d, *J*=2.83 Hz, 1 H) 8.57 (d, *J*=2.07 Hz, 1 H) 8.72 (s, 1 H) 10.38 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and methyl 1-(2-(methylsulfonyl)ethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate **Intermediate 434**
Example 1021	 Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 629 (M+1) for $C_{25}H_{21}ClF_4N_6O_5S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.36 (s, 3 H) 3.07 (s, 3 H) 3.59 (t, *J*=6.78 Hz, 2 H) 3.65 (s, 3 H) 4.37 (t, *J*=6.78 Hz, 2 H) 6.80 (s, 1 H) 7.22 (d, *J*=2.64 Hz, 1 H) 7.41 (t, *J*=9.04 Hz, 1 H) 7.64 (ddd, *J*=9.04, 4.24, 2.73 Hz, 1 H) 8.05 (dd, *J*=6.69, 2.54 Hz, 1 H) 8.26 (d, *J*=2.83 Hz, 1 H) 8.87 (s, 1 H) 10.42 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 113** and methyl 1-(2-(methylsulfonyl)ethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate **Intermediate 434**

Ex	Compound	Data	SM
Example 1022	 Methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 623 (M+1) for $C_{26}H_{25}F_3N_6O_7S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.06 (s, 3 H) 3.61 (t, *J*=6.88 Hz, 2 H) 3.68 (s, 3 H) 3.74 (s, 6 H) 4.38 (t, *J*=6.78 Hz, 2 H) 6.21 (t, *J*=2.26 Hz, 1 H) 7.08 (d, *J*=2.26 Hz, 3 H) 7.66 (d, *J*=2.64 Hz, 1 H) 8.21 (d, *J*=2.64 Hz, 1 H) 8.54 (dd, *J*=2.64, 0.75 Hz, 1 H) 8.69 (s, 1 H) 10.14 (s, 1 H)	5-Bromo-N-(3,5-dimethoxyphenyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine **Intermediate 215** and methyl 1-(2-(methylsulfonyl)ethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate **Intermediate 434**
Example 1023	 Methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 637 (M+1) for $C_{27}H_{27}F_3N_6O_7S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.33 (s, 3 H) 3.07 (s, 3 H) 3.59 (t, *J*=6.69 Hz, 2 H) 3.65 (s, 3 H) 3.72 (s, 6 H) 4.37 (t, *J*=6.97 Hz, 2 H) 6.21 (t, *J*=2.17 Hz, 1 H) 6.78 (s, 1 H) 7.03 (d, *J*=2.26 Hz, 2 H) 7.22 (d, *J*=2.83 Hz, 1 H) 8.26 (d, *J*=2.83 Hz, 1 H) 8.85 (s, 1 H) 10.18 (s, 1 H)	5-Bromo-N-(3,5-dimethoxyphenyl)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine **Intermediate 216** and methyl 1-(2-(methylsulfonyl)ethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate **Intermediate 434**

Ex	Compound	Data	SM
Example 1024	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxy-N-(methylsulfonyl)nicotinamide	MS(ES): 586 (M+1) for $C_{22}H_{16}ClF_4N_7O_4S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.31 (s, 3 H) 3.97 (s, 3 H) 7.04 (d, *J*=2.64 Hz, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.72 (dd, *J*=4.80, 2.73 Hz, 1 H) 7.85 (d, *J*=2.45 Hz, 1 H) 8.09 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.17 (d, *J*=2.64 Hz, 1 H) 8.47 (s, 1 H) 8.79 (s, 1 H) 10.41 (s, 1 H) 11.68 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and 2-methoxy-N-(methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinamide **Intermediate 368**
Example 1025	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxy-N-(methylsulfonyl)nicotinamide	MS(ES): 600 (M+1) for $C_{23}H_{18}ClF_4N_7O_4S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.34 (s, 3 H) 3.32 (s, 3 H) 3.94 (s, 3 H) 6.78 (s, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.55 - 7.77 (m, 2 H) 7.89 - 8.21 (m, 2 H) 8.96 (s, 1 H) 10.44 (s, 1 H) 11.71 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 113** and 2-methoxy-N-(methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinamide **Intermediate 368**

Ex	Compound	Data	SM
Example 1026	 5-(2-(3,5-Dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-N-(methylsulfonyl)-2-oxo-1,2-dihydropyridine-3-carboxamide	MS(ES): 608 (M+1) for $C_{25}H_{24}F_3N_7O_6S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.46 (br. s., 3 H) 3.28 (s, 3 H) 3.62 (br. s., 3 H) 3.73 (s, 6 H) 6.22 (t, *J*=2.17 Hz, 1 H) 6.80 (s, 1 H) 7.03 (d, *J*=2.07 Hz, 2 H) 7.72 (br. s., 1 H) 8.40 (br. s., 1 H) 8.87 (s, 1 H) 10.17 (s, 1 H) 12.68 (s, 1 H)	5-Bromo-N-(3,5-dimethoxyphenyl)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine **Intermediate 216** and 1-methyl-N-(methylsulfonyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxamide **Intermediate 432**

Example 1027: (5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxypyridin-3-yl)methanol



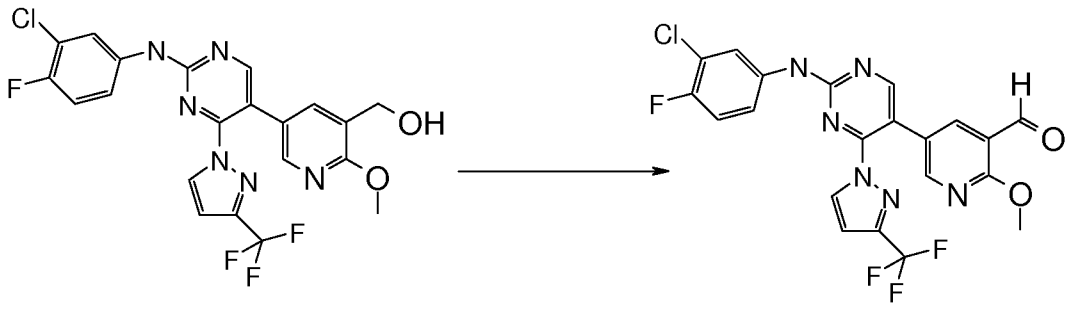
Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinate (**Example 1010**, 0.788 g mg, 1.51 mmol) was dissolved in THF(10 mL) to give a yellow solution. The reaction mixture was cooled to -40 °C. 1M DIBAL-H in toluene (9 mL, 9 mmol) was slowly added to the reaction mixture. The reaction was allowed to warm up to room temperature overnight. The reaction was diluted with EtOAc and washed with 1M NH_4Cl. Purification by flash chromatography, silica gel, 40-100% ethyl acetate in hexanes

gave a crude solid. Trituration with hexane / ether and filtration gave the title compound (103 mg).

MS (Electrospray): 495.83, (MH^+) for $C_{21}H_{15}ClF_4N_6O_2$

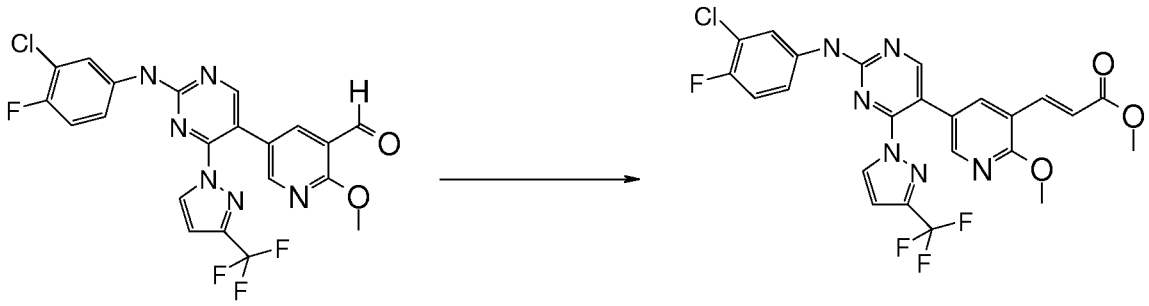
^{1}H NMR (300 MHz, DMSO-d_6) δ : 3.88 (s, 3 H) 5.15 (s, 2 H) 7.00 (d, *J*=2.45 Hz, 1 H) 7.20 - 7.47 (m, 2H) 7.59 - 7.83 (m, 1 H) 7.90 (d, *J*=2.26 Hz, 1 H) 7.99 - 8.23 (m, 1 H) 8.38 (d, *J*=1.51 Hz, 1 H) 8.76 (s, 1 H), 10.39 (s, 1 H)

Example 1028: 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinaldehyde



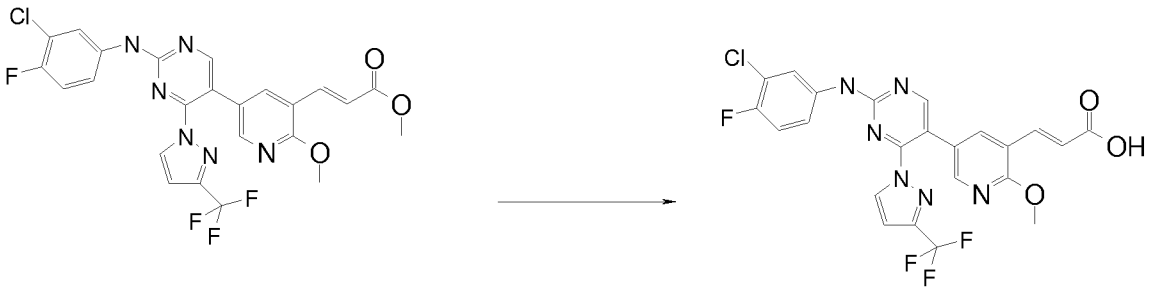
(5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxypyridin-3-yl)methanol (243 mg, 0.49 mmol) **Example 1027** and manganese dioxide (427 mg, 4.91 mmol) were combined in dichloromethane to give a black suspension. The reaction mixture was allowed to stir at room temperature for 6 hours. Additional manganese dioxide (427 mg, 4.91 mmol) was added and the mixture was allowed to stir for 48 hours. The mixture was filtered through celite and washed with methanol and dichloromethane. The filtrate was concentrated to yield the title compound (145 mg). MS (Electrospray): 493.81 (MH^+) for $C_{21}H_{13}ClF_4N_6O_2$

Example 1029: (E)-methyl 3-(5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxypyridin-3-yl)acrylate



Methyl 2-(diethoxyphosphoryl)acetate (68.0 mg, 0.32 mmol) and NaH (17.65 mg, 0.44 mmol) were combined in THF (2 ml) to give a colorless solution. The reaction mixture was allowed to stir for 5 minutes then added to a solution of 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinaldehyde (145 mg, 0.29 mmol) **Example 1028** in THF (2 ml). The mixture was allowed to stir at RT for 45 min, water and ethyl acetate were added. The organic layer was then dried with MgSO4 and concentrated. The solid was purified by flash chromatography over silica gel. The product was eluted using 30% ethyl acetate in hexanes to give the title compound (114 mg). MS (Electrospray): 548.88 (MH^+) for C24H17ClF4N6O3

Example 1030: (E)-3-(5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxypyridin-3-yl)acrylic acid

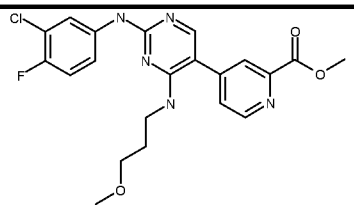


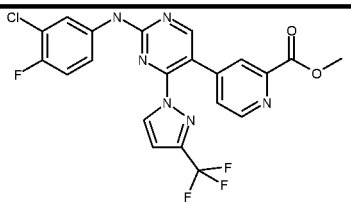
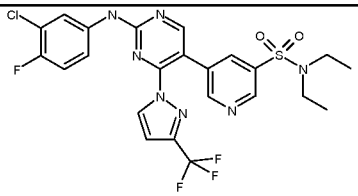
(E)-methyl 3-(5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxypyridin-3-yl)acrylate **Example 1029** (114 mg, 0.21 mmol) was dissolved in Dioxane (5 mL) to give a yellow solution. 1M NaOH (0.312 mL, 0.31 mmol) was added at room temp and then allowed to stir overnight. The reaction mixture was acidified with 1M HCl then extracted with ethyl acetate. The ethyl acetate was evaporated and the solid purified using reverse phase chromatography (C18, 20 to 95%.CH_3CN / H_2O / 0.1% Trifluoroacetic acid) to yield the title compound (28 mg).

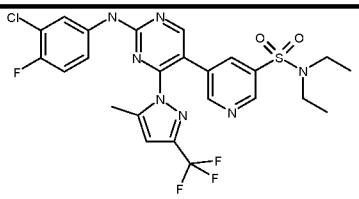
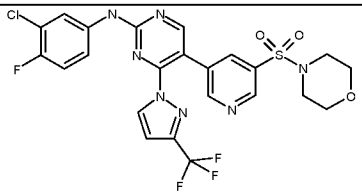
MS (Electrospray): 535 (MH^+) for C23H15ClF4N6O3

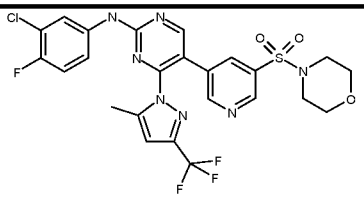
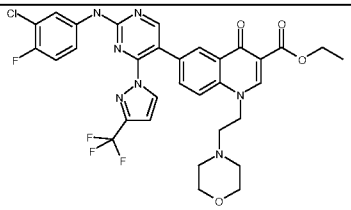
^{1}H NMR (300 MHz, DMSO-d_6) δ : 3.92 - 4.02 (m, 3 H) 6.49 (d, J=16.01 Hz, 1 H) 7.04 (d, J=2.64 Hz, 1 H) 7.42 (t, J=9.14 Hz, 1 H) 7.64 (d, J=16.20 Hz, 2 H) 7.68 - 7.77 (m, 1 H) 7.91 (d, J=2.26 Hz, 1 H) 8.00 - 8.20(m, 2 H) 8.48 (s, 1 H) 8.82 (s, 1 H) 10.40 (s, 1 H) 12.45 (br. s., 1 H)

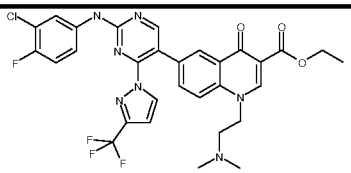
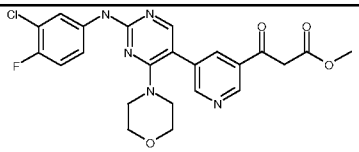
The following examples were prepared using the general method described for **Example 158** using [1,1′-bis (diphenylphosphino) ferrocene] dichloropalladium(II), sodium carbonate and the starting materials (SM) indicated.

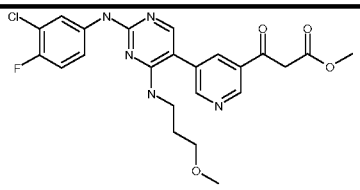
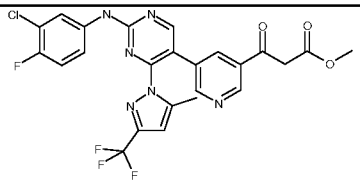
Ex	Compound	Data	SM
Example 1031	 Methyl 4-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)picolinate	MS(ES): 446 (M+1) for $C_{21}H_{21}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.74 - 1.97 (m, 2 H) 3.21 (s, 3 H) 3.37 - 3.54 (m, 4 H) 3.90 (s, 3 H) 7.07 (t, *J*=4.90 Hz, 1 H) 7.31 (t, *J*=9.14 Hz, 1 H) 7.52 - 7.75 (m, 2 H) 7.94 (s, 1 H) 8.05 (d, *J*=0.94 Hz, 1 H) 8.24 (dd, *J*=6.97, 2.45 Hz, 1 H) 8.73 (d, *J*=5.09 Hz, 1 H) 9.56 (s, 1 H)	5-Bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)pyrimidine-2,4-diamine **Intermediate 119** and methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinate

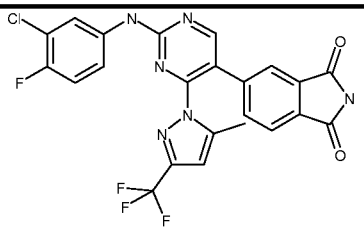
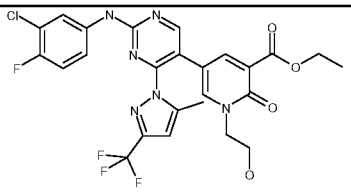
Ex	Compound	Data	SM
Example 1032	 Methyl 4-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)picolinate	MS(ES): 493 (M+1) for $C_{21}H_{13}ClF_4N_6O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.85 (s, 3 H) 7.08 (d, *J*=2.64 Hz, 1 H) 7.32 - 7.59 (m, 2 H) 7.65 - 7.82 (m, 2 H) 8.07 (dd, *J*=6.69, 2.54 Hz, 1 H) 8.55 (d, *J*=1.70 Hz, 1 H) 8.68 (d, *J*=4.90 Hz, 1 H) 8.85 (s, 1 H) 10.54 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoro-methyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinate
Example 1033	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N,N-diethylpyridine-3-sulfonamide	MS(ES): 570 (M+1) for $C_{23}H_{20}ClF_4N_7O_2S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.04 (t, 6 H) 3.14 (q, *J*=7.16 Hz, 4 H) 7.05 (d, *J*=2.83 Hz, 1 H) 7.44 (t, *J*=9.14 Hz, 1 H) 7.74 (ddd, *J*=9.00, 4.10, 2.73 Hz, 1 H) 7.95 - 8.18 (m, 2 H) 8.57 (d, *J*=1.70 Hz, 1 H) 8.70 (d, *J*=2.07 Hz, 1 H) 8.81 (s, 1 H) 8.90 (d, *J*=2.07 Hz, 1 H) 10.49 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoro-methyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and N,N-diethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide **Intermediate 412**

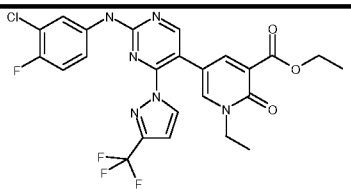
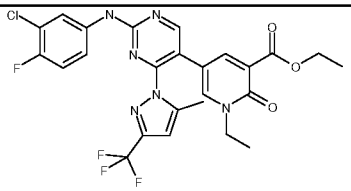
Ex	Compound	Data	SM
Example 1034	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N,N-diethylpyridine-3-sulfonamide	MS(ES): 584 (M+1) for $C_{24}H_{22}ClF_4N_7O_2S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.03 (t, 6 H) 2.50 (s, 3H) 3.11 (q, *J*=7.10 Hz, 4 H) 6.79 (s, 1 H) 7.44 (t, *J*=9.14 Hz, 1 H) 7.56 - 7.75 (m, 1 H) 7.87 (t, *J*=1.88 Hz, 1 H) 8.07 (dd, *J*=6.59, 2.26 Hz, 1 H) 8.59 (d, *J*=1.88 Hz, 1 H) 8.87 (d, *J*=2.07 Hz, 1 H) 8.96 (s, 1 H) 10.50 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 113** and N,N-diethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-sulfonamide **Intermediate 412**
Example 1035	 N-(3-chloro-4-fluorophenyl)-5-(5-(morpholinosulfonyl)pyridin-3-yl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine	MS(ES): (M+1) for $C_{23}H_{18}ClF_4N_7O_3S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.79 - 3.00 (m, 4 H) 3.49 - 3.76 (m, 4 H) 7.06 (d, *J*=2.64 Hz, 1 H) 7.44 (t, *J*=9.14 Hz, 1 H) 7.63 - 7.83 (m, 1 H) 7.96 - 8.15 (m, 2 H) 8.59 (d, *J*=1.70 Hz, 1 H) 8.77 (d, *J*=2.07 Hz, 1 H) 8.80 - 8.91 (m, 2 H) 10.49 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoro-methyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-ylsulfonyl)morpholine **Intermediate 413**

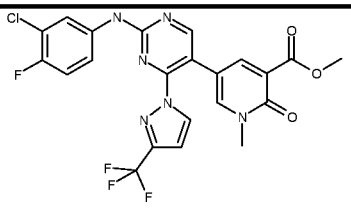
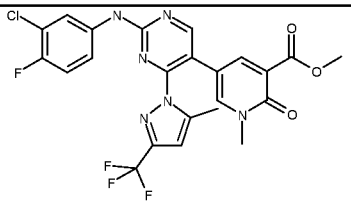
Ex	Compound	Data	SM
Example 1036	 N-(3-chloro-4-fluorophenyl)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-5-(5-(morpholinosulfonyl)pyridin-3-yl)pyrimidin-2-amine	MS(ES): 598 (M+1) for $C_{24}H_{20}ClF_4N_7O_3S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.54 (s, 3 H) 2.77 - 2.96 (m, 4 H) 3.52 - 3.77 (m, 4 H) 6.79 (s, 1 H) 7.44 (t, *J*=9.14 Hz, 1 H) 7.66 (ddd, *J*=8.95, 4.24, 2.83 Hz, 1 H) 7.86 (t, *J*=2.17 Hz, 1 H) 7.98 - 8.18 (m, 1 H) 8.67 (d, *J*=2.07 Hz, 1 H) 8.82 (d, *J*=2.07 Hz, 1 H) 8.98 (s, 1 H) 10.50 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 113** and 4-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-ylsulfonyl)morpholine **Intermediate 413**
Example 1037	 Ethyl 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-morpholinoethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate	MS(ES): 686 (M+1) for $C_{32}H_{28}ClF_4N_7O_4$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.29 (t, *J*=7.06 Hz, 3 H) 2.33 - 2.45 (m, 4 H) 2.60 (t, *J*=5.46 Hz, 2 H) 3.43 - 3.61 (m, 4 H) 4.23 (q, *J*=7.03 Hz, 2 H) 4.49 (t, *J*=4.99 Hz, 2 H) 7.00 (d, *J*=2.64 Hz, 1 H) 7.32 - 7.59 (m, 2 H) 7.67 - 7.89 (m, 2 H) 8.05 (d, *J*=2.26 Hz, 1 H) 8.12 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.44 (d, *J*=1.51 Hz, 1 H) 8.62 (s, 1 H) 8.84 (s, 1 H) 10.44 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and Ethyl 1-(2-methoxyethyl)-4-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydroquinoline-3-carboxylate **Intermediate 134**

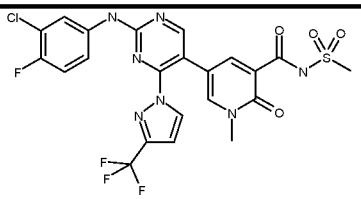
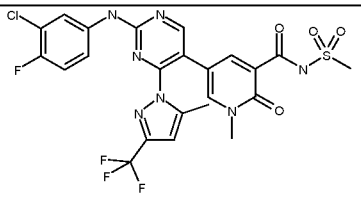
Ex	Compound	Data	SM
Example 1038	 Ethyl 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(dimethylamino)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate	MS(ES): 644 (M+1) for $C_{30}H_{26}ClF_4N_7O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.29 (t, *J*=7.06 Hz, 3 H) 2.18 (s, 6 H) 2.57 (t, *J*=5.56 Hz, 2 H) 4.23 (q, *J*=7.03 Hz, 2 H) 4.47 (t, *J*=5.09 Hz, 2 H) 7.00 (d, *J*=2.64 Hz, 1 H) 7.32 - 7.62 (m, 2 H) 7.63 - 7.89 (m, 2 H) 7.98 - 8.19 (m, 2 H) 8.45 (d, *J*=1.88 Hz, 1 H) 8.61 (s, 1 H) 8.84 (s, 1 H) 10.44 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and ethyl 1-(2-(dimethylamino)ethyl)-4-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydroquinoline-3-carboxylate **Intermediate 414**
Example 1039	 Methyl 3-(5-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)pyridin-3-yl)-3-oxopropanoate	MS(ES): 486 (M+1) for $C_{23}H_{21}ClFN_5O_4$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.09 - 3.42 (m, 4 H) 3.46 - 3.61 (m, 4 H) 3.68 (s, 3 H) 4.34 (s, 2 H) 7.38 (t, *J*=9.14 Hz, 1 H) 7.59 (ddd, *J*=9.09, 4.19, 2.73 Hz, 1 H) 8.07 (dd, *J*=6.88, 2.54 Hz, 1 H) 8.18 (s, 1 H) 8.38 (t, *J*=2.17 Hz, 1 H) 8.94 (d, *J*=2.26 Hz, 1 H) 9.07 (d, *J*=2.07 Hz, 1 H) 10.01 (s, 1 H)	5-Bromo-N-(3-chloro-4-fluorophenyl)-4-morpholin-4-ylpyrimidin-2-amine **Intermediate 111** and methyl 3-oxo-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)propanoate **Intermediate 417**

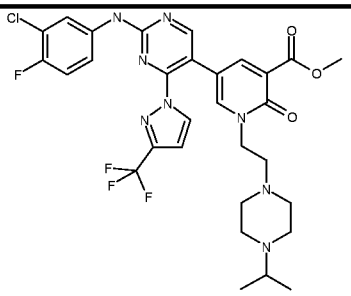
Ex	Compound	Data	SM
Example 1040	 Methyl 3-(5-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)pyridin-3-yl)-3-oxopropanoate	MS(ES): 488 (M+1) for $C_{23}H_{23}ClFN_5O_4$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.64 - 1.94 (m, 2 H) 3.19 (s, 3 H) 3.27 - 3.55 (m, 4 H) 3.68 (s, 3 H) 4.35 (s, 2 H) 7.31 - 7.47 (m, 1 H) 7.57 (ddd, *J*=9.00, 4.19, 2.64 Hz, 1 H) 7.71 (br. s., 1 H) 7.85 - 7.98 (m, 1 H) 8.09 (dd, *J*=6.78, 2.45 Hz, 1 H) 8.30 (t, *J*=2.17 Hz, 1 H) 8.83 (d, *J*=2.07 Hz, 1 H) 9.14 (d, *J*=2.07 Hz, 1 H) 9.99 (br. s., 1 H)	5-Bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(3-methoxypropyl)pyrimidine-2,4-diamine **Intermediate 119** and methyl 3-oxo-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)propanoate **Intermediate 417**
Example 1041	 Methyl 3-(5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)pyridin-3-yl)-3-oxopropanoate	MS(ES): 549 (M+1) for $C_{24}H_{17}ClF_4N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.45 (s, 3 H) 3.65 (s, 3 H) 4.24 (s, 2 H) 6.78 (s, 1 H) 7.43 (t, *J*=9.14 Hz, 1 H) 7.66 (ddd, *J*=8.95, 4.14, 2.73 Hz, 1 H) 7.81 - 8.16 (m, 2 H) 8.48 (d, *J*=2.07 Hz, 1 H) 8.85 - 9.16 (m, 2 H) 10.48 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 113** and methyl 3-oxo-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)propanoate **Intermediate 417**

Ex	Compound	Data	SM
Example 1042	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)isoindoline-1,3-dione	MS(ES): 517 (M+1) for $C_{23}H_{13}ClF_4N_6O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.41 (s, 3 H) 6.76 (s, 1 H) 7.33 - 7.59 (m, 3 H) 7.67 (ddd, *J*=9.09, 4.19, 2.73 Hz, 1 H) 7.77 (d, *J*=7.72 Hz, 1 H) 8.07 (dd, *J*=6.78, 2.45 Hz, 1 H) 8.98 (s, 1 H) 10.48 (s, 1 H) 11.36 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 113** and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindoline-1,3-dione **Intermediate 427**
Example 1043	 Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 581 (M+1) for $C_{25}H_{21}ClF_4N_6O_4$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.19 (t, *J*=7.06 Hz, 3 H) 2.35 (s, 3 H) 3.54 - 3.70 (m, 2 H) 3.92 - 4.19 (m, 4 H) 4.91 (t, *J*=5.18 Hz, 1 H) 6.79 (s, 1 H) 7.20 - 7.47 (m, 2 H) 7.57 - 7.73 (m, 1 H) 7.90 - 8.18 (m, 2 H) 8.86 (s, 1 H) 10.40 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 113** and ethyl 1-(2-hydroxyethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate **Intermediate 430**

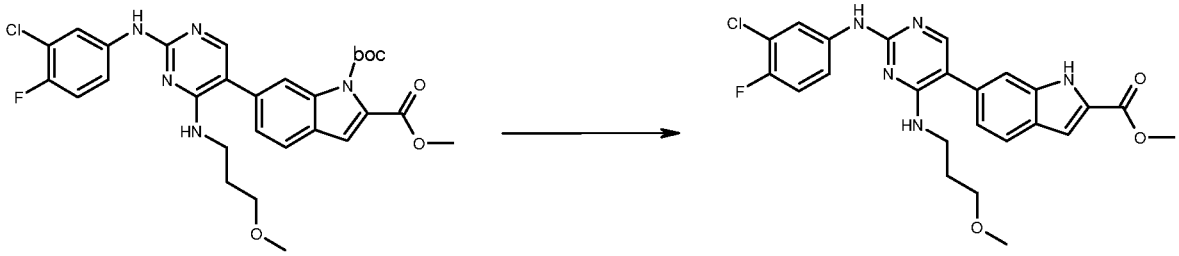
Ex	Compound	Data	SM
Example 1044	 Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-ethyl-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 551 (M+1) for $C_{24}H_{19}ClF_4N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.18 - 1.33 (m, 6 H) 3.96 (q, *J*=7.03 Hz, 2 H) 4.15 (q, *J*=7.16 Hz, 2 H) 7.08 (d, *J*=2.64 Hz, 1 H) 7.41 (t, *J*=9.14 Hz, 1 H) 7.62 (d, *J*=2.64 Hz, 1 H) 7.70 (ddd, *J*=9.00, 4.29, 2.73 Hz, 1 H) 7.96 - 8.16 (m, 2 H) 8.56 (dd, *J*=2.54, 0.85 Hz, 1 H) 8.78 (s, 1 H) 10.36 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoro-methyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and ethyl 1-ethyl-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate **Intermediate 370**
Example 1045	 Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-ethyl-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 565 (M+1) for $C_{25}H_{21}ClF_4N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.16 - 1.24 (m, 6 H) 2.40 (s, 3 H) 3.92 - 4.28 (m, 4 H) 6.80 (s, 1 H) 7.25 - 7.49 (m, 2 H) 7.64 (ddd, *J*=9.14, 4.24, 2.64 Hz, 1 H) 7.97 - 8.15 (m, 2 H) 8.92 (s, 1 H) 10.39 (s, 1 H)	5-bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 113** and ethyl 1-ethyl-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate **Intermediate 370**

Ex	Compound	Data	SM
Example 1046	 Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 523 (M+1) for $C_{22}H_{15}ClF_4N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.50 (s, 3 H) 3.68 (s, 3 H) 7.08 (d, *J*=2.64 Hz, 1 H) 7.41 (t, *J*=9.14 Hz, 1 H) 7.57 - 7.79 (m, 2 H) 8.05 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.16 (d, *J*=2.64 Hz, 1 H) 8.57 (dd, *J*=2.64, 0.94 Hz, 1 H) 8.75 (s, 1 H) 10.36 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoro-methyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and methyl 1-methyl-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate **Intermediate 369**
Example 1047	 Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 537 (M+1) for $C_{23}H_{17}ClF_4N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.38 (s, 3 H) 3.48 (s, 3 H) 3.65 (s, 3 H) 6.80 (s, 1 H) 7.27 (d, *J*=2.64 Hz, 1 H) 7.41 (t, *J*=9.04 Hz, 1 H) 7.64 (ddd, *J*=9.04, 4.14, 2.83 Hz, 1 H) 8.04 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.16 (d, *J*=2.64 Hz, 1 H) 8.89 (s, 1 H) 10.39 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 113** and methyl 1-methyl-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate **Intermediate 369**

Ex	Compound	Data	SM
Example 1048	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-N-(methylsulfonyl)-2-oxo-1,2-dihydropyridine-3-carboxamide	MS(ES): 586 (M+1) for $C_{22}H_{16}ClF_4N_7O_4S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.35 (s, 3 H) 3.65 (s, 3 H) 7.09 (d, *J*=2.64 Hz, 1 H) 7.43 (t, *J*=9.14 Hz, 1 H) 7.72 (ddd, *J*=9.09, 4.29, 2.64 Hz, 1 H) 7.94 - 8.19 (m, 2 H) 8.43 (d, *J*=2.45 Hz, 1 H) 8.61 (d, *J*=1.70 Hz, 1 H) 8.76 (s, 1 H) 10.40 (s, 1 H) 12.79 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and 1-methyl-N-(methylsulfonyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxamide **Intermediate 432**
Example 1049	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-N-(methylsulfonyl)-2-oxo-1,2-dihydropyridine-3-carboxamide	MS(ES): 600 (M+1) for $C_{23}H_{18}ClF_4N_7O_4S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.49 (br. s., 3 H) 3.33 (s, 3 H) 3.63 (s, 3 H) 6.82 (s, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.54 - 7.78 (m, 2 H) 8.04 (dd, *J*=6.78, 2.45 Hz, 1 H) 8.40 (d, *J*=2.45 Hz, 1 H) 8.90 (s, 1 H) 10.41 (s, 1 H) 12.68 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 113** and 1-methyl-N-(methylsulfonyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxamide **Intermediate 432**

Ex	Compound	Data	SM
Example 1050	 Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(4-isopropylpiperazin-1-yl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 663 (M+1) for $C_{30}H_{31}ClF_4N_8O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.92 (d, *J*=5.65 Hz, 6 H) 2.30 - 2.70 (m, 14 H) 4.03 (t, *J*=5.65 Hz, 2 H) 7.08 (d, *J*=2.64 Hz, 1 H) 7.41 (t, *J*=9.14 Hz, 1 H) 7.59 - 7.78 (m, 2 H) 7.96 - 8.17 (m, 2 H) 8.57 (d, *J*=1.70 Hz, 1 H) 8.71 (s, 1 H) 10.36 (s, 1 H)	5-Bromo-*N*-(3-chloro-4-fluorophenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine **Intermediate 115** and methyl 1-(2-(4-isopropylpiperazin-1-yl)ethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate **Intermediate 433**

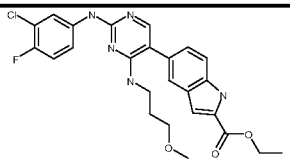
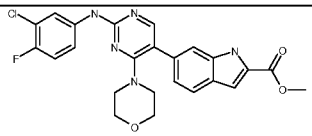
Example 1051: methyl 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)-1H-indole-2-carboxylate

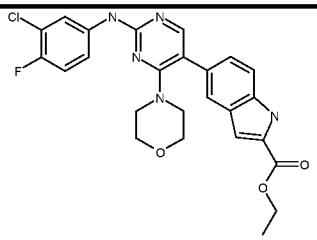


1-tert-butyl 2-methyl 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)-1H-indole-1,2-dicarboxylate (**Example 983**, 104 mg, 0.18 mmol) was suspended in DCM (4 mL). The solution was then treated with trifluoroacetic acid (0.274 ml, 3.56 mmol) and stirred at room temperature for 1 hr. The solvent was removed at reduced pressure and the residue was

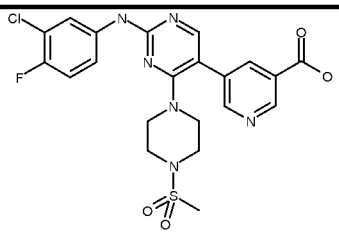
washed with Et_2O/hexanes to afford methyl 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)-1H-indole-2-carboxylate in 98% yield (84 mg).
MS(ES): 484 (M+1) for $C_{24}H_{23}ClFN_5O_3$.
^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.60 - 1.93 (m, 2 H) 3.13 (s, 3 H) 3.23 - 3.55 (m, 4 H) 3.89 (s, 3 H) 7.06 (dd, *J*=8.29, 1.32 Hz, 1 H) 7.23 (d, *J*=0.94 Hz, 1 H) 7.31 - 7.65 (m, 3 H) 7.80 (dd, *J*=4.90, 3.39 Hz, 2 H) 7.89 - 8.06 (m, 1 H) 8.10 (s, 1 H) 10.34 (s, 1 H) 12.16 (s, 1 H).

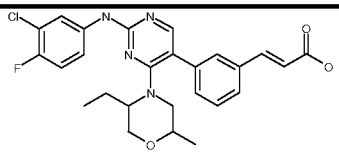
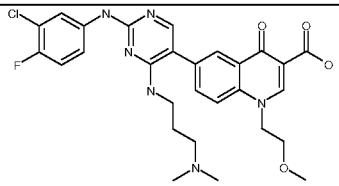
The following examples were prepared using the general method described above for **Example 1051** using the starting material (SM) indicated.

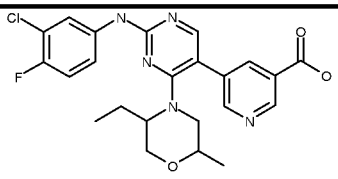
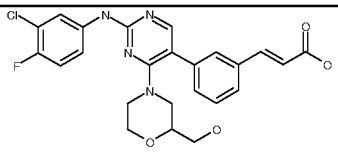
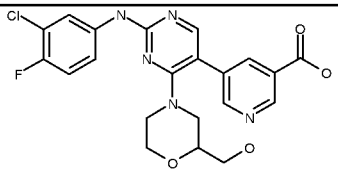
Ex	Compound	Data	SM
Example 1052	 Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)-1H-indole-2-carboxylate	MS(ES): 498 (M+1) for $C_{25}H_{25}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.34 (t, *J*=7.16 Hz, 3 H) 1.61 - 1.91 (m, 2 H) 3.12 (s, 3 H) 3.23 - 3.55 (m, 4 H) 4.35 (q, *J*=6.97 Hz, 2 H) 7.14 - 7.34 (m, 2 H) 7.34 - 7.65 (m, 3 H) 7.68 (s, 1 H) 7.77 (d, *J*=1.51 Hz, 1 H) 7.84 - 8.12 (m, 2 H) 10.24 (s, 1 H) 10.87 (none, 1 H) 12.09 (s, 1 H)	1-tert-butyl 2-ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)-1H-indole-1,2-dicarboxylate **Example 984**
Example 1053	 Methyl 6-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)-1H-indole-2-carboxylate	MS(ES): 482 (M+1) for $C_{24}H_{21}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 3.14 - 3.42 (m, 4 H) 3.45 - 3.60 (m, 4 H) 3.87 (s, 3 H) 7.04 - 7.26 (m, 2 H) 7.36 (t, *J*=9.04 Hz, 1 H) 7.51 (s, 1 H) 7.53 - 7.69 (m, 1 H) 7.72 (d, *J*=8.29 Hz, 1 H) 7.94 - 8.21 (m, 2 H) 9.77 (s, 1 H) 12.04 (s, 1 H)	1-tert-butyl 2-methyl 6-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)-1H-indole-1,2-dicarboxylate **Example 985**

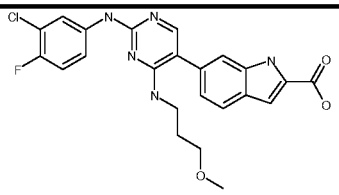
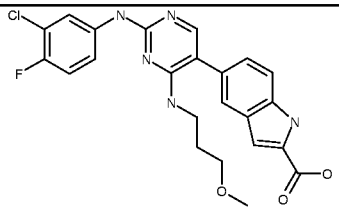
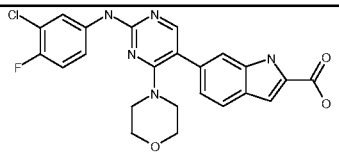
Ex	Compound	Data	SM
Example 1054	 Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)-1H-indole-2-carboxylate	MS(ES): 496 (M+1) for $C_{25}H_{23}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.34 (t, *J*=7.06 Hz, 3 H) 3.16 - 3.39 (m, 4 H) 3.42 - 3.64 (m, 4 H) 4.34 (q, *J*=6.97 Hz, 2 H) 7.09 - 7.26 (m, 1 H) 7.26 - 7.46 (m, 2 H) 7.44 - 7.66 (m, 2 H) 7.71 (s, 1 H) 7.89 - 8.21 (m, 2 H) 9.84 (s, 1 H) 12.02 (s, 1 H)	1-tert-butyl 2-ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)-1H-indole-1,2-dicarboxylate **Example 986**

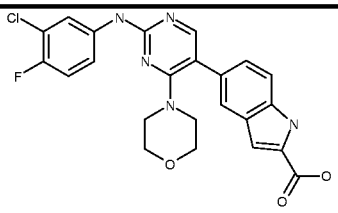
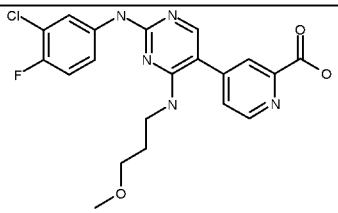
The following examples were prepared using the general method described for **Example 214** using 1N sodium hydroxide, THF/MeOH, and the starting material (SM) indicated.

Ex	Compound	Data	SM
Example 1055	 5-(2-(3-chloro-4-fluorophenylamino)-4-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-5-yl)nicotinic acid	MS(ES): 507 (M+1) for $C_{21}H_{20}ClFN_6O_4S$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 2.86 (s, 3 H) 2.98 - 3.19 (m, 4 H) 3.29 - 3.47 (m, 4 H) 7.35 (t, *J*=9.14 Hz, 1 H) 7.53 - 7.75 (m, 1 H) 8.12 (dd, *J*=6.97, 2.64 Hz, 1 H) 8.20 (s, 1 H) 8.34 (t, *J*=2.17 Hz, 1 H) 8.91 (d, *J*=2.07 Hz, 1 H) 9.00 (d, *J*=2.07 Hz, 1 H) 9.78 (s, 1 H) 13.56 (s, 1 H)	ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-5-yl)nicotinate **Example 976**

Ex	Compound	Data	SM
Example 1056	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(5-ethyl-2-methylmorpholino)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 497 (M+1) for $C_{26}H_{26}ClFN_4O_3$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 0.56 (t, *J*=7.35 Hz, 3 H) 1.02 (d, *J*=6.03 Hz, 3 H) 1.35 - 1.83 (m, 2 H) 2.65 - 2.87 (m, 1 H) 3.40 - 3.86 (m, 5 H) 6.60 (d, *J*=16.01 Hz, 1 H) 7.33 (t, *J*=9.14 Hz, 1 H) 7.40 - 7.70 (m, 5 H) 7.74 (s, 1 H) 7.99 (s, 1 H) 8.17 (dd, *J*=6.88, 2.35 Hz, 1 H) 9.63 (s, 1 H) 12.45 (s, 1 H)	(E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(5-ethyl-2-methylmorpholino)pyrimidin-5-yl)phenyl)acrylate **Example 979**
Example 1057	 6-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(dimethylamino)propylamino)pyrimidin-5-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	MS(ES): 569 (M+1) for $C_{28}H_{30}ClFN_6O_4$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.82 - 2.07 (m, 2 H) 2.78 (s, 6 H) 2.99 - 3.16 (m, 2 H) 3.24 (s, 3 H) 3.35 - 3.52 (m, 2 H) 3.61 - 3.82 (m, 2 H) 4.84 (t, *J*=4.52 Hz, 2 H) 7.40 (t, *J*=9.04 Hz, 1 H) 7.51 - 7.69 (m, 1 H) 7.86 - 8.07 (m, 2 H) 8.04 - 8.33 (m, 2 H) 8.41 (d, *J*=2.07 Hz, 1 H) 8.97 (s, 1 H) 9.35 (s, 1 H) 9.95 (s, 1 H) 15.14 (s, 1 H)	Ethyl 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-(dimethylamino)propylamino)pyrimidin-5-yl)-1-(2-methoxyethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **Example 980**

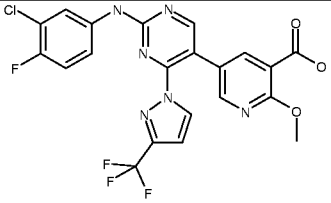
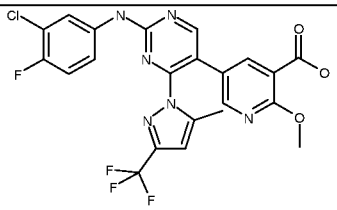
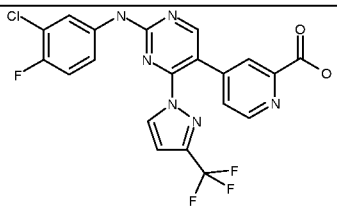
Ex	Compound	Data	SM
Example 1058	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(5-ethyl-2-methylmorpholino)pyrimidin-5-yl)nicotinic acid	MS(ES): 472 (M+1) for $C_{23}H_{23}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 0.58 (t, *J*=7.44 Hz, 3 H) 1.03 (d, *J*=5.84 Hz, 3 H) 1.39 - 1.86 (m, 2 H) 2.78 (dd, *J*=13.47, 11.21 Hz, 1 H) 3.36 - 3.71 (m, 5 H) 7.16 - 7.45 (m, 1 H) 7.45 - 7.73 (m, 1 H) 8.00 - 8.25 (m, 2 H) 8.29 (t, *J*=2.07 Hz, 1 H) 8.86 (d, *J*=2.07 Hz, 1 H) 9.00 (d, *J*=1.88 Hz, 1 H) 9.69 (s, 1 H) 13.53 (s, 1 H)	Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-ethyl-2-methylmorpholino)pyrimidin-5-yl)nicotinate **Example 981**
Example 1059	 (E)-3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(2-(hydroxymethyl)morpholino)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 485 (M+1) for $C_{24}H_{22}ClFN_4O_4$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 2.56 - 2.98 (m, 2 H) 3.16 - 3.58 (m, 5 H) 3.59 - 4.00 (m, 2 H) 4.48 - 5.01 (m, 1 H) 6.58 (d, *J*=16.01 Hz, 1 H) 7.12 - 7.85 (m, 7 H) 7.96 - 8.27 (m, 2 H) 9.62 (s, 1 H)	(E)-ethyl 3-(3-(2-(3-chloro-4-fluorophenylamino)-4-(2-(hydroxymethyl)morpholino)pyrimidin-5-yl)phenyl)acrylate **Example 977**
Example 1060	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(2-(hydroxymethyl)morpholino)pyrimidin-5-yl)nicotinic acid	MS(ES): 460 (M+1) for $C_{21}H_{19}ClFN_5O_4$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 2.57 - 2.79 (m, 1 H) 2.77 - 3.04 (m, 1 H) 3.12 - 3.59 (m, 5 H) 3.59 - 3.90 (m, 2 H) 4.47 - 4.83 (m, 1 H) 7.32 (t, *J*=9.14 Hz, 1 H) 7.54 - 7.82 (m, 1 H) 8.03 - 8.22 (m, 2 H) 8.32 (t, *J*=2.07 Hz, 1 H) 8.88 (d, *J*=2.26 Hz, 1 H) 8.98 (d, *J*=1.88 Hz, 1 H) 9.73 (s, 1 H) 13.54 (s, 1 H)	Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(2-(hydroxymethyl)morpholino)pyrimidin-5-yl)nicotinate **Example 978**

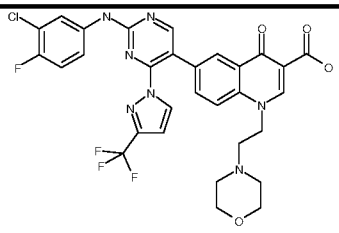
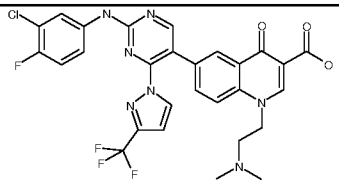
Ex	Compound	Data	SM
Example 1061	 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)-1H-indole-2-carboxylic acid	MS(ES): 470 (M+1) for $C_{23}H_{21}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.66 - 1.93 (m, 2 H) 3.13 (s, 3 H) 3.33 - 3.56 (m, 4 H) 6.54 (t, *J*=5.46 Hz, 1 H) 6.68 (s, 1 H) 6.93 (dd, *J*=8.19, 1.22 Hz, 1 H) 7.15 - 7.43 (m, 2 H) 7.50 - 7.74 (m, 2 H) 7.77 (s, 1 H) 8.25 (dd, *J*=7.06, 2.54 Hz, 1 H) 9.42 (s, 1 H) 11.19 (s, 1 H)	Methyl 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)-1H-indole-2-carboxylate **Example 1051**
Example 1062	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)-1H-indole-2-carboxylic acid	MS(ES): 470 (M+1) for $C_{23}H_{21}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.62 - 1.94 (m, 2 H) 3.13 (s, 3 H) 3.22 - 3.60 (m, 4 H) 6.90 (s, 1 H) 7.12 (s, 1 H) 7.21 (dd, *J*=8.48, 1.51 Hz, 1 H) 7.32 (t, *J*=9.14 Hz, 1 H) 7.51 (d, *J*=8.48 Hz, 1 H) 7.55 - 7.70 (m, 2 H) 7.76 (s, 1 H) 8.02 - 8.33 (m, 1 H) 9.55 (s, 1 H) 11.87 (s, 1 H) 13.03 (s, 1 H)	Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)-1H-indole-2-carboxylate **Example 1052**
Example 1063	 6-(2-(3-Chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)-1H-indole-2-carboxylic acid	MS(ES): 468 (M+1) for $C_{23}H_{19}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 3.10 - 3.26 (m, 4 H) 3.45 - 3.65 (m, 4 H) 6.74 - 7.04 (m, 1 H) 7.12 (dd, *J*=8.38, 1.22 Hz, 1 H) 7.31 (t, *J*=9.23 Hz, 1 H) 7.48 (s, 1 H) 7.56 - 7.78 (m, 2 H) 8.03 (s, 1 H) 8.16 (dd, *J*=6.97, 2.64 Hz, 1 H) 9.57 (s, 1 H) 11.58 (s, 1 H)	Methyl 6-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)-1H-indole-2-carboxylate **Example 1053**

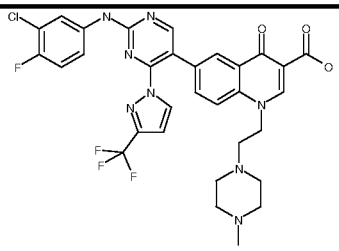
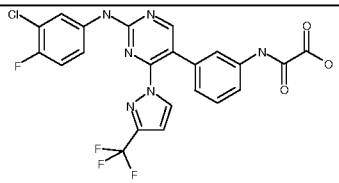
Ex	Compound	Data	SM
Example 1064	 5-(2-(3-Chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)-1H-indole-2-carboxylic acid	MS(ES): 468 (M+1) for $C_{23}H_{19}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 3.13 - 3.26 (m, 4 H) 3.42 - 3.69 (m, 4 H) 7.08 (s, 1 H) 7.21 - 7.41 (m, 2 H) 7.47 (d, *J*=8.67 Hz, 1 H) 7.55 - 7.84 (m, 2 H) 8.02 (s, 1 H) 8.15 (dd, *J*=6.69, 2.35 Hz, 1 H) 9.54 (s, 1 H) 11.81 (s, 1 H) 12.99 (s, 1 H)	Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-morpholinopyrimidin-5-yl)-1H-indole-2-carboxylate **Example 1054**
Example 1065	 4-(2-(3-Chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)picolinic acid	MS(ES): 432 (M+1) for $C_{20}H_{19}ClFN_5O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.70 - 1.96 (m, 2 H) 3.20 (s, 3 H) 3.35 - 3.55 (m, 4 H) 6.89 (t, *J*=5.75 Hz, 1 H) 7.17 - 7.45 (m, 2 H) 7.57 - 7.71 (m, 1 H) 7.86 (s, 1 H) 7.89 (s, 1 H) 8.22 (dd, *J*=6.88, 2.54 Hz, 1 H) 8.53 (d, *J*=4.71 Hz, 1 H) 9.50 (s, 1 H)	Methyl 4-(2-(3-chloro-4-fluorophenylamino)-4-(3-methoxypropylamino)pyrimidin-5-yl)picolinate **Example 1031**

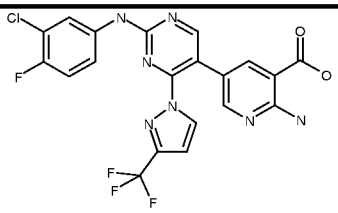
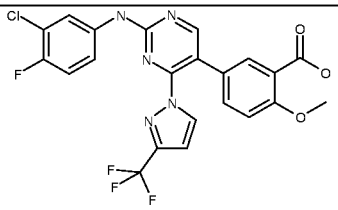
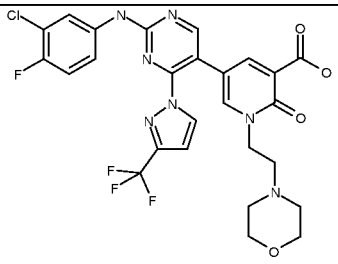
Methyl-ester Hydrolysis: The following examples were prepared using the general method described for **Example 214** using 1N sodium hydroxide, THF : 1,4-dioxane (1:1), and the starting material (SM) indicated.

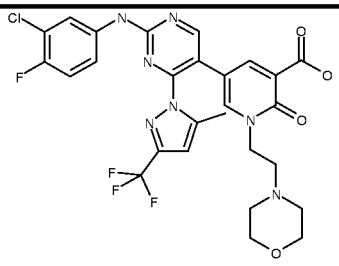
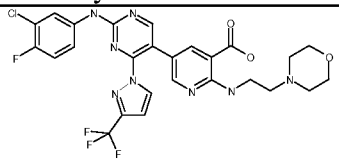
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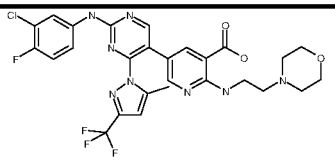
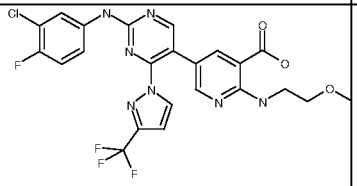
Ex	Compound	Data	SM
Example 1066	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinic acid	MS(ES): 509 (M+1) for $C_{21}H_{13}ClF_4N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.93 (s, 3 H) 7.04 (d, *J*=2.45 Hz, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.64 - 7.78 (m, 1 H) 7.82 (d, *J*=2.45 Hz, 1 H) 8.08 (dd, *J*=6.69, 2.54 Hz, 1 H) 8.24 (d, *J*=2.45 Hz, 1 H) 8.50 (s, 1 H) 8.80 (s, 1 H) 10.41 (s, 1 H) 12.95 (br. s., 1 H)	Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinate **Example 991**
Example 1067	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinic acid	MS(ES): 523 (M+1) for $C_{22}H_{15}ClF_4N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.34 (s, 3 H) 3.90 (s, 3 H) 6.76 (s, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.54 - 7.78 (m, 2 H) 8.06 (d, *J*=6.78 Hz, 1 H) 8.17 (d, *J*=2.45 Hz, 1 H) 8.96 (s, 1 H) 10.44 (s, 1 H) 12.97 (br. s., 1 H)	Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinate **Example 992**
Example 1068	 4-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)picolinic acid	MS(ES): 479 (M+1) for $C_{20}H_{11}ClF_4N_6O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.07 (d, 1 H) 7.30 - 7.60 (m, 2 H) 7.63 - 7.83 (m, 2 H) 8.08 (dd, *J*=6.69, 2.54 Hz, 1 H) 8.55 (d, *J*=1.70 Hz, 1 H) 8.67 (d, *J*=5.09 Hz, 1 H) 8.85 (s, 1 H) 10.53 (s, 1 H)	Methyl 4-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)picolinate **Example 1032**

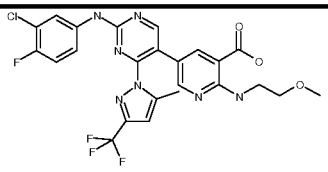
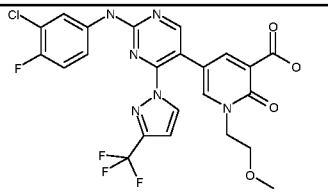
Ex	Compound	Data	SM
Example 1069	 6-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-morpholinoethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	MS(ES): 658 (M+1) for $C_{30}H_{24}ClF_4N_7O_4$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 2.79 - 3.34 (m, 4 H) 3.31 - 4.22 (m, 6 H) 4.77 - 5.19 (m, 2 H) 7.04 (d, *J*=2.64 Hz, 1 H) 7.44 (t, *J*=9.14 Hz, 1 H) 7.60 - 7.89 (m, 2 H) 8.01 (d, *J*=9.04 Hz, 1 H) 8.13 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.20 (d, *J*=2.07 Hz, 1 H) 8.47 (d, *J*=1.51 Hz, 1 H) 8.88 (s, 1 H) 9.10 (s, 1 H) 10.49 (s, 1 H) 15.03 (br. s., 1 H)	Ethyl 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-morpholinoethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **Example 1037**
Example 1070	 6-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(dimethylamino)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	MS(ES): 616 (M+1) for $C_{28}H_{22}ClF_4N_7O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.89 (br. s., 6 H) 3.53 - 3.74 (m, 2 H) 4.93 (t, *J*=5.93 Hz, 2 H) 7.04 (d, *J*=2.83 Hz, 1 H) 7.44 (t, *J*=9.04 Hz, 1 H) 7.60 - 7.88 (m, 2 H) 8.02 (d, *J*=9.04 Hz, 1 H) 8.07 - 8.28 (m, 2 H) 8.47 (d, *J*=1.70 Hz, 1 H) 8.88 (s, 1 H) 9.14 (s, 1 H) 10.50 (s, 1 H) 15.01 (br. s., 1 H)	Ethyl 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(dimethylamino)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **Example 1038**

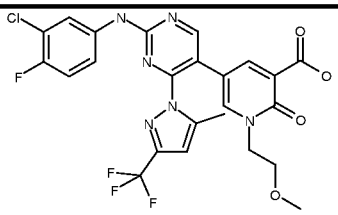
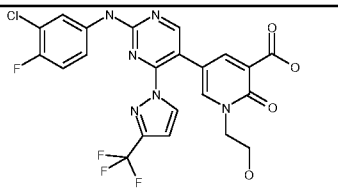
Ex	Compound	Data	SM
Example 1071	 6-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(4-methylpiperazin-1-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	MS(ES): 671 (M+1) for $C_{31}H_{27}ClF_4N_8O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.39 (t, 2 H) 2.63 - 2.92 (m, 7 H) 3.00 (d, *J*=13.37 Hz, 2 H) 3.38 (d, *J*=11.11 Hz, 2 H) 4.71 (t, *J*=4.99 Hz, 2 H) 7.03 (d, *J*=2.64 Hz, 1 H) 7.44 (t, *J*=9.04 Hz, 1 H) 7.60 - 7.83 (m, 2 H) 8.04 (d, *J*=9.04 Hz, 1 H) 8.12 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.21 (d, *J*=2.07 Hz, 1 H) 8.50 (d, *J*=1.51 Hz, 1 H) 8.89 (s, 1 H) 8.98 (s, 1 H) 10.48 (s, 1 H)	Ethyl 6-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(4-methylpiperazin-1-yl)ethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate **Example 994**
Example 1072	 2-(3-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenylamino)-2-oxoacetic acid	MS(ES): 521 (M+1) for $C_{22}H_{13}ClF_4N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 6.89 (d, 1 H) 6.97 (d, *J*=2.64 Hz, 1 H) 7.19 - 7.53 (m, 2 H) 7.54 - 7.88 (m, 3 H) 8.12 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.29 (d, *J*=1.70 Hz, 1 H) 8.73 (s, 1 H) 10.39 (s, 1 H) 10.70 (s, 1 H) 14.19 (br. s., 1 H)	Ethyl 2-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenylamino)-2-oxoacetate **Example 996**

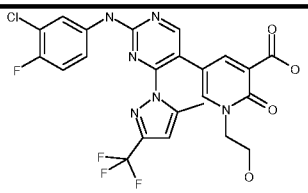
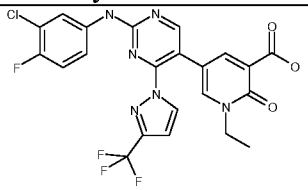
Ex	Compound	Data	SM
Example 1073	 2-Amino-5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinic acid	MS(ES): 494 (M+1) for $C_{20}H_{12}ClF_4N_7O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.03 (d, 1 H) 7.41 (t, *J*=9.14 Hz, 1 H) 7.70 (ddd, *J*=9.09, 4.19, 2.73 Hz, 1 H) 7.86 (d, *J*=2.45 Hz, 1 H) 7.99 - 8.19 (m, 2 H) 8.46 (d, *J*=1.70 Hz, 1 H) 8.77 (s, 1 H) 10.35 (s, 1 H)	Methyl 2-amino-5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinate **Example 999**
Example 1074	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxybenzoic acid	MS(ES): 508 (M+1) for $C_{22}H_{14}ClF_4N_5O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.82 (s, 3 H) 6.97 (d, *J*=2.64 Hz, 1 H) 7.12 (d, *J*=8.85 Hz, 1 H) 7.21 - 7.53 (m, 3 H) 7.70 (ddd, *J*=9.09, 4.19, 2.73 Hz, 1 H) 8.12 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.30 (d, *J*=1.51 Hz, 1 H) 8.76 (s, 1 H) 10.36 (s, 1 H) 12.56 (br. s., 1 H)	Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxybenzoate **Example 1001**
Example 1075	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-morpholinoethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 608 (M+1) for $C_{26}H_{22}ClF_4N_7O_4$ ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 2.80 - 3.77 (m, 6 H) 4.02 (br. s., 4 H) 4.67 (t, *J*=5.93 Hz, 2 H) 6.73 (d, *J*=2.64 Hz, 1 H) 7.20 (t, *J*=8.67 Hz, 1 H) 7.38 (dd, *J*=3.77, 2.83 Hz, 1 H) 7.83 (dd, *J*=6.41, 2.64 Hz, 1 H) 7.97 (br. s., 1 H) 8.14 (br. s., 1 H) 8.32 - 8.49 (m, 2 H) 8.52 (s, 1 H)	Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-morpholinoethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1004**

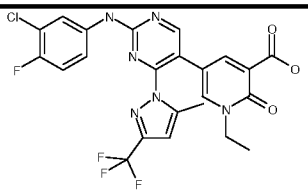
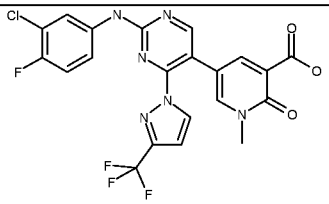
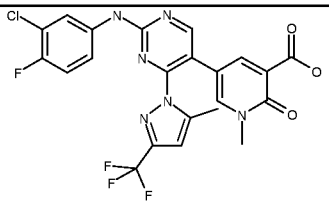
Ex	Compound	Data	SM
Example 1076	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-morpholinoethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 622 (M+1) for $C_{27}H_{24}ClF_4N_7O_4$ ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 2.58 (s, 3 H) 2.90 - 3.66 (m, 6 H) 4.01 (br. s., 4 H) 4.61 (br. s., 2 H) 6.47 (s, 1 H) 7.16 (t, *J*=8.57 Hz, 1 H) 7.31 - 7.46 (m, 1 H) 7.66 (br. s., 1 H) 7.81 (d, *J*=3.96 Hz, 2 H) 8.17 (br. s., 1 H) 8.56 (br. s., 1 H)	Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-morpholinoethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1005**
Example 1077	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-morpholinoethylamino)nicotinic acid	MS(ES): 607 (M+1) for $C_{26}H_{23}ClF_4N_8O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.10 - 4.10 (m, 12 H) 7.03 (d, *J*=2.64 Hz, 1 H) 7.41 (t, *J*=9.14 Hz, 1 H) 7.70 (ddd, *J*=9.04, 4.24, 2.73 Hz, 1 H) 7.83 (d, *J*=2.45 Hz, 1 H) 8.10 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.19 (d, *J*=2.45 Hz, 1 H) 8.32 (s, 1 H) 8.46 (d, *J*=1.51 Hz, 1 H) 8.78 (s, 1 H) 10.35 (s, 1 H)	Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-morpholinoethylamino)nicotinate **Example 1006**

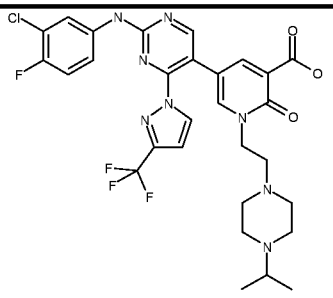
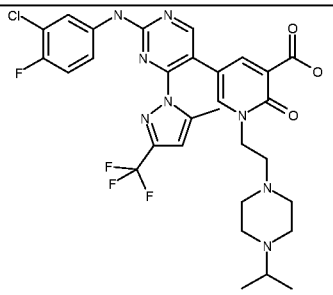
Ex	Compound	Data	SM
Example 1078	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-morpholinoethylamino)nicotinic acid	MS(ES): 621 (M+1) for $C_{27}H_{25}ClF_4N_8O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.88 - 4.20 (m, 12 H) 6.75 (s, 1 H) 7.41 (t, *J*=9.14 Hz, 1 H) 7.54 - 7.78 (m, 2 H) 7.98 - 8.22 (m, 2 H) 8.20 - 8.44 (m, 1 H) 8.93 (s, 1 H) 9.63 (br. s., 1 H) 10.39 (s, 1 H)	Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-morpholinoethylamino)nicotinate **Example 1007**
Example 1079	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-methoxyethylamino)nicotinic acid	MS(ES): 552 (M+1) for $C_{23}H_{18}ClF_4N_7O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.27 (s, 3 H) 3.42 - 3.67 (m, 4 H) 6.97 (d, *J*=2.64 Hz, 1 H) 7.39 (t, *J*=9.14 Hz, 1 H) 7.60 - 7.80 (m, 2 H) 7.87 (br. s., 1 H) 8.12 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.30 (s, 1 H) 8.73 (s, 1 H) 9.29 (br. s., 1 H) 10.31 (s, 1 H)	Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-methoxyethylamino)nicotinate **Example 1011**

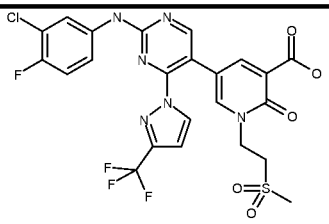
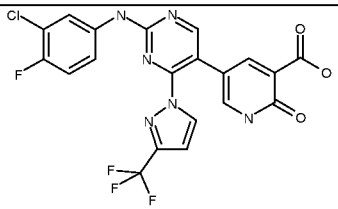
Ex	Compound	Data	SM
Example 1080	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-methoxyethylamino)nicotinic acid	MS(ES): 566 (M+1) for $C_{24}H_{20}ClF_4N_7O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.19 (s, 3 H) 3.26 (s, 3 H) 3.39 - 3.66 (m, 4 H) 6.71 (s, 1 H) 7.39 (t, *J*=9.14 Hz, 1 H) 7.52 - 7.88 (m, 3 H) 8.06 (dd, *J*=6.78, 2.45 Hz, 1 H) 8.86 (s, 1 H) 9.24 (s, 1 H) 10.33 (s, 1 H) 13.09 (s, 1 H)	Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-methoxyethylamino)nicotinate **Example 1012**
Example 1081	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 553 (M+1) for $C_{23}H_{17}ClF_4N_6O_4$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.23 (s, 3 H) 3.68 (t, *J*=5.27 Hz, 2 H) 4.29 (t, *J*=5.37 Hz, 2 H) 7.08 (d, *J*=2.64 Hz, 1 H) 7.43 (t, *J*=9.04 Hz, 1 H) 7.72 (ddd, *J*=6.83, 4.47, 2.07 Hz, 1 H) 7.98 - 8.18 (m, 2 H) 8.27 (d, *J*=2.64 Hz, 1 H) 8.60 (d, *J*=1.70 Hz, 1 H) 8.71 (s, 1 H) 10.40 (s, 1 H) 14.34 (br. s., 1 H)	Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1013**

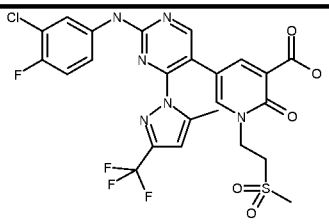
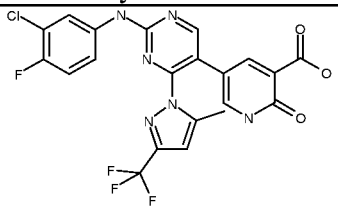
Ex	Compound	Data	SM
Example 1082	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 567 (M+1) for $C_{24}H_{19}ClF_4N_6O_4$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 2.47 (s, 3 H) 3.23 (s, 3 H) 3.65 (t, *J*=5.09 Hz, 2 H) 4.27 (t, *J*=4.99 Hz, 2 H) 6.80 (s, 1 H) 7.42 (t, *J*=9.04 Hz, 1 H) 7.55 - 7.71 (m, 1 H) 7.75 (d, *J*=2.45 Hz, 1 H) 8.05 (dd, *J*=6.59, 2.45 Hz, 1 H) 8.25 (d, *J*=2.45 Hz, 1 H) 8.85 (s, 1 H) 10.41 (s, 1 H) 14.18 (br. s., 1 H)	Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1014**
Example 1083	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 539 (M+1) for $C_{22}H_{15}ClF_4N_6O_4$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.73 (t, *J*=5.56 Hz, 2 H) 4.19 (t, *J*=5.56 Hz, 2 H) 7.08 (d, *J*=2.64 Hz, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.72 (ddd, *J*=9.09, 4.19, 2.73 Hz, 1 H) 7.96 - 8.17 (m, 2 H) 8.28 (d, *J*=2.64 Hz, 1 H) 8.51 - 8.63 (m, 1 H) 8.71 (s, 1 H) 10.41 (s, 1 H)	Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1015**

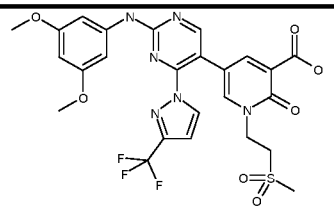
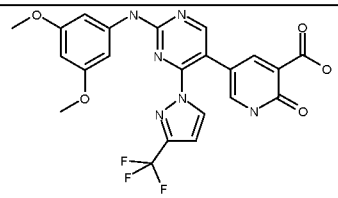
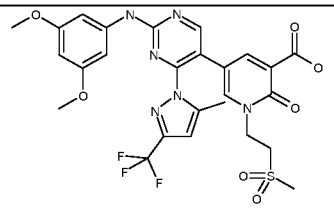
Ex	Compound	Data	SM
Example 1084	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 553 (M+1) for $C_{23}H_{17}ClF_4N_6O_4$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.45 (s, 3 H) 3.71 (t, *J*=5.37 Hz, 2 H) 4.16 (t, *J*=5.46 Hz, 2 H) 6.80 (s, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.55 - 7.79 (m, 2 H) 8.05 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.25 (d, *J*=2.83 Hz, 1 H) 8.86 (s, 1 H) 10.42 (s, 1 H) 14.27 (br. s., 1 H)	Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1043**
Example 1085	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-ethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 523 (M+1) for $C_{22}H_{15}ClF_4N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.32 (t, 3 H) 4.15 (q, *J*=7.10 Hz, 2 H) 7.09 (d, *J*=2.64 Hz, 1 H) 7.43 (t, *J*=9.04 Hz, 1 H) 7.59 - 7.82 (m, 1 H) 7.92 - 8.23 (m, 2 H) 8.38 (d, *J*=2.64 Hz, 1 H) 8.61 (d, *J*=1.70 Hz, 1 H) 8.78 (s, 1 H) 10.41 (s, 1 H) 14.55 (s, 1 H)	Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-ethyl-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1044**

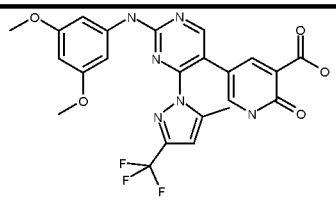
Ex	Compound	Data	SM
Example 1086	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-ethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 537 (M+1) for $C_{23}H_{17}ClF_4N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.28 (t, *J*=7.16 Hz, 3 H) 2.48 (s, 3 H) 4.12 (q, *J*=7.22 Hz, 2 H) 6.81 (s, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.64 (ddd, *J*=9.04, 4.14, 2.64 Hz, 1 H) 7.80 (d, *J*=2.64 Hz, 1 H) 8.05 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.30 (d, *J*=2.64 Hz, 1 H) 8.92 (s, 1 H) 10.41 (s, 1 H) 14.42 (s, 1 H)	Ethyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-ethyl-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1045**
Example 1087	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 509 (M+1) for $C_{21}H_{13}ClF_4N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.70 (s, 3 H) 7.09 (d, *J*=2.83 Hz, 1 H) 7.43 (t, *J*=9.14 Hz, 1 H) 7.72 (ddd, *J*=9.14, 4.24, 2.64 Hz, 1 H) 7.92 - 8.17 (m, 2 H) 8.42 (d, *J*=2.64 Hz, 1 H) 8.52 - 8.68 (m, 1 H) 8.75 (s, 1 H) 10.40 (s, 1 H) 14.49 (s, 1 H)	Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1046**
Example 1088	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 523 (M+1) for $C_{22}H_{15}ClF_4N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.49 (s, 3 H) 3.67 (s, 3 H) 6.82 (s, 1 H) 7.42 (t, *J*=9.04 Hz, 1 H) 7.49 - 7.84 (m, 2 H) 8.04 (dd, *J*=6.78, 2.45 Hz, 1 H) 8.41 (d, *J*=2.45 Hz, 1 H) 8.89 (s, 1 H) 10.40 (s, 1 H) 14.36 (s, 1 H)	Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1047**

Ex	Compound	Data	SM
Example 1089	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(4-isopropylpiperazin-1-yl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 649 (M+1) for $C_{29}H_{29}ClF_4N_8O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.19 (d, *J*=6.59 Hz, 6 H) 2.31 - 2.46 (m, 2 H) 2.74 - 2.98 (m, 4 H) 3.07 (d, *J*=11.68 Hz, 2 H) 3.20 - 3.58 (m, 3 H) 4.24 (t, *J*=5.84 Hz, 2 H) 7.11 (d, *J*=2.83 Hz, 1 H) 7.43 (t, *J*=9.04 Hz, 1 H) 7.71 (ddd, *J*=9.09, 4.19, 2.73 Hz, 1 H) 7.97 - 8.17 (m, 2 H) 8.34 (d, *J*=2.45 Hz, 1 H) 8.53 - 8.67 (m, 1 H) 8.73 (s, 1 H) 9.10 (br. s., 1 H) 10.41 (s, 1 H)	Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(4-isopropylpiperazin-1-yl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1050**
Example 1090	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(4-isopropylpiperazin-1-yl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 663 (M+1) for $C_{30}H_{31}ClF_4N_8O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.20 (d, *J*=6.59 Hz, 6 H) 2.35 - 2.49 (m, 5 H) 2.65 - 2.97 (m, 4 H) 3.06 (d, *J*=12.62 Hz, 2 H) 3.25 - 3.53 (m, 3 H) 4.23 (t, *J*=5.65 Hz, 2 H) 6.82 (s, 1 H) 7.43 (t, *J*=9.14 Hz, 1 H) 7.55 - 7.71 (m, 2 H) 8.08 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.36 (d, *J*=2.64 Hz, 1 H) 8.87 (s, 1 H) 9.11 (br. s., 1 H) 10.42 (s, 1 H)	Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(4-isopropylpiperazin-1-yl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1018**

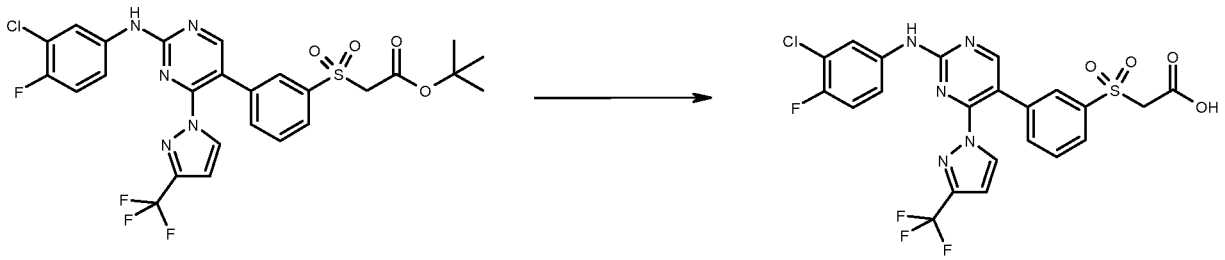
Ex	Compound	Data	SM
Example 1091	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 601 (M+1) for $C_{23}H_{17}ClF_4N_6O_5S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.10 (s, 3 H) 3.71 (t, *J*=6.97 Hz, 2 H) 4.56 (t, *J*=6.78 Hz, 2 H) 7.10 (d, *J*=2.64 Hz, 1 H) 7.43 (t, *J*=9.14 Hz, 1 H) 7.63 - 7.81 (m, 1 H) 7.99 - 8.16 (m, 2 H) 8.44 (d, *J*=2.64 Hz, 1 H) 8.54 - 8.66 (m, 1 H) 8.72 (s, 1 H) 10.42 (s, 1 H)	Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1020**
Example 1092	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 495 (M+1) for $C_{20}H_{11}ClF_4N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.07 (d, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.62 - 7.83 (m, 1 H) 7.90 - 8.20 (m, 3 H) 8.59 (s, 1 H) 8.74 (s, 1 H) 10.37 (s, 1 H) 14.64 (br. s., 1 H)	Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1020**

Ex	Compound	Data	SM
Example 1093	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 615 (M+1) for $C_{24}H_{19}ClF_4N_6O_5S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.46 (s, 3 H) 3.10 (s, 3 H) 3.69 (t, *J*=6.69 Hz, 2 H) 4.54 (t, *J*=6.69 Hz, 2 H) 6.81 (s, 1 H) 7.42 (t, *J*=9.04 Hz, 1 H) 7.49 - 7.77 (m, 2 H) 8.05 (dd, *J*=6.59, 2.26 Hz, 1 H) 8.48 (d, *J*=2.45 Hz, 1 H) 8.87 (s, 1 H) 10.44 (s, 1 H)	Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1021**
Example 1094	 5-(2-(3-Chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 509 (M+1) for $C_{21}H_{13}ClF_4N_6O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.49 (s, 3 H) 6.80 (s, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.64 (ddd, *J*=9.04, 4.24, 2.73 Hz, 1 H) 7.78 (d, *J*=2.64 Hz, 1 H) 7.87 - 8.16 (m, 2 H) 8.88 (s, 1 H) 10.37 (s, 1 H) 13.53 (br. s., 1 H)	Methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1021**

Ex	Compound	Data	SM
Example 1095	 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 609 (M+1) for $C_{25}H_{23}F_3N_6O_7S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.10 (s, 3 H) 3.71 (t, *J*=7.06 Hz, 2 H) 3.75 (s, 6 H) 4.56 (t, *J*=6.88 Hz, 2 H) 6.22 (t, *J*=2.17 Hz, 1 H) 6.99 - 7.17 (m, 3 H) 8.05 (d, *J*=2.64 Hz, 1 H) 8.45 (d, *J*=2.64 Hz, 1 H) 8.58 (d, *J*=1.70 Hz, 1 H) 8.70 (s, 1 H) 10.19 (s, 1 H)	Methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1022**
Example 1096	 5-(2-(3,5-Dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 503 (M+1) for $C_{22}H_{17}F_3N_6O_5$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.75 (s, 6 H) 6.21 (t, *J*=2.17 Hz, 1 H) 6.93 - 7.20 (m, 3 H) 8.02 (br. s., 1 H) 8.10 (d, *J*=2.64 Hz, 1 H) 8.47 - 8.63 (m, 1 H) 8.72 (s, 1 H) 10.13 (s, 1 H) 13.48 (br. s., 1 H)	Methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1022**
Example 1097	 5-(2-(3,5-Dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 623 (M+1) for $C_{26}H_{25}F_3N_6O_7S$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.44 (s, 3 H) 3.10 (s, 3 H) 3.58 - 3.83 (m, 8 H) 4.54 (t, *J*=6.78 Hz, 2 H) 6.22 (t, *J*=2.17 Hz, 1 H) 6.80 (s, 1 H) 6.91 - 7.13 (m, 2 H) 7.57 (d, *J*=2.64 Hz, 1 H) 8.48 (d, *J*=2.64 Hz, 1 H) 8.85 (s, 1 H) 10.20 (s, 1 H)	Methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(methylsulfonyl)ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1023**

Ex	Compound	Data	SM
Example 1098	 5-(2-(3,5-Dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 517 (M+1) for $C_{23}H_{19}F_3N_6O_5$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.43 - 2.49 (m, 3 H) 3.73 (s, 6 H) 6.22 (t, *J*=2.17 Hz, 1 H) 6.78 (s, 1 H) 6.92 - 7.14 (m, 2 H) 7.79 (d, *J*=2.64 Hz, 1 H) 7.96 (d, *J*=1.13 Hz, 1 H) 8.86 (s, 1 H) 10.13 (s, 1 H) 13.51 (br. s., 1 H)	Methyl 5-(2-(3,5-dimethoxypheny lamino)-4-(5-methyl-3-(trifluoromethyl) -1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-(methylsulfonyl) ethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1023**

Example 1099: 2-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenylsulfonyl)acetic acid

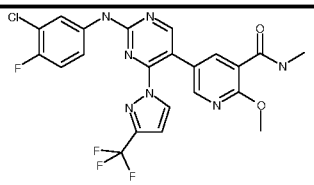
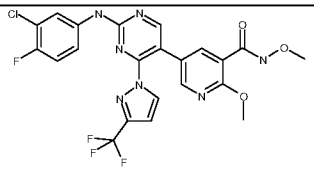


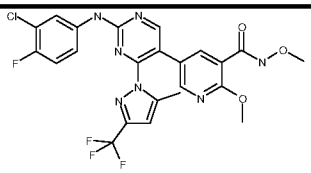
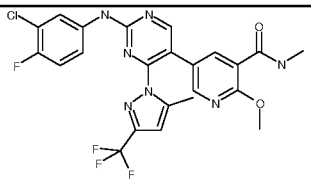
tert-butyl 2-(3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenylsulfonyl)acetate **Example 1003** (164 mg, 0.27 mmol) was dissolved in THF (2 mL), cooled to 0°C, treated with trifluoroacetic acid (2 mL), and allowed to stir at room temperature for 2 days. The solvent was removed at reduced pressure and the residue was purified by reverse phase preparative HPLC (C18: 45-95% ACN in H_2O containing 0.1% TFA) to afford the desired product (120 mg).

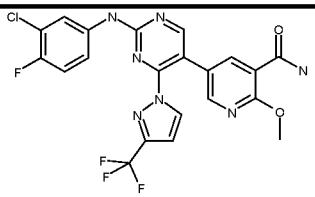
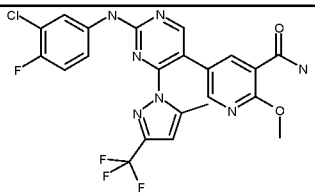
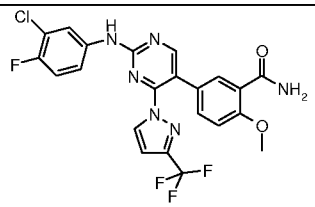
MS(ES): 556 (M+1) for $C_{22}H_{14}ClF_4N_5O_4S$

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 4.42 (s, 2 H) 7.00 (d, *J*=2.64 Hz, 1 H) 7.41 (t, *J*=9.14 Hz, 1 H) 7.47 - 7.57 (m, 1 H) 7.63 (t, *J*=7.72 Hz, 1 H) 7.68 - 7.81 (m, 2 H) 7.87 (d, *J*=7.91 Hz, 1 H) 8.11 (dd, *J*=6.69, 2.54 Hz, 1 H) 8.42 (d, *J*=1.51 Hz, 1 H) 8.82 (s, 1 H) 10.45 (s, 1 H)

The following examples were prepared using the general HATU coupling method described for **Example 360** using the starting materials (SM) indicated.

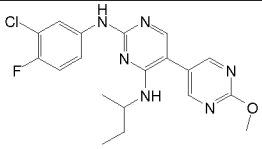
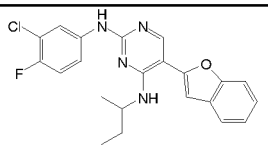
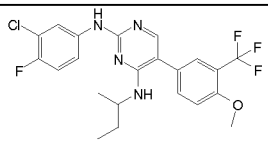
Ex	Compound	Data	SM
Example 1100	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxy-N-methylnicotinamide	MS(ES): 522 (M+1) for $C_{22}H_{16}ClF_4N_7O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.79 (d, 3 H) 3.99 (s, 3 H) 7.03 (d, *J*=2.64 Hz, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.72 (ddd, *J*=8.90, 4.10, 2.64 Hz, 1 H) 7.91 (d, *J*=2.45 Hz, 1 H) 8.09 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.16 (d, *J*=2.45 Hz, 1 H) 8.19 - 8.35 (m, 1 H) 8.47 (s, 1 H) 8.78 (s, 1 H) 10.42 (s, 1 H)	Methylamine and 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinic acid **Example 1066**
Example 1101	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N,2-dimethoxynicotinamide	MS(ES): 538 (M+1) for $C_{22}H_{16}ClF_4N_7O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.68 (s, 3 H) 3.96 (s, 3 H) 7.04 (d, *J*=2.64 Hz, 1 H) 7.42 (t, *J*=9.04 Hz, 1 H) 7.64 - 7.79 (m, 1 H) 7.83 (d, *J*=2.64 Hz, 1 H) 8.09 (dd, *J*=6.69, 2.73 Hz, 1 H) 8.17 (d, *J*=2.45 Hz, 1 H) 8.48 (s, 1 H) 8.79 (s, 1 H) 10.42 (s, 1 H) 11.31 (s, 1 H)	O-methylhydroxylamine hydrochloride and 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinic acid **Example 1066**

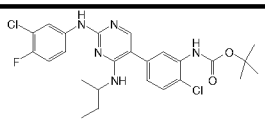
Ex	Compound	Data	SM
Example 1102	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N,2-dimethoxynicotinamide	MS(ES): 552 (M+1) for $C_{23}H_{18}ClF_4N_7O_3$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.33 (s, 3 H) 3.67 (s, 3 H) 3.92 (s, 3 H) 6.76 (s, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.55 - 7.77 (m, 2 H) 7.97 - 8.15 (m, 2 H) 8.95 (s, 1 H) 10.45 (s, 1 H) 11.30 (s, 1 H)	O-methylhydroxylamine hydrochloride and 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinic acid **Example 1067**
Example 1103	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxy-N-methylnicotinamide	MS(ES): 536 (M+1) for $C_{23}H_{18}ClF_4N_7O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.34 (s, 3 H) 2.78 (d, *J*=4.71 Hz, 3 H) 3.96 (s, 3 H) 6.76 (s, 1 H) 7.42 (t, *J*=9.04 Hz, 1 H) 7.58 - 7.72 (m, 1 H) 7.76 (d, *J*=2.64 Hz, 1 H) 7.99 - 8.14 (m, 2 H) 8.14 - 8.27 (m, 1 H) 8.83 - 9.00 (m, 1 H) 10.44 (s, 1 H)	Methylamine and 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinic acid **Example 1067**

Ex	Compound	Data	SM
Example 1104	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinamide	MS(ES): 508 (M+1) for $C_{21}H_{14}ClF_4N_7O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 4.00 (s, 3 H) 7.03 (d, *J*=2.83 Hz, 1 H) 7.42 (t, *J*=9.14 Hz, 1 H) 7.61 - 7.82 (m, 3 H) 7.93 (d, *J*=2.45 Hz, 1 H) 8.09 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.18 (d, *J*=2.45 Hz, 1 H) 8.48 (d, *J*=1.51 Hz, 1 H) 8.79 (s, 1 H) 10.41 (s, 1 H)	Ammonia and 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinic acid **Example 1066**
Example 1105	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinamide	MS(ES): 522 (M+1) for $C_{22}H_{16}ClF_4N_7O_2$ ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.34 (s, 3 H) 3.96 (s, 3 H) 6.75 (s, 1 H) 7.42 (t, *J*=9.04 Hz, 1 H) 7.56 - 7.74 (m, 3 H) 7.78 (d, *J*=2.64 Hz, 1 H) 7.95 - 8.16 (m, 2 H) 8.94 (s, 1 H) 10.44 (s, 1 H)	Ammonia and 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinic acid **Example 1067**
Example 1106	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxybenzamide	MS(ES): 507 (M+1) for $C_{22}H_{15}ClF_4N_6O_2$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 3.90 (s, 3 H) 6.88 - 7.01 (m, 1 H) 7.08 - 7.19 (m, 1 H) 7.20 - 7.31 (m,1 H) 7.33 - 7.45 (m, 1 H) 7.46 - 7.55 (m, 1 H) 7.62 (d, *J*=2.26 Hz, 2 H) 7.65 - 7.76 (m, 1 H) 8.06 - 8.18 (m, 1H) 8.23 - 8.33 (m, 1 H) 8.75 (s, 1 H) 10.36 (s, 1 H)	Ammonia and 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxybenzoic acid **Example 1074**

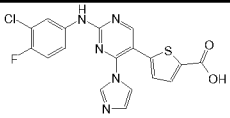
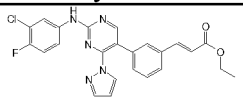
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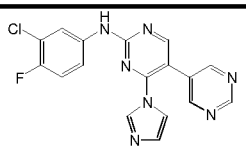
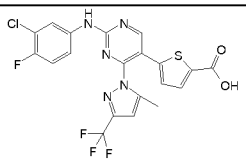
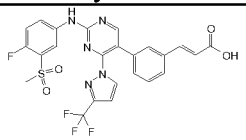
The following examples were prepared using the general method described above for **Example 1** using **Intermediate 436** and the starting material (SM) indicated

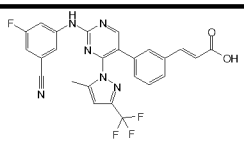
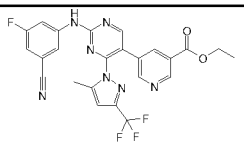
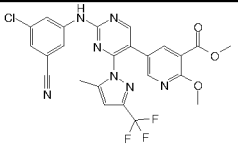
Ex	Compound	Data	SM
Example 1107	 N'-butan-2-yl-N-(3-chloro-4-fluorophenyl)-5-(2-methoxypyrimidin-5-yl)pyrimidine-2,4-diamine	MS(ES): 403.1 (M+H) for C19H20ClFN6O. 1H NMR (300 MHz, DMSO-D6) δ ppm 0.86 (t, *J*=7.44 Hz, 3 H) 1.06 - 1.25 (m, 3 H), 1.36 - 1.81 (m, 2 H), 3.98 (s, 3 H), 4.03 - 4.24 (m, 1 H), 7.35 - 7.54 (m, 2 H), 7.75 (s, 1 H), 7.84 (s, 1 H), 8.07 (dd, *J*=6.88, 2.35 Hz, 1 H), 8.57 (s, 2 H), 10.23 (s, 1 H).	2-methoxypyrimidin-5-ylboronic acid
Example 1108	 5-(1-benzofuran-2-yl)-N'-butan-2-yl-N-(3-chloro-4-fluorophenyl)pyrimidine-2,4-diamine	MS(ES): 411 (M+H) for C22H20ClFN4O. 1H NMR (300 MHz, DMSO-D6) δ ppm 0.95 (t, *J*=7.35 Hz, 3 H) 1.25 (d, *J*=6.59 Hz, 3 H) 1.44 - 1.93 (m, 2 H) 4.05 - 4.43 (m, 1 H) 7.17 (s, 1 H) 7.22 - 7.47 (m, 4 H) 7.49 - 7.58 (m, 1 H) 7.66 (dd, 2 H) 8.17 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.33 (s, 1 H) 10.04 (s, 1 H).	benzofuran-2-ylboronic acid
Example 1109	 N'-butan-2-yl-N-(3-chloro-4-fluorophenyl)-5-[4-methoxy-3-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine	MS(ES): 468.9 (M+H) for C22H21ClF4N4O. 1H NMR (300 MHz, DMSO-D6) δ ppm 0.87 (t, *J*=7.35 Hz, 3 H), 1.14 (d, *J*=6.59 Hz, 3 H), 1.39 - 1.78 (m, 2 H), 3.95 (s, 3 H), 4.03 - 4.28 (m, 1 H), 7.28 - 7.71 (m, 6 H), 7.80 (s, 1 H), 8.06 (dd, *J*=6.97, 2.07 Hz, 1 H), 10.23 (s, 1 H).	4-methoxy-3-(trifluoromethyl)phenylboronic acid

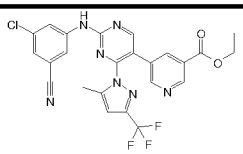
Ex	Compound	Data	SM
Example 1110	 tert-butyl N-[5-[4-(butan-2-ylamino)-2-[(3-chloro-4-fluorophenyl)amino]pyrimidin-5-yl]-2-chlorophenyl]carbamate	MS(ES): 520 (M+H) for C25H28Cl2FN5O2. 1H NMR (300 MHz, DMSO-D6) δ ppm 0.80 (t, *J*=7.35 Hz, 3 H), 1.08 (d, *J*=6.59 Hz, 3 H), 1.28 - 1.72 (m, 11 H), 4.05 (dd, 1 H), 7.07 (dd, *J*=8.29, 2.07 Hz, 2 H), 7.30 - 7.55 (m, 3 H), 7.65 (d, *J*=2.07 Hz, 1 H,) 7.72 (s, 1 H), 8.01 (dd, *J*=6.78, 2.45 Hz, 1 H), 8.77 (s, 1 H), 9.99 (s, 1 H).	3-(tert-butoxycarbonylamino)-4-chlorophenyl boronic acid

The following examples were prepared using the general method described above for **Example 1** using the starting materials (SM) indicated.

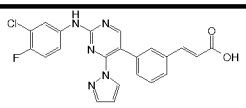
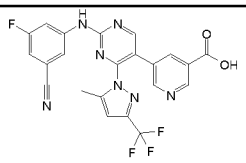
Ex	Compound	Data	SM
Example 1111	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-imidazol-1-ylpyrimidin-5-yl]thiophene-2-carboxylic acid	MS(ES): 414 (M-H) for C18H11ClFN5O2S. 1H NMR (300 MHz, DMSO-D6) δ ppm 7.10 (d, *J*=3.96 Hz, 1 H), 7.25 (s, 1 H), 7.30 - 7.49 (m, 2 H), 7.56 - 7.70 (m, 2 H), 7.97 (dd, *J*=6.69, 2.54 Hz, 1 H), 8.30 (s, 1 H), 8.83 (s, 1 H), 10.46 (s, 1 H), 13.0 (br. s, 1 H).	5-boronothiophene-2-carboxylic acid and **Intermediate 437**
Example 1112	 ethyl (E)-3-[3-[2-[(3-chloro-4-fluorophenyl)amino]-4-pyrazol-1-ylpyrimidin-5-yl]phenyl]prop-2-enoate	MS(ES): 464 (M+H) for C24H19ClFN5O2. 1H NMR (300 MHz, DMSO-D6) δ ppm 1.27 (t, 3 H), 4.18 (dd, 2 H), 6.55 (dd, *J*=2.54, 1.60 Hz, 1 H), 6.62 (d, *J*=16.20 Hz, 1 H), 7.15 (d, *J*=7.72 Hz, 1 H), 7.28 - 7.51 (m, 2 H), 7.56 - 7.70 (m, 4 H), 7.69 - 7.81 (m, 1 H), 8.11 (dd, *J*=6.78, 2.64 Hz, 1 H), 8.31 (d, *J*=2.26 Hz, 1 H), 8.69 (s, 1 H), 10.29 (s, 1 H).	(E)-3-(3-ethoxy-3-oxoprop-1-enyl)phenylboronic acid and **Intermediate 438**

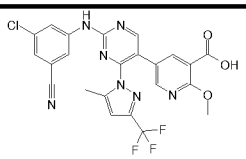
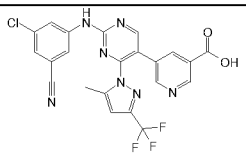
Ex	Compound	Data	SM
Example 1113	 N-(3-chloro-4-fluorophenyl)-4-imidazol-1-yl-5-pyrimidin-5-ylpyrimidin-2-amine	MS(ES): 368 (M+H) for C17H11ClFN7. 1H NMR (300 MHz, DMSO-D6) δ ppm 7.23 (s, 1 H), 7.31 - 7.45 (m, 2 H), 7.61 - 7.73 (m, 1 H), 7.99 (dd, *J*=6.69, 2.54 Hz, 1 H), 8.38 (s, 1 H), 8.65 (s, 2 H), 8.82 (s, 1 H), 9.13 (s, 1 H), 10.46 (s, 1 H).	pyrimidin-5-ylboronic acid and **Intermediate 437**
Example 1114	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[5-methyl-3-(trifluoromethyl)pyrazol-1-yl]pyrimidin-5-yl]thiophene-2-carboxylic acid	MS(ES): 498 (M+H) for C20H12ClF4N5O2S. 1H NMR (300 MHz, DMSO-D6) δ ppm 2.20 (s, 3 H), 6.80 (s, 1 H), 7.10 (d, *J*=3.96 Hz, 1 H), 7.37 - 7.46 (m, 2 H), 7.55 - 7.60 (m, 1 H), 7.90 - 8.03 (m, *J*=3.96 Hz, 1 H), 9.10 (s, 1 H), 10.54 (s, 1 H), 13.08 (s, 1 H).	5-boronothiophene-2-carboxylic acid and **Intermediate 113**
Example 1115	 (E)-3-(3-(2-(4-fluoro-3-(methylsulfonyl)phenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 546 (M-H) for C24H17F4N5O4S. 1H NMR (300 MHz, DMSO-D6) δ ppm 3.29 (s, 3 H), 6.41 (d, *J*=16.01 Hz, 1 H), 6.94 (d, *J*=2.64 Hz, 1 H), 7.11 (d, *J*=7.91 Hz, 1 H), 7.31 (t, *J*=7.72 Hz, 1 H), 7.38 - 7.53 (m, 3 H), 7.53 - 7.64 (m, *J*=7.72 Hz, 1 H), 7.89 - 8.07 (m, 1 H), 8.43 (s, 1 H), 8.50 (dd, *J*=6.12, 2.73 Hz, 1 H), 8.76 (s, 1 H), 10.53 (s, 1 H), 12.31 (s, 1 H).	(E)-3-(3-boronophenyl) acrylic acid and **Intermediate 445**

Ex	Compound	Data	SM
Example 1116	 (E)-3-(3-(2-(3-cyano-5-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenyl)acrylic acid	MS(ES): 507 (M-H) for C25H16F4N6O2. 1H NMR (300 MHz, DMSO-D6) δ ppm 2.15 (s, 3 H), 6.38 (d, *J*=16.01 Hz, 1 H), 6.67 (s, 1 H), 7.00 (d, *J*=8.29 Hz, 1 H), 7.22 - 7.33 (m, 2 H), 7.35 - 7.50 (m, 2 H,) 7.56 (d, *J*=7.91 Hz, 1 H), 7.88 - 8.13 (m, 2 H), 9.00 (s, 1 H), 10.74 (s, 1 H), 12.34 (s, 1 H).	(E)-3-(3-boronophenyl) acrylic acid and **Intermediate 446**
Example 1117	 ethyl 5-(2-(3-cyano-5-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinate	MS(ES): 512 (M+H) for C24H17F4N7O2. 1H NMR (300 MHz, CHLOROFORM-D) δ ppm 1.42 (t, *J*=7.06 Hz, 3 H), 2.46 (s, 3 H), 4.44 (q, *J*=7.16 Hz, 2 H), 6.46 (s, 1 H), 7.00 - 7.23 (m, 1 H), 7.71 (s, 1 H), 7.75 - 7.90 (m, 2 H), 8.03 (t, *J*=2.07 Hz, 1 H), 8.49 (d, *J*=2.26 Hz, 1 H), 8.76 (s, 1 H), 9.20 (d, *J*=1.88 Hz, 1 H).	ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate and **Intermediate 446**
Example 1118	 methyl 5-(2-(3-chloro-5-cyanophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinate	MS(ES): 544 (M+H) for C24H17ClF3N7O3. 1H NMR (300 MHz, DMSO-D6) δ ppm 2.35 (s, 3 H), 3.76 (s, 3 H), 3.92 (s, 3 H), 6.79 (s, 1 H), 7.53 - 7.75 (m, 2 H), 8.05 - 8.40 (m, 3 H), 9.05 (s, 1 H), 10.76 (s, 1 H).	**Intermediate 447** and **Intermediate 175**

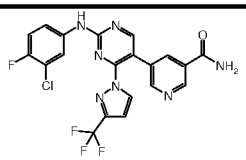
Ex	Compound	Data	SM
Example 1119	 ethyl 5-(2-(3-chloro-5-cyanophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinate	MS(ES): 528 (M+H) for C24H17ClF3N7O2. 1H NMR (300 MHz, DMSO-D6) δ ppm 1.27 - 1.38 (t, J=7.1 Hz, 3 H), 2.45 (s, 3 H), 4.25 - 4.38 (q, *J*=7.10 Hz, 2 H), 6.81 (s, 1 H), 7.62 - 7.73 (m, 1 H), 7.84 (t, *J*=2.07 Hz, 1 H), 8.17 (d, *J*=1.32 Hz, 1 H), 8.21 (d, *J*=1.98 Hz, 1 H), 8.63 (d, *J*=2.26 Hz, 1 H), 9.01 (d, *J*=2.07 Hz, 1 H), 9.10 (s, 1 H), 10.80 (s, 1 H).	**Intermediate 447** and ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate

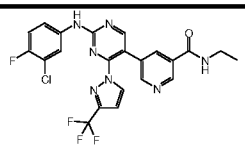
The following examples were prepared using the general method described for **example 214** using 1N sodium hydroxide, 1,4-dioxane and the starting material (SM) indicated.

Ex	Compound	Data	SM
Example 1120	 (E)-3-[3-[2-[(3-chloro-4-fluorophenyl)amino]-4-pyrazol-1-ylpyrimidin-5-yl]phenyl]prop-2-enoic acid	MS(ES): 436 (M+H) for C22H15ClFN5O2. 1H NMR (300 MHz, DMSO-D6) δ ppm 6.42 - 6.61 (m, 2 H), 7.15 (d, *J*=7.91 Hz, 1 H), 7.30 - 7.48 (m, 2 H), 7.49 - 7.66 (m, 4 H), 7.73 (dd, 1 H), 8.11 (dd, *J*=6.78, 2.64 Hz, 1 H), 8.31 (d, *J*=2.26 Hz, 1 H), 8.69 (s, 1 H), 10.28 (s, 1 H), 12.43 (s, 1 H).	**Example 1112**
Example 1121	 5-(2-(3-cyano-5-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinic acid	MS(ES): 484 (M+H) for C22H13F4N7O2. 1H NMR (300 MHz, DMSO-D6) δ ppm 2.44 (s, 3 H), 6.79 (s, 1 H), 7.42 - 7.58 (m, 1 H), 7.86 (t, *J*=2.17 Hz, 1 H), 7.95 - 8.13 (m, 2 H), 8.57 (d, *J*=2.26 Hz, 1 H), 8.98 (d, *J*=1.88 Hz, 1 H), 9.08 (s, 1 H), 10.82 (s, 1 H), 13.44 (s, 1 H).	**Example 1117**

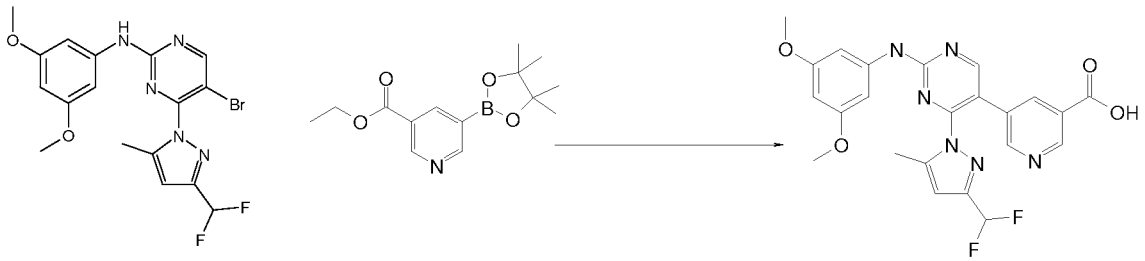
Ex	Compound	Data	SM
Example 1122	 5-(2-(3-chloro-5-cyanophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinic acid	MS(ES): 529.8 (M+H) for C23H15ClF3N7O3. 1H NMR (300 MHz, DMSO-D6) δ ppm 2.36 (s, 3 H), 3.92 (s, 3 H), 6.78 (s, 1 H), 7.49 - 7.82 (m, 2 H, 8.04 - 8.38 (m, 3 H), 9.04 (s, 1 H), 10.74 (s, 1 H), 12.94 (s, 1 H).	**Example 1118**
Example 1123	 5-(2-(3-chloro-5-cyanophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinic acid	MS(ES): 500 (M+H) for C22H13ClF3N7O2. 1H NMR (300 MHz, DMSO-D6) δ ppm 2.45 (s, 3 H), 6.80 (s, 1 H), 7.68 (d, *J*=1.51 Hz, 1 H), 7.86 (t, *J*=2.07 Hz, 1 H), 8.08 - 8.30 (m, 2 H), 8.57 (d, *J*=2.26 Hz, 1 H), 8.98 (d, *J*=1.88 Hz, 1 H), 9.08 (s, 1 H), 10.78 (s, 1 H), 13.44 (s, 1 H).	**Example 1119**

The following examples were prepared using the general HATU coupling method described for **Example 360** using **Example 320** and the starting material indicated.

Ex	Compound	Data	SM
Example 1124	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)pyrazol-1-yl]pyrimidin-5-yl]pyridine-3-carboxamide	MS(ES): 478 (M+H) for C20H12ClF4N7O. 1H NMR (300 MHz, DMSO-D6) δ ppm 6.99 (d, *J*=2.64 Hz, 1 H), 7.37 (t, *J*=9.14 Hz, 1 H), 7.57 (s, 1 H), 7.62 - 7.76 (m, 1 H), 7.94 - 8.16 (m, 3 H), 8.42 (d, *J*=2.26 Hz, 1 H), 8.48 (d, *J*=1.70 Hz, 1 H), 8.77 (s, 1 H), 8.91 (d, *J*=2.07 Hz, 1 H), 10.41 (s, 1 H).	Ammonia in dioxane (0.5M)

Ex	Compound	Data	SM
Example 1125	 5-[2-[(3-chloro-4-fluorophenyl)amino]-4-[3-(trifluoromethyl)pyrazol-1-yl]pyrimidin-5-yl]-N-ethylpyridine-3-carboxamide	MS(ES): 504 (M-H) for C22H16ClF4N7O. 1H NMR (300 MHz, DMSO-D^6) δ ppm 1.06 (t, *J*=7.25 Hz, 3 H); 3.11 - 3.41 (m, 2 H); 6.99 (d, *J*=2.64 Hz, 1 H); 7.37 (t, *J*=9.14 Hz, 1 H); 7.59 - 7.76 (m, 1 H); 7.95 - 8.14 (m, 2 H); 8.41 (d, *J*=2.07 Hz, 1 H); 8.48 (t, *J*=1.51 Hz, 1 H); 8.61 (t, *J*=5.46 Hz, 1 H); 8.77 (s, 1 H); 8.88 (d, *J*=2.07 Hz, 1 H); 10.42 (s, 1 H).	ethylamine

Intermediate 1126: 5-(4-(3-(difluoromethyl)-5-methyl-1H-pyrazol-1-yl)-2-(3,5-dimethoxyphenylamino)pyrimidin-5-yl)nicotinic acid

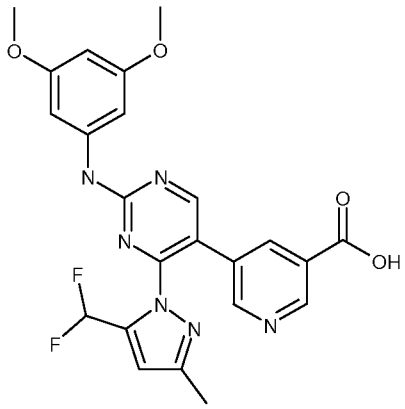
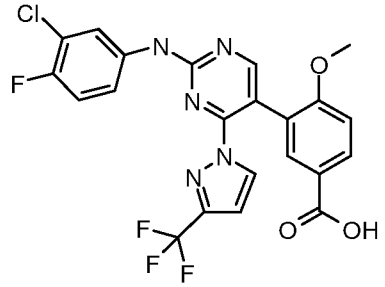


5-bromo-4-(3-(difluoromethyl)-5-methyl-1H-pyrazol-1-yl)-N-(3,5-dimethoxyphenyl)pyrimidin-2-amine **Intermediate 449** (210 mg, 0.48 mmol), ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (159 mg, 0.57 mmol), and PdCl2(dppf)-CH2Cl2Adduct (117 mg, 0.14 mmol) were combined in acetonitrile (10 mL) to give a yellow suspension. Sodium carbonate (60.7 mg, 0.57 mmol) was added, followed by water (2.500 mL) and the mixture was degassed with argon then heated at 80 °C for 4 hours. Adsorption onto silica gel, followed by flash chromatography (0.5-10% methanol in dichloromethane) gave the intermediate ester compound (235 mg) which was hydrolyzed to the corresponding carboxylic acid without further characterization as follows: The ester was dissolved in Dioxane (5 ml), then 1N NaOH solution (0.690 ml, 0.69 mmol) was added and the mixture was allowed to stir at room temperature for 6 hours. The reaction mixture was neutralized with 1M HCl followed by purification by reverse

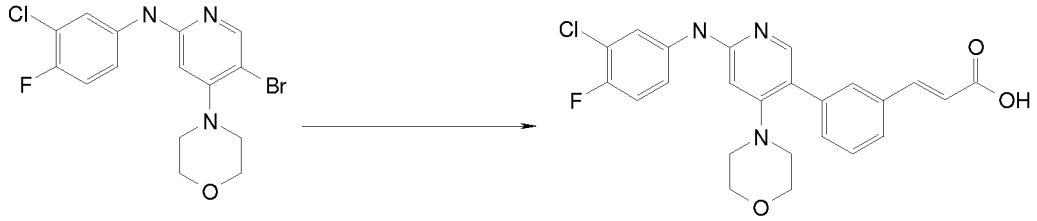
phase chromatography (C18: 5-95% acetonitrile in water, 0.5% TFA) to give the title compound (89 mg). MS:ES+ 482.44 for $C_{23}H_{20}F_2N_6O_4$

1H NMR (300 MHz, DMSO-d6) δ ppm 2.41 (s, 3 H) 3.73 (s, 6 H) 6.10 - 6.37 (m, 1 H) 6.55 (s, 2 H) 7.06 (s, 2H) 7.75 - 7.99 (m, 1 H) 8.39 - 8.65 (m, 1 H) 8.93 (br. s., 2 H) 10.05 - 10.34 (m, 1 H) 13.25 - 13.64 (m, 1 H)

The compounds in the below table were prepared using this procedure and the specified starting materials.

Ex	Compound	Data	SM
Example 1127	 5-(4-(5-(difluoromethyl)-3-methyl-1H-pyrazol-1-yl)-2-(3,5-dimethoxyphenylamino)pyrimidin-5-yl)nicotinic acid	MS:ES+ 482.44 for $C_{23}H_{20}F_2N_6O_4$ 1H NMR (300 MHz, DMSO-*d6*) □ppm 1.98 (s, 3 H) 3.74 (s, 6 H) 6.23 (br. s., 1 H) 6.72 (s, 1 H) 7.01 (d,*J*=1.32 Hz, 2 H) 7.96 (br. s., 2 H) 8.50 (br. s., 1 H) 8.79 (s, 1 H) 8.96 (br. s., 1 H) 9.97 (s, 1 H) 13.21 - 13.86(m, 1 H)	ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate and **Intermediate 450**
Example 1128	 3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-4-methoxybenzoic acid	MS: ES+ 508.82 for $C_{22}H_{14}ClF_4N_5O_3$ H NMR (300 MHz, DMSO-d6) d ppm 3.44 (br. s., 3 H) 6.97 (br. s., 2 H) 7.41 (br. s., 1 H) 7.73 (br. s., 1 H) 7.87 (br. s., 2 H) 8.10 (br. s., 1 H) 8.42 (br. s., 1 H) 8.67 (br. s., 1 H) 10.34 (br. s., 1 H) 12.35 - 13.05 (m, 1 H)	2-methoxy-5-(methoxycarbonyl)phenylboronic acid And **Intermediate 115**

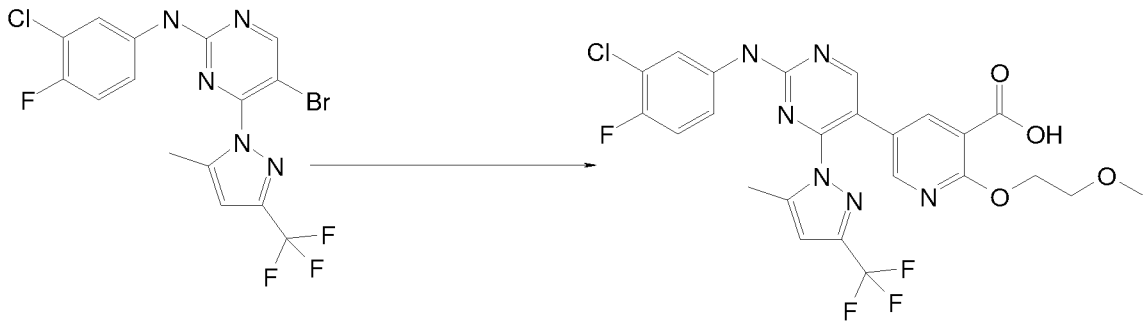
Example 1129: (E)-3-(3-(6-(3-chloro-4-fluorophenylamino)-4-morpholinopyridin-3-yl)phenyl)acrylic acid



5-bromo-N-(3-chloro-4-fluorophenyl)-4-morpholinopyridin-2-amine **Intermediate 454** (80 mg, 0.21 mmol), (E)-3-(3-boronophenyl)acrylic acid (55.6 mg, 0.29 mmol), and Pd2(dba)3 (18.95 mg, 0.02 mmol) were combined in acetonitrile (8 mL) to give a suspension. Dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (29.6 mg, 0.06 mmol) and Na_2CO_3 (43.9 mg, 0.41 mmol) were added followed by water (2.000 mL). The reaction was degassed with argon then heated at 80 °C for 30 minutes. Adsorption onto silica gel followed by purification by flash chromatography (3-25% methanol in dichloromethane) gave the title compound (52 mg). MS (Electrospray): 454.89 (MH^+) for $C_{24}H_{21}ClFN_3O_3$

1H NMR (300 MHz, DMSO-d6) δ ppm 2.82 (br. s., 4 H) 3.54 (br. s., 4 H) 6.37 (s, 1 H) 6.49 - 6.64 (m, 1 H) 7.29 (s, 1 H) 7.48 (d, J=7.35 Hz, 3H) 7.61 (s, 2 H) 7.80 - 7.99 (m, 2 H) 8.05 - 8.26 (m, 1 H) 9.26 (s, 1 H),12.22 - 12.74 (m, 1 H)

Example 1130: 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-methoxyethoxy)nicotinic acid



5-bromo-N-(3-chloro-4-fluorophenyl)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine **Intermediate 113** (191 mg, 0.42 mmol), methyl 2-(2-methoxyethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate, **Intermediate 465** (200 mg, 0.59 mmol), $Pd_2(dba)_3$ (38 mg, 0.04 mmol) and dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (60 mg, 0.13 mmol) were combined in acetonitrile (10 mL) to give a yellow suspension. Sodium carbonate (67 mg, 0.64 mmol) was added, followed by water (2.500 mL) and the mixture was degassed using argon then heated at 80 °C for 4 hours. Purification by flash chromatography (0.5-10% methanol in dichloromethane) gave the intermediate carboxylic ester (265 mg), which was hydrolyzed to the corresponding carboxylic acid as below.

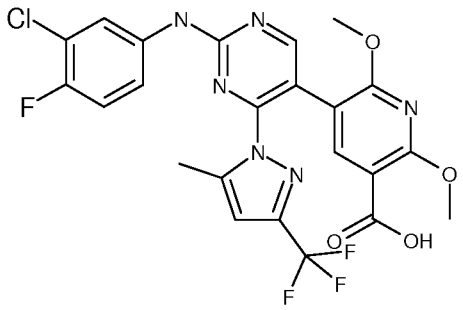
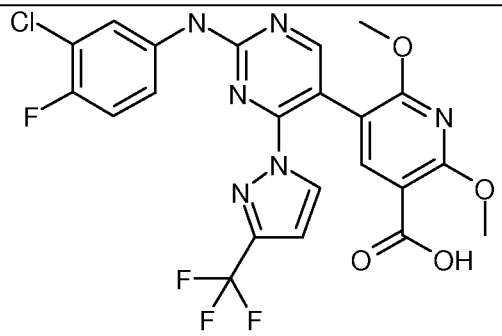
MS (Electrospray): 581.92 (MH^+) for $C_{25}H_{21}ClF_4N_6O_4$

The intermediate ester, methyl 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-methoxyethoxy)nicotinate (265mg, 0.45 mmol), was dissolved in THF (1 ml) and Dioxane (3 ml). 1N NaOH (1.12 ml, 1.12 mmol) was added and the mixture was allowed to stir at room temperature overnight. The reaction mixture was neutralized with 1M HCl then evaporated. The residue was purified by reverse phase chromatography (C18: 35-95% acetonitrile in water, 0.1% TFA) to give the title compound (60 mg). MS (Electrospray): 567 (MH^+) for $C_{24}H_{19}ClF_4N_6O_4$

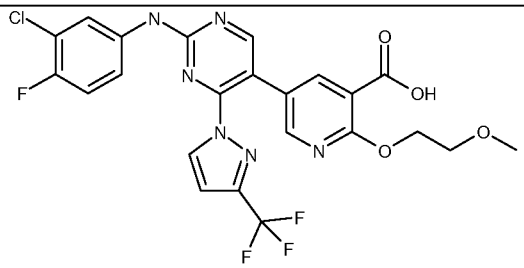
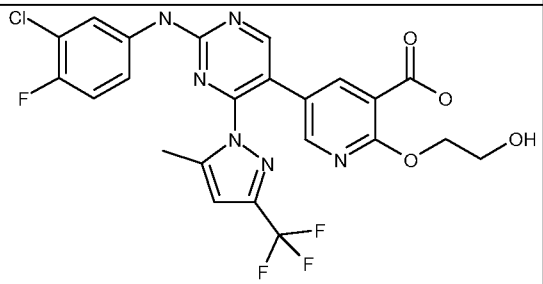
1H NMR (300 MHz, DMSO-*d*6) δ ppm 2.36 (s, 3 H) 3.30 (s, 3 H) 3.63 - 3.70 (m, 2 H), 4.33-4.54 (m, 2H), 6.76 (s, 1 H) 7.42 (t,*J*=9.14 Hz, 1 H) 7.64 (d, *J*=2.45 Hz, 2 H) 7.93 - 8.30 (m, 2 H) 8.95 (s, 1 H) 10.42 (s, 1 H) 12.90 (s, 1 H)

The Compounds in the below table were prepared using this procedure and the specified starting materials.

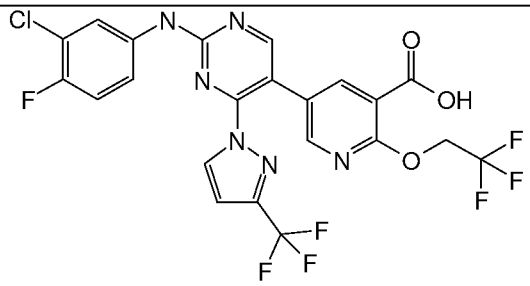
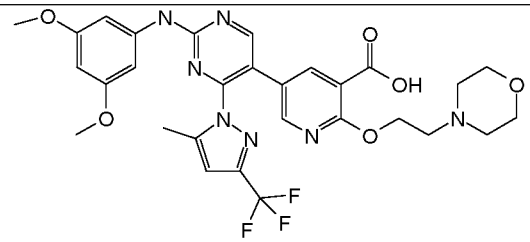
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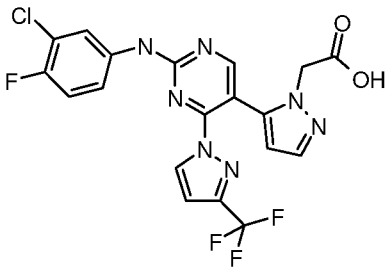
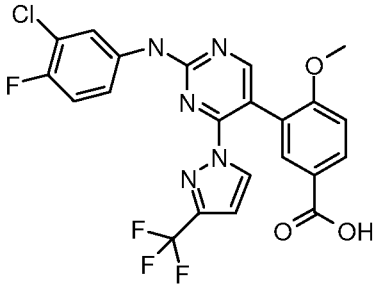
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1131	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2,6-dimethoxynicotinic acid	MS: ES+ 553.87 for $C_{23}H_{17}ClF_4N_6O_4$ 1H NMR (300 MHz, DMSO-*d6*) δ ppm 3.64 (s, 3 H) 3.94 (s, 3 H) 6.73 - 6.78 (m, 1 H) 7.39 - 7.49 (m, 1 H) 7.65 - 7.74 (m, 1 H) 8.05 (s, 1 H) 8.06 - 8.13 (m, 1 H) 8.82 (s, 1 H) 10.29 - 10.43 (m, 1 H) 12.48 - 12.68 (m, 1H)	methyl 2,6-dimethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 466** and **Intermediate 113**
Example 1132	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2,6-dimethoxynicotinic acid	MS: ES+ 539.84 for C22H15ClF4N6O4 1H NMR (300 MHz, DMSO-*d6*) δ ppm 3.58 (s, 3 H) 3.93 (s, 3 H) 7.02 (d, *J*=2.26 Hz, 1 H) 7.35 - 7.50 (m, 1H) 7.66 - 7.82 (m, 1 H) 8.01 - 8.13 (m, 2 H) 8.54 (br. s., 1 H) 8.69 (s, 1 H) 10.33 (s, 1 H) 12.24 - 12.92 (m, 1)	methyl 2,6-dimethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 466** and **Intermediate 115**

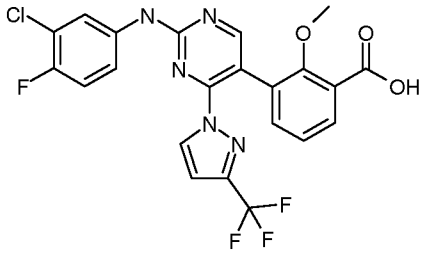
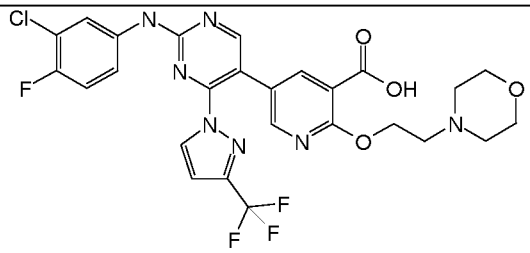
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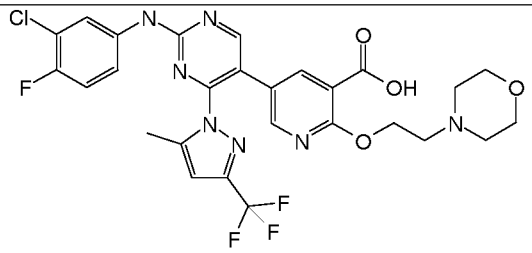
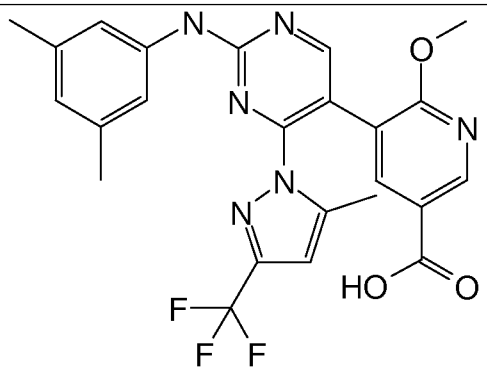
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1133	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-methoxyethoxy)nicotinic acid	552.87 $C_{23}H_{17}ClF_4O_4$ 1H NMR (300 MHz, DMF) δ ppm 3.31 (s, 3 H) 3.62 - 3.75 (m, 2 H) 4.42 - 4.54 (m, 2 H) 7.03 (d, J=2.64 Hz, 1H) 7.42 (s, 1 H) 7.66 - 7.78 (m, 1 H) 7.84 (d, J=2.45 Hz, 1 H) 8.00 - 8.13 (m, 1 H) 8.20 (d, J=2.45 Hz, 1 H) 8.50 (d, J=1.70 Hz, 1 H) 8.79 (s, 1 H) 10.38 (s, 1 H) 12.77 - 13.00 (m, 1 H)	methyl 2-(2-methoxyethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 465** and **Intermediate 115**
Example 1134	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-hydroxyethoxy)nicotinic acid	552.88 $C_{23}H_{17}ClF_4O_4$ 1H NMR (300 MHz, DMSO-*d6*) δppm 2.34 (s, 3 H) 3.70 (t, *J*=5.46 Hz, 2 H) 4.36 (t, *J*=5.37 Hz, 2 H) 6.75 (s,1 H) 7.42 (t, *J*=9.04 Hz, 1 H) 7.90 - 8.27 (m, 2 H) 8.95 (s, 1 H) 10.41 (s, 1 H)	methyl 2-(2-hydroxyethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 467** and **Intermediate 113**

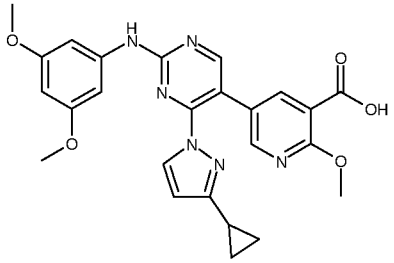
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Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1135	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2,2,2-trifluoroethoxy)nicotinic acid	MS: ES+ 577.81 for $C_{22}H_{12}ClF_7N_6O_3$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 5.11 (d, J=8.85 Hz, 2 H) 7.04 (d, J=2.64 Hz, 1 H) 7.42 (s, 1 H) 7.67 -7.80 (m, 1 H) 7.95 (d, J=2.45 Hz, 1 H) 7.99 - 8.14 (m, 1 H) 8.27 (d, J=2.45 Hz, 1 H) 8.53 (d, J=1.51 Hz, 1 H) 8.80 (s, 1 H) 10.40 (s, 1 H) 13.10 (s, 1 H)	methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(2,2,2-trifluoroethoxy) nicotinate **Intermediate 469** and **Intermediate 115**
Example 1136	 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-morpholinoethoxy)nicotinic acid	MS: ES+ 630.59 for $C_{29}H_{30}F_3N_7O_6$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 2.35 (s, 3 H) 3.09 - 4.29 (m, 10 H) 3.74 (s, 6 H) 4.70 (br. s., 2 H) 6.14 - 6.34 (m, 1 H) 6.77 (s, 1 H) 7.06 (d, J=2.07 Hz, 2 H) 7.74 (d, J=2.45 Hz, 1 H) 8.22 (d, J=2.45 Hz, 1 H) 8.93 (s, 1 H) 10.20 (s, 1 H)	methyl 2-(2-morpholinoethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 468 and** **Intermediate 216**

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1137	 2-(5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1H-pyrazol-1-yl)acetic acid	MS: ES+ 482.79 $C_{19}H_{12}ClF_4N_7O_2$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 4.94 (s, 2 H) 7.06 (d, J=2.45 Hz, 1 H) 7.24 (s, 1 H) 7.39 (s, 1 H) 7.68(s, 2 H) 7.95 - 8.17 (m, 1 H) 8.39 (d, J=1.70 Hz, 1 H) 8.93 (s, 1 H) 10.33 (s, 1 H) 13.07 (s, 1 H)	ethyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)acetate and **Intermediate 115**
Example 1138	 3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-4-methoxybenzoic acid	MS: ES+ 508.82 for $C_{22}H_{14}ClF_4N_5O_3$ H NMR (300 MHz, DMSO-d6) d ppm 3.44 (br. s., 3 H) 6.97 (br. s., 2 H) 7.41 (br. s., 1 H) 7.73 (br. s., 1 H) 7.87 (br. s., 2 H) 8.10 (br. s., 1 H) 8.42 (br. s., 1 H) 8.67 (br. s., 1 H) 10.34 (br. s., 1 H) 12.35 - 13.05 (m, 1 H)	2-methoxy-5-(methoxycarbonyl)phenylboronic acid and **Intermediate 115**

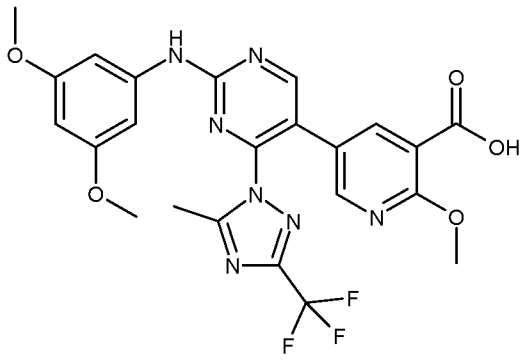
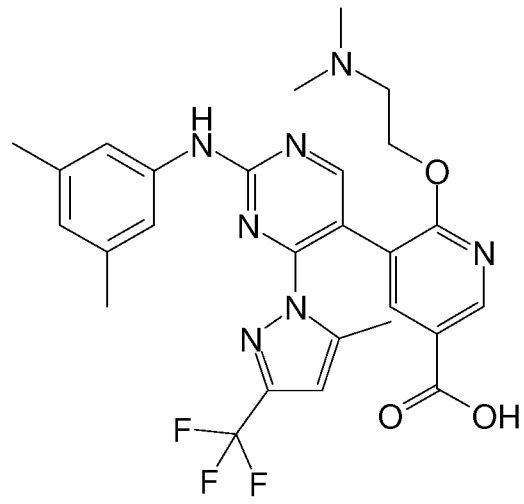
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1139	 3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxybenzoic acid	MS: ES+ 508.82 for $C_{22}H_{14}ClF_4N_5O_3$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 3.37 (br. s., 3 H) 6.97 (br. s., 1 H) 7.21 (br. s., 1 H) 7.41 (br. s., 3 H)7.71 (br. s., 2 H) 8.11 (br. s., 1 H) 8.46 (br. s., 1 H) 8.66 (br. s., 1 H) 10.35 (br. s., 1 H) 12.75 - 13.01 (m, 1 H)	3-borono-2-methoxybenzoic acid and **Intermediate 115**
Example 1140	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-morpholinoethoxy)nicotinic acid	MS: ES+ 608.94 (M+1) $C_{26}H_{22}ClF_4N_7O_4$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 3.18 - 4.06 (m, 10 H) 4.66 - 4.80 (m, 2 H) 7.04 (d, J=2.64 Hz, 1 H)7.42 (t, J=9.14 Hz, 1 H) 7.63 - 7.78 (m, 1 H) 7.93 (d, 1 H) 8.08 (dd, J=6.78, 2.64 Hz, 1 H) 8.29 (d, J=2.45 Hz,1 H) 8.52 (d, J=1.70 Hz, 1 H) 8.79 (s, 1 H) 10.41 (s, 1 H)	methyl 2-(2-morpholinoethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 468** and **Intermediate 115**

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1141	 5-(2-(3-chloro-4-fluorophenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-(2-morpholinoethoxy)nicotinic acid	MS:ES+ 622.97 (m+1) $C_{27}H_{24}ClF_4N_7O_4$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 2.38 (s, 3 H) 3.20 - 4.09 (m, 8 H) 3.62 (d, J=4.90 Hz, 2 H) 4.70 (br. s.,2 H) 6.78 (s, 1 H) 7.38 - 7.51 (m, 1 H) 7.61 - 7.70 (m, 1 H) 7.73 (d, J=2.64 Hz, 1 H) 8.02 - 8.15 (m, 1 H) 8.23(d, J=2.45 Hz, 1 H) 8.96 (s, 1 H) 10.44 (s, 1 H)	methyl 2-(2-morpholinoethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 468** and **Intermediate 113**
Example 1142	 5-(2-(3,5-dimethylphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-6-methoxynicotinic acid	MS:ES+ 499.46 (M+1) $C_{24}H_{21}F_3N_6O_3$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 1.90 (s, 3 H) 2.26 (s, 6 H) 3.52 (s, 3 H) 6.69 (s, 1 H) 7.36 (s, 2 H) 8.00- 8.11 (m, 1 H) 8.45 - 8.61 (m, 2 H) 8.65 - 8.82 (m, 1 H) 9.93 - 10.06 (m, 1 H)	methyl 5-bromo-6-methoxynicotinate **Intermediate 470** and **Intermediate 218**

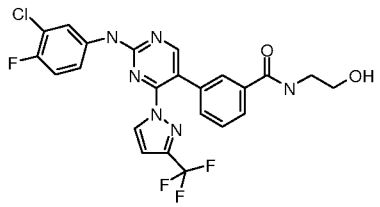
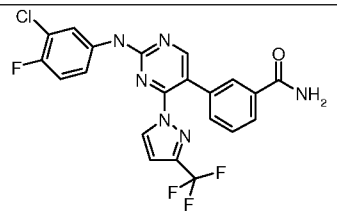
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1143	 5-(4-(3-cyclopropyl-1H-pyrazol-1-yl)-2-(3,5-dimethoxyphenylamino)pyrimidin-5-yl)-2-methoxynicotinic acid	MS:ES+ 489.50 (M+1) for $C_{25}H_{24}N_6O_5$ 1H NMR (300 MHz, DMSO-*d*6) δppm 0.15 (d, *J*=2.45 Hz, 2 H) 0.49 (dd, *J*=8.10, 2.26 Hz, 2 H) 1.31 - 1.54(m, 1 H) 3.51 (s, 6 H) 3.72 (s, 3 H) 5.95 (br. s., 1 H) 6.15 (d, *J*=2.45 Hz, 1 H) 6.84 (s, 2 H) 7.68 (d, *J*=2.26 Hz,1 H) 7.95 (d, *J*=2.26 Hz, 1 H) 8.07 (d, *J*=2.45 Hz, 1 H) 8.28 (s, 1 H) 9.65 (s, 1 H) 12.50 - 12.85 (m, 1 H)	methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 175** And methyl 5-(4-(3-cyclopropyl-1H-pyrazol-1-yl)-2-(3,5-dimethoxyphenylamino)pyrimidin-5-yl)-2-methoxynicotinate **Intermediate 471**

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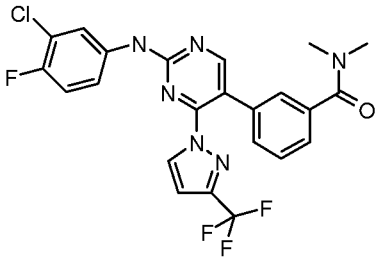
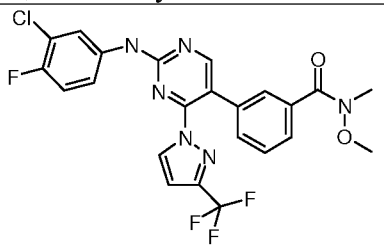
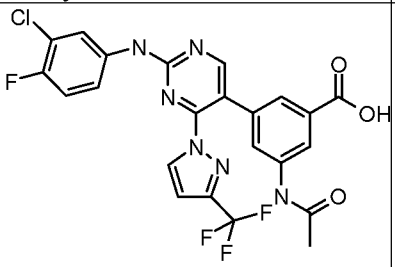
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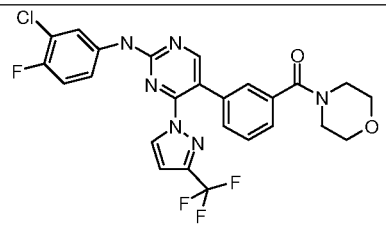
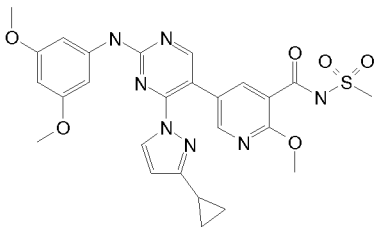
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1144	 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinic acid	MS:ES+ 531.44(M+1)for $C_{23}H_{20}F_3N_7O_5$ 1H NMR (300 MHz, DMSO-*d6*) δ ppm 2.56 (s, 3 H) 3.73 (s, 6 H) 3.93 (s, 3 H) 6.07 - 6.30 (m, 1 H) 7.03 (d, *J*=2.26 Hz, 2 H) 7.66 - 7.89 (m, 1 H) 8.12 - 8.36 (m, 1 H) 8.95 (s, 1 H) 10.05 - 10.41 (m, 1 H) 12.68 - 13.13 (m, 1 H)	methyl 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 175** and 5-bromo-N-(3,5-dimethoxyphenyl)-4-(5-methyl-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)pyrimidin-2-amine **Intermediate 472**
Example 1145	 6-(2-(dimethylamino)ethoxy)-5-(2-(3,5-dimethylphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinic acid	MS:ES+ 556.55 (M+1)for $C_{27}H_{28}F_3N_7O_3$ 1H NMR (300 MHz, DMSO-*d6*) δppm 2.27 (s, 6 H) 2.57 (s, 3 H) 2.74 (s, 6 H) 3.28 - 3.36 (m, 2 H) 4.29 - 4.47 (m, 2 H) 6.72 (d, *J*=2.83 Hz, 2 H) 7.36 (s, 2 H) 8.01 (d, *J*=2.26 Hz, 1 H) 8.67 (d, *J*=2.26 Hz, 1 H) 8.79 (s,1 H) 9.38 - 9.59 (m, 1 H) 10.03 (s, 1 H) 12.88 - 13.43 (m, 1 H)	methyl 6-(2-(dimethylamino) ethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate **Intermediate 476-B** And **Intermediate 218**

5 The compounds in the below table were prepared using the procedure described for **Example 1** and the specified starting materials.

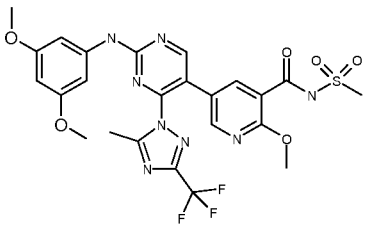
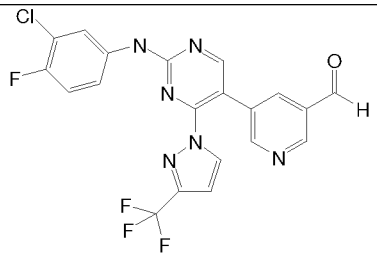
Compound	**Structure**	**Mass spectrum and ^{1}H NMR**	**SM**
Example 1146	 3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(2-hydroxyethyl)benzamide	MS: 521.89 ES+ for $C_{23}H_{17}ClF_4N_6O_2$ 1H NMR (300 MHz, DMSO-*d*6) δ ppm 3.33 (d, *J*=5.84 Hz, 2 H) 3.51 (d, *J*=5.84 Hz, 2 H) 4.71 (t, *J*=5.65 Hz,1 H) 6.98 (d, *J*=2.83 Hz, 1 H) 7.16 (d, *J*=7.91 Hz, 1 H) 7.31 - 7.46 (m, 2 H) 7.57 - 7.74 (m, 1 H) 7.75 - 7.91(m, 2 H) 8.13 (dd, *J*=6.78, 2.64 Hz, 1 H) 8.34 (d, *J*=1.70 Hz, 1 H) 8.43 (s, 1 H) 8.82 (s, 1 H) 10.41 (s, 1 H)	N(2-hydroxyethyl)-3-(4,4,5,5-tetramethyl1,3,2dioxaborolan-2yl)benzamide And **Intermediate 115**
Example 1147	 3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)benzamide	MS: ES+ 477.81 for $C_{21}H_{13}ClF_4N_6O$ 1H NMR (300 MHz, DMSO-*d*6) δ ppm 6.98 (d, *J*=2.64 Hz, 1 H) 7.18 - 7.24 (m, 1 H) 7.41 (d, *J*=2.83 Hz, 3 H)7.67 - 7.76 (m, 1 H) 7.78 (s, 1 H) 7.81 - 7.88 (m, 2 H) 7.88 - 8.00 (m, 1 H) 8.06 - 8.19 (m, 1 H) 8.26 - 8.43 (m,1 H) 8.82 (s, 1 H) 10.41 (s, 1 H)	3-carbamoylphenyl boronic acid And **Intermediate 115**

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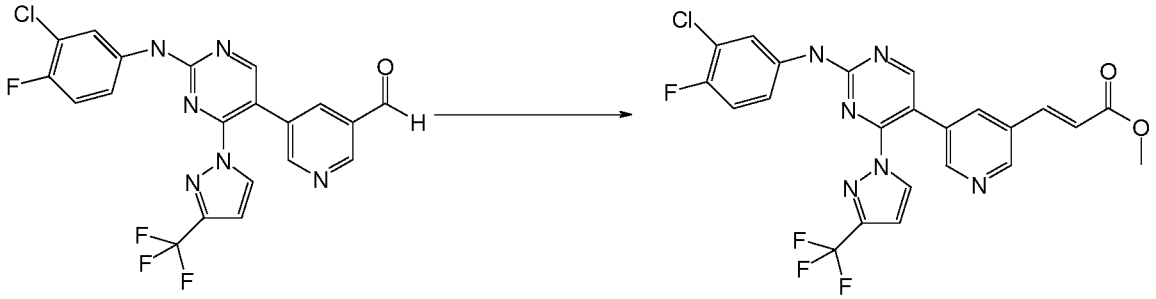
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1148	 3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N,N-dimethylbenzamide	MS: ES+ 505.87 for $C_{23}H_{17}ClF_4N_6O$ 1H NMR (300 MHz, DMSO-*d*6) δ ppm 2.73 - 3.01 (m, 6 H) 6.94 - 7.04 (m, 1 H) 7.10 - 7.19 (m, 1 H) 7.42 (d,*J*=8.85 Hz, 4 H) 7.67 - 7.78 (m, 1 H) 8.06 - 8.13 (m, 1 H) 8.34 - 8.46 (m, 1 H) 8.75 (s, 1 H) 10.15 - 10.48 (m, 1H)	3-(dimethylcarbamoyl)phenylboronic acid And **Intermediate 115**
Example 1149	 3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-methoxy-N-methylbenzamide	MS: ES+ 521.87 for $C_{23}H_{17}ClF_4N_6O_2$ 1H NMR (300 MHz, DMSO-*d*6) δ ppm 3.22 (s, 3 H) 3.50 (s, 3 H) 6.93 - 7.08 (m, 1 H) 7.26 - 7.50 (m, 5 H)7.51 - 7.61 (m, 1 H) 7.66 - 7.87 (m, 2 H) 8.06 - 8.18 (m, 1 H) 8.32 - 8.41 (m, 1 H) 8.77 (s, 1 H) 10.40 (s, 1 H)	3-(methoxy(methyl)carbamoyl)phenylboronic acid And **Intermediate 115**
Example 1150	 3-acetamido-5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)benzoic acid	MS: ES+ 535.85 for $C_{23}H_{15}ClF_4N_6O_3$ 1H NMR (300 MHz, DMSO-*d*6) δ ppm 2.05 (s, 3 H) 6.99 (d, *J*=2.64 Hz, 1 H) 7.33 (s, 1 H) 7.42 (s, 1 H) 7.69(s, 2 H) 8.16 (s, 2 H) 8.28 - 8.49 (m, 1 H) 8.75 (s, 1 H) 10.00 - 10.23 (m, 1 H) 10.41 (s, 1 H) 12.85 - 13.06 (m,1 H)	3-acetamido-5-boronobenzoic acid And **Intermediate 115**

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1151	 (3-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)phenyl)(morpholino)methanone	MS: ES+ 546.90 for $C_{25}H_{19}ClF_4N_6O_2$ 1H NMR (300 MHz, DMSO-*d*6) δ ppm 3.35 - 3.69 (m, 8 H) 6.97 - 7.04 (m, 1 H) 7.14 - 7.19 (m, 1 H) 7.30 -7.52 (m, 5 H) 7.61 - 7.80 (m, 1 H) 8.04 - 8.15 (m, 1 H) 8.36 - 8.45 (m, 1 H) 10.16 - 10.66 (m, 1 H)	3-(morpholine-4-carbonyl)phenylboronic acid And **Intermediate 115**
Example 1152	 5-(4-(3-cyclopropyl-1H-pyrazol-1-yl)-2-(3,5-dimethoxyphenylamino)pyrimidin-5-yl)-2-methoxy-N-(methylsulfonyl)nicotinamide	MS:ES+ 566.60 for (M+1) $C_{26}H_{27}N_7O_6S$ 1H NMR (300 MHz, DMSO-*d*6) δ ppm 0.36 - 0.52 (m, 2 H) 0.69 - 0.83 (m, 2 H) 1.63 - 1.84 (m, 1 H) 3.35 (s,3 H) 3.75 (s, 6 H) 4.00 (s, 3 H) 6.13 - 6.26 (m, 1 H) 6.31 - 6.46 (m, 1 H) 7.03 - 7.15 (m, 2 H) 7.85 - 7.97 (m, 1H) 8.15 - 8.24 (m, 1 H) 8.26 - 8.36 (m, 1 H) 8.49 - 8.58 (m, 1 H) 9.95 (s, 1 H) 11.67 (s, 1 H)	5-bromo-4-(3-cyclopropyl-1H-pyrazol-1-yl)-N-(3,5-dimethoxyphenyl)pyrimidin-2-amine **Intermediate 368** and **Intermediate 471**

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Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1153	 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)pyrimidin-5-yl)-2-methoxy-N-(methylsulfonyl)nicotinamide	MS:ES+ 609.55 for (M+1) $C_{24}H_{23}F_3N_8O_6S$ 1H NMR (300 MHz, DMSO-d_6) δ ppm 2.56 (s, 3 H) 3.33 (s, 3 H) 3.73 (s, 6 H) 3.95 (s, 3 H) 6.12 - 6.33 (m, 1H) 7.03 (d, J=2.07 Hz, 2 H) 7.72 - 7.98 (m, 1 H) 8.01 - 8.18 (m, 1 H) 8.94 (s, 1 H) 10.08 - 10.39 (m, 1 H)11.67 - 11.81 (m, 1 H)	2-methoxy-N-(methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinamide **Intermediate 368** and 5-bromo-N-(3,5-dimethoxyphenyl)-4-(5-methyl-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)pyrimidin-2-amine **Intermediate 472**
Example 1154	 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinaldehyde	MS:ES+ 463.79 for (M+1) $C_{20}H_{11}ClF_4N_6O$	5-bromo-N-(3-chloro-4-fluorophenyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine **Intermediate 115** And 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinaldehyde

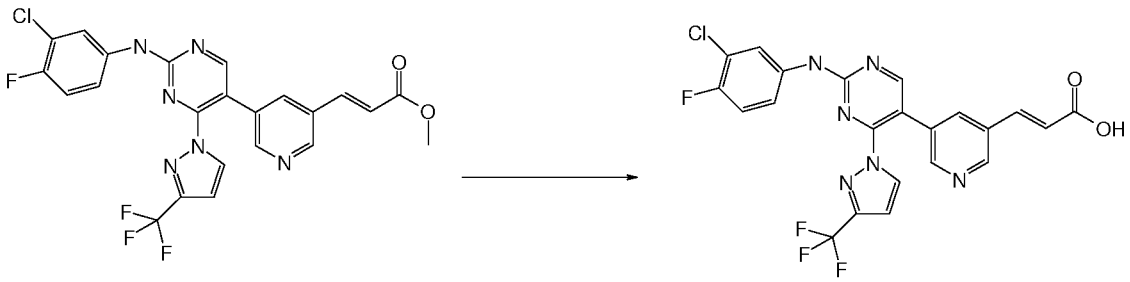
Example 1155: (E)-methyl 3-(5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)pyridin-3-yl)acrylate



Methyl 2-(diethoxyphosphoryl)acetate (0.102 mL, 0.51 mmol) was dissolved in THF (1 mL). NaH, 60% dispersion in oil, (30.7 mg, 0.77 mmol) was added and the suspension was stirred for 5 minutes to give a solution. The solution was then added to a mixture of 5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)nicotinaldehyde **Example 1154** (227 mg, 0.51 mmol) in THF (3 ml). The reaction mixture was then heated at 50 °C for 1 hour. Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, then dried with MgSO4, filtered and concentrated. The residue was triturated with diethyl ether to give a solid mass, which was collected and further rinsed with diethyl ether to give the title compound as an off white solid. (227 mg).

MS (Electrospray): 519 (MH^+) for $C_{23}H_{15}ClF_4N_6O_2$

Example 1156: (E)-3-(5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)pyridin-3-yl)acrylic acid



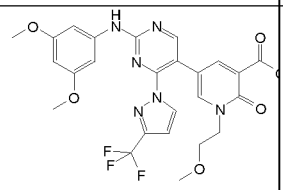
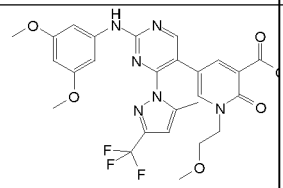
(E)-methyl 3-(5-(2-(3-chloro-4-fluorophenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)pyridin-3-yl)acrylate **Example 1155** (100 mg, 0.19 mmol) and 2M KOH (0.289 mL, 0.58 mmol) were combined in Dioxane (2 mL). The reaction mixture was allowed to stir at RT overnight, then neutralized with 1M HCl to pH 6. Water and 10% methanol in ethyl acetate were added and the layers were separated. The organic layer was dried with MgSO4 then concentrated down to a residue which was purified by reverse phase chromatography (C18: 15-95% acetonitrile in water with 0.1% TFA) to give the title compound (10 mg).

MS (Electrospray): 505.28 (MH^+) for $C_{22}H_{13}ClF_4N_6O_2$

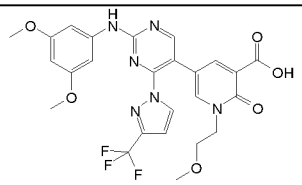
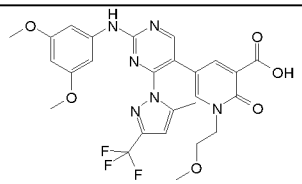
1H NMR (300 MHz, DMSO-*d6*) δppm 6.61 (d, *J*=16.20 Hz, 1 H) 7.06 (d, *J*=2.64 Hz, 1 H) 7.43 (t, *J*=9.04 Hz,1 H) 7.50 - 7.62 (m, 1 H) 7.74 (ddd, *J*=7.35, 4.52, 4.14 Hz, 1 H) 8.02 (s, 1 H) 8.09 (dd, *J*=6.69, 2.54 Hz, 1 H) 8.32 (d, *J*=1.88 Hz, 1 H) 8.53 (s, 1 H) 8.77 (d, *J*=1.70 Hz, 1 H) 8.85 (s, 1 H) 10.48 (s, 1 H) 12.65 (br. s., 1 H)

The compounds in the below table were prepared using the general method described above for **Example 1** using the specified starting materials.

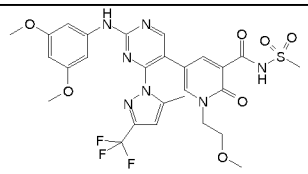
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Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1157	 methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 575 (M+1) for $C_{26}H_{25}F_3N_6O_6$. 1H NMR (300 MHz, DMSO-d6) δ ppm 3.23 (s, 3 H) 3.59 (t, J=5.37 Hz, 2 H) 3.69 (s, 3 H) 3.74 (s, 6 H) 4.10 (t, J=5.46 Hz, 2 H) 6.21 (t, J=2.17 Hz, 1 H) 6.99 - 7.14 (m, 3 H) 7.70 (d, J=2.64 Hz, 1 H) 8.01 (d, J=2.83 Hz, 1 H) 8.43 - 8.60 (m, 1 H) 8.68 (s, 1 H) 10.12 (s, 1 H)	methyl 1-(2-methoxyethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate **Intermediate 476** and 5-bromo-N-(3,5-dimethoxyphenyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine **Intermediate 215**
Example 1158	 methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 589 (M+1) for $C_{27}H_{27}F_3N_6O_6$. 1H NMR (300 MHz, DMSO-d6) δ ppm 2.32 (s, 3 H) 3.22 (s, 3 H) 3.56 (t, J=5.27 Hz, 2 H) 3.66 (s, 3 H) 3.72 (s, 6 H) 3.95 - 4.19 (m, 2 H) 6.21 (t, J=2.26 Hz, 1 H) 6.77 (s, 1 H) 7.03 (d, J=2.26 Hz, 2 H) 7.35 (d, J=2.83 Hz, 1 H) 8.01 (d, J=2.83 Hz, 1 H) 8.82 (s, 1 H) 10.16 (s, 1 H))	methyl 1-(2-methoxyethyl)-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate **Intermediate 476** And 5-bromo-N-(3,5-dimethoxyphenyl)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine **Intermediate 216**

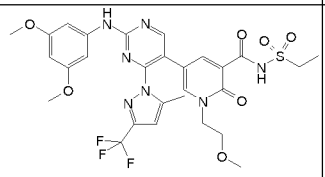
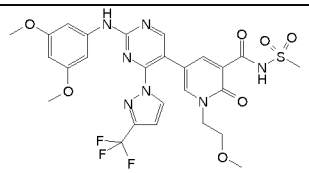
The compounds in the below table were prepared using the general method described above for Example **214** using 1N sodium hydroxide (2 equivalents), dioxane : THF (1:1) as solvent and the specified starting material.

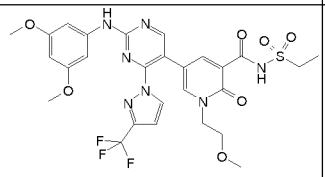
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1159	 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 561 (M+1) for $C_{25}H_{23}F_3N_6O_6$. 1H NMR (300 MHz, DMSO-d6) δ ppm 3.23 (s, 3 H) 3.67 (t, J=5.27 Hz, 2 H) 3.75 (s, 6 H) 4.29 (t, J=5.37 Hz, 2 H) 6.22 (t, J=2.17 Hz, 1 H) 6.97 - 7.16 (m, 3 H) 8.11 (d, J=2.64 Hz, 1 H) 8.27 (d, J=2.64 Hz, 1 H) 8.57 (dd, 1 H) 8.69 (s, 1 H) 10.17 (s, 1 H)	methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1157**
Example 1160	 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 575 (M+1) for $C_{26}H_{25}F_3N_6O_6$. 1H NMR (300 MHz, DMSO-d6) d ppm 2.45 (s, 3 H) 3.23 (s, 3 H) 3.65 (t, J=5.27 Hz, 2 H) 3.73 (s, 6 H) 4.27 (t, J=5.27 Hz, 2 H) 6.22 (t, J=2.17 Hz, 1 H) 6.79 (s, 1 H) 7.03 (d, J=2.07 Hz, 2 H) 7.75 (d, J=2.64 Hz, 1 H) 8.25 (d, J=2.83 Hz, 1 H) 8.82 (s, 1 H) 10.17 (s, 1 H) 14.27 (s, 1 H)	methyl 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1158**

The compounds in the below table were prepared using the general method described above for **Example 800** using 2-chloro-1-methylpyridinium iodide, 4-(Dimethylamino)pyridine and triethylamine, with CH_2Cl_2 as solvent and the carboxylic acid and sulfonamide starting materials listed.

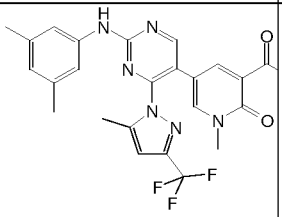
Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 1161	 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-methoxyethyl)-N-(methylsulfonyl)-2-oxo-1,2-dihydropyridine-3-carboxamide	MS(ES): 652 (M+1) for $C_{27}H_{28}F_3N_7O_7S$. 1H NMR (300 MHz, DMSO-d6) δ ppm 2.43 (s, 3 H) 3.23 (s, 3 H) 3.35 (s, 3 H) 3.62 (t, J=5.27 Hz, 2 H) 3.73 (s, 6 H) 4.11 - 4.35 (m, 2 H) 6.22 (t, J=2.17 Hz, 1 H) 6.79 (s, 1 H) 7.03 (d, J=2.26 Hz, 2 H) 7.83 (d, J=2.64 Hz, 1 H) 8.23 (d, J=2.45 Hz, 1 H) 8.83 (s, 1 H) 10.18 (s, 1 H) 12.61 (s, 1 H)	5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid **Example 1160** And Methanesulfonamide

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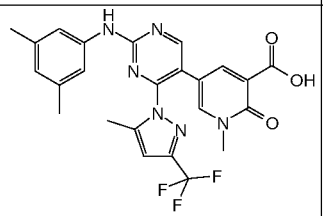
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1162	 5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(ethylsulfonyl)-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxamide	MS(ES): 666 (M+1) for $C_{28}H_{30}F_3N_7O_7S$. 1H NMR (300 MHz, DMSO-d6) δ ppm 1.22 (t, J=7.35 Hz, 3 H) 2.45 (s, 3 H) 3.23 (s, 3 H) 3.41 - 3.56 (m, 2 H) 3.63 (t, J=5.09 Hz, 2 H) 3.73 (s, 6 H) 4.24 (t, J=5.18 Hz, 2 H) 6.22 (t, J=2.17 Hz, 1 H) 6.79 (s, 1 H) 7.03 (d, J=2.07 Hz, 2 H) 7.79 (d, J=2.64 Hz, 1 H) 8.25 (d, J=1.88 Hz, 1 H) 8.83 (s, 1 H) 10.17 (s, 1 H) 12.56 (s, 1 H)	5-(2-(3,5-dimethoxyphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid **Example 1160** And Ethanesulfonamide
Example 1163	 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-methoxyethyl)-N-(methylsulfonyl)-2-oxo-1,2-dihydropyridine-3-carboxamide	MS(ES): 638 (M+1) for $C_{26}H_{26}F_3N_7O_7S$. 1H NMR (300 MHz, DMSO-d6) δ ppm 3.23 (s, 3 H) 3.36 (s, 3 H) 3.65 (t, J=5.27 Hz, 2 H) 3.75 (s, 6 H) 4.25 (t, J=4.14 Hz, 2 H) 6.22 (t, J=2.26 Hz, 1 H) 6.95 - 7.14 (m, 3 H) 8.16 (br. s., 1 H) 8.27 (br. s., 1 H) 8.56 (s, 1 H) 8.70 (s, 1 H) 10.17 (s, 1 H) 12.73 (s, 1 H))	5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid **Example 1159** And Methanesulfonamide

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1164	 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-N-(ethylsulfonyl)-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxamide	MS(ES): 652(M+1) for $C_{27}H_{28}F_3N_7O_7S$. 1H NMR (300 MHz, DMSO-d6) δ ppm 1.22 (t, J=7.35 Hz, 3 H) 3.23 (s, 3 H) 3.49 (q, J=7.66 Hz, 2 H) 3.66 (t, J=5.18 Hz, 2 H) 3.75 (s, 6 H) 4.26 (t, J=5.09 Hz, 2 H) 6.22 (t, J=2.17 Hz, 1 H) 6.69 (s, 1 H) 7.08 (d, J=2.07 Hz, 2 H) 8.13 (d, J=2.26 Hz, 1 H) 8.28 (s, 1 H) 8.57 (s, 1 H) 8.69 (s, 1 H) 10.16 (s, 1 H) 12.68 (s, 1 H)	5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid **Example 1159** And Ethanesulfonamide

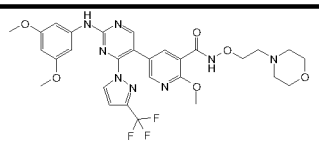
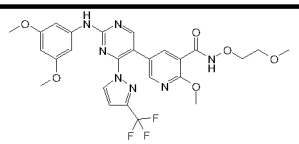
The compound in the below table was prepared using the general method described above for **Example 858** using the specified starting materials.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1165	 methyl 5-(2-(3,5-dimethylphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 513 (M+1) for $C_{25}H_{23}F_3N_6O_3$. 1H NMR (300 MHz, DMSO-d6) δ ppm 2.25 (s, 6 H) 2.40 (s, 3 H) 3.47 (s, 3 H) 3.65 (s, 3 H) 6.68 (s, 1 H) 6.78 (s, 1 H) 7.28 (d, J=2.83 Hz, 1 H)7.34 (s, 2 H) 8.15 (d, J=2.64 Hz, 1 H) 8.83 (s, 1 H) 10.03 (s, 1 H)	[5-(methoxycarbonyl)-1-methyl-6-oxo-1,6-dihydropyridin-3-yl]boronic acid **Intermediate 323** And 5-bromo-N-(3,5-dimethylphenyl)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-2-amine **Intermediate 218**

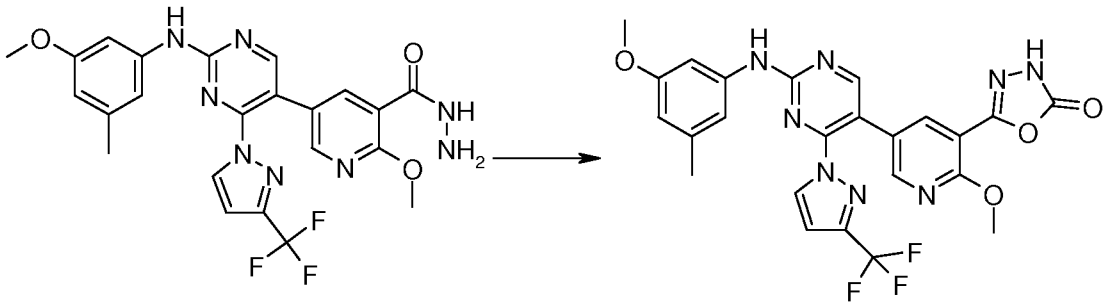
The compound in the below table was prepared using the general method described above for **Example 859** using the specified starting material.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1166	 5-(2-(3,5-dimethylphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 499 (M+1) for $C_{24}H_{21}F_3N_6O_3$. 1H NMR (300 MHz, DMSO-d6) δ ppm 2.26 (s, 6 H) 2.51 (br. s., 3 H) 3.67 (s, 3 H) 6.70 (s, 1 H) 6.79 (s, 1 H) 7.34 (s, 2 H) 7.65 (d, J=2.64 Hz, 1 H)8.40 (d, J=2.64 Hz, 1 H) 8.83 (s, 1 H) 10.06 (s, 1 H) 14.39 (s, 1 H))	methyl 5-(2-(3,5-dimethylphenylamino)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate **Example 1165**

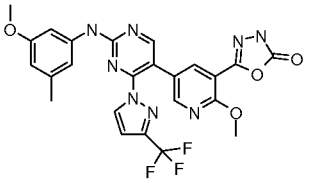
The following examples were prepared using the general HATU coupling method described for **Example 360** using the starting materials (SM) indicated.

Ex	Compound	Mass spectrum and ^{1}H NMR	SM
Example 1167	 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxy-N-(2-morpholinoethoxy)nicotinamide	MS(ES): 645 (M+1) for $C_{29}H_{31}F_3N_8O_6$ 1H NMR (300 MHz, DMSO-D6) δ ppm 3.21 (br s, 2 H) 3.40 - 3.53 (m, 2 H) 3.60 (s, 2 H) 3.75 (s, 8 H) 3.93 - 4.07 (m, 5 H) 4.24 (t, 2 H) 6.22 (t, J=2.17 Hz, 1 H) 7.04 (d, J=2.64 Hz, 1 H) 7.10 (d, J=2.07 Hz, 2 H) 7.91 (d, J=2.45 Hz, 1 H) 8.21 (d, J=2.45 Hz, 1 H) 8.48 (d, J=1.70 Hz, 1 H) 8.66 - 8.89 (m, 1 H) 10.17 (s, 1 H) 11.67 (s, 1 H).	O-(2-morpholinoethyl)hydroxylamine and 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinic acid **Example 675**
Example 1168	 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxy-N-(2-methoxyethoxy)nicotinamide	MS(ES): 590 (M+1) for $C_{26}H_{26}F_3N_7O_6$ 1H NMR (300 MHz, DMSO-D6) δ ppm 3.30 (s, 3 H) 3.51 - 3.64 (m, 2 H) 3.75 (s, 6 H) 3.90 - 4.09 (m, 5 H) 6.21 (t, J=2.26 Hz, 1 H) 7.02 (d, J=2.64 Hz, 1 H) 7.11 (d, J=2.26 Hz, 2 H) 7.82 (d, J=2.45 Hz, 1 H) 8.16 (d, J=2.45 Hz, 1 H) 8.44 (d, J=1.51 Hz, 1 H) 8.75 (s, 1 H) 10.16 (s, 1 H) 11.26 (s, 1 H).	O-(2-methoxyethyl)hydroxylamine and 5-(2-(3,5-dimethoxyphenylamino)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyrimidin-5-yl)-2-methoxynicotinic acid **Example 675**

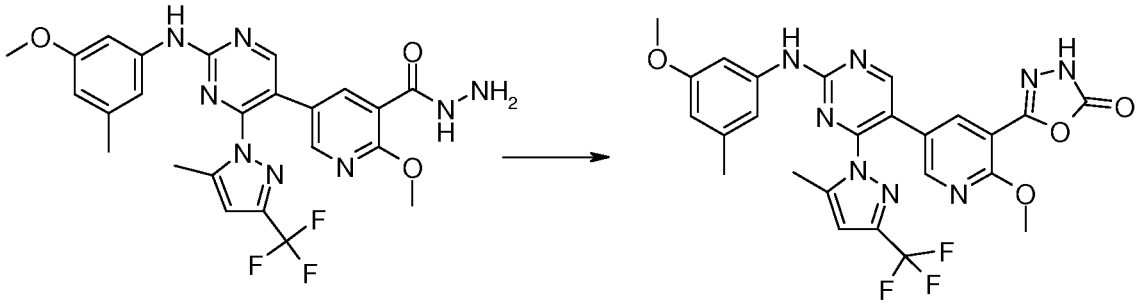
Example 1169: 5-(2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridin-3-yl)-1,3,4-oxadiazol-2(3*H*)-one



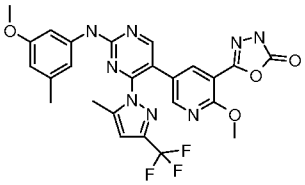
To a mixture of 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carbohydrazide (**Intermediate 477**, 0.58 mmol, 300 mg) and *N*,*N*-diisopropylethylamine (0.88 mmol, 0.16 mL) in DMF, was added 1,1′-carbonyldiimidazole (0.88 mmol, 142 mg) and the reaction mixture was stirred at RT for 1 h and further at 50 °C for another hour. The reaction mass was diluted with ethyl acetate (20 mL). The organic layer was separated, washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by silica gel column chromatography using ethyl acetate/hexanes (40:60) to obtain 90 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1169	 5-(2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridin-3-yl)-1,3,4-oxadiazol-2(3*H*)-one	MS (ES): 541 (M+1) for $C_{24}H_{19}F_3N_8O_4$. 400 MHz, DMSO-d_6: δ 2.28 (s, 3H), 3.74 (s, 3H), 3.99 (s, 3H), 6.46 (s, 1H), 7.03 (d, *J* = 2.60 Hz, 1H), 7.15 (s, 1H), 7.35 (s, 1H), 7.83 (d, *J* = 2.40 Hz, 1H), 8.25 (d, *J* = 2.40 Hz, 1H), 8.49 (d, *J* = 1.68 Hz, 1H), 8.77 (s, 1H), 10.14 (s, 1H), 12.64 (s, 1H).	**Intermediate 477** 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carbohydrazide

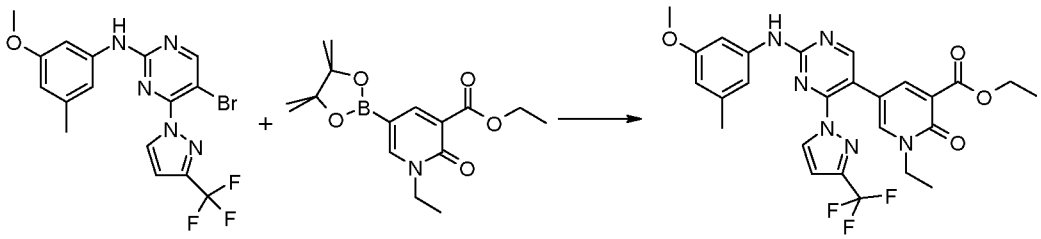
Example 1170: 5-(2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridin-3-yl)-1,3,4-oxadiazol-2(3*H*)-one



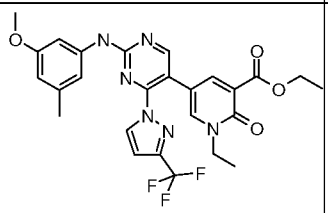
To a solution of the 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carbohydrazide (**Intermediate 478**, 0.13 mmol, 70 mg) in dry DMF(1 mL) was added *N*,*N*-diisopropylethylamine (0.20 mmol, 26 mg, 0.34 mL) and 1,1′-carbonyldiimidazole (0.20 mmol, 32 mg). The mixture was stirred for 1 h at RT and further heated at 50 °C for 1 h. The reaction mixture was diluted with DCM (15 mL) and further washed with water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by flash chromatography (product eluted with 40% EtOAc/hexanes) to afford the title compound as 35 mg of white solid.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1170	 5-(2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridin-3-yl)-1,3,4-oxadiazol-2(3*H*)-one	MS(ES): 555 (M+1) for $C_{25}H_{21}F_3N_8O_4$. 400 MHz, DMSO-d_6: δ 2.26 (s, 3H), 2.36 (s, 3H), 3.71 (s, 3H), 3.96 (s, 3H), 6.46 (s, 1H), 6.75 (s, 1H), 7.13 (s, 1H), 7.28 (s, 1H), 7.61 (d, *J* = 1.64 Hz, 1H), 8.13 (d, *J* = 1.60 Hz, 1H), 8.92 (s, 1H), 10.16 (s, 1H), 12.65 (s, 1H).	**Intermediate 478** 2-methoxy-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}pyridine-3-carbohydrazide

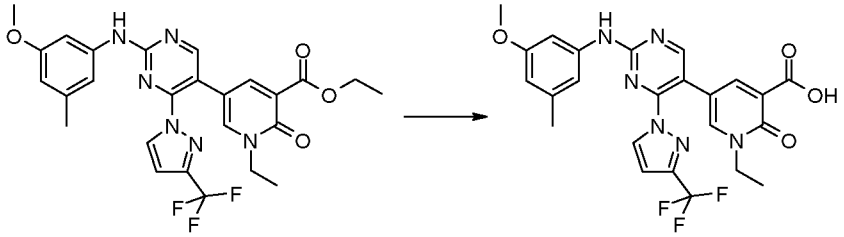
Example 1171: ethyl 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-oxo-1,2-dihydropyridine-3-carboxylate



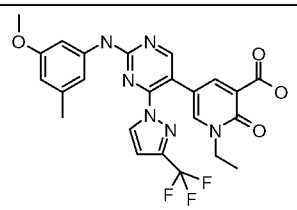
A solution of 5-bromo-*N*-(3-methoxy-5-methylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine (**Intermediate 293**, 0.9 mmol, 400 mg), a mixture of ethyl 1-ethyl-2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2-dihydropyridine-3-carboxylate and [5-(ethoxycarbonyl)-1-ethyl-6-oxo-1,6-dihydropyridin-3-yl]boronic acid (**Intermediate 361**, 1.1 mmol based on the boronic ester, 360 mg), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)complex with CH_2Cl_2 (0.18 mmol, 146 mg) and sodium carbonate (0.9 mmol, 95 mg) in acetonitrile (40 mL)/water (10 mL) was degassed and heated to 90 °C for 30 minutes under nitrogen. The reaction mixture was concentrated *in vacuo*. The residue obtained was taken in ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated. The crude mass was purified by silica gel column chromatography (60-120 mesh) using 2% methanol/chloroform to obtain 350 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1171	 ethyl 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-oxo-1,2-dihydropyridine-3-carboxylate	MS(ES): 543 (M+1) for $C_{26}H_{25}F_3N_6O_4$. 400 MHz, $CDCl_3$: δ 1.36-1.42 (m, 6H), 2.37 (s, 3H), 3.83 (s, 3H), 4.06 (q, *J* = 7.20 Hz, 2H), 4.35 (q, *J* = 7.16 Hz, 2H), 6.52 (s, 1H), 6.70 (d, *J* = 2.64 Hz, 1H), 6.92 (s, 1H), 7.20 (s, 1H), 7.41 (br s, 1H), 7.56 (d, *J* = 2.68 Hz, 1H), 7.98 (d, *J* = 2.72 Hz, 1H), 8.44 (s, 1H), 8.49 (d, *J* = 1.80 Hz, 1H) .	**Intermediate 361** and **Intermediate 293** 5-bromo-*N*-(3-methoxy-5-methylphenyl)-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-2-amine

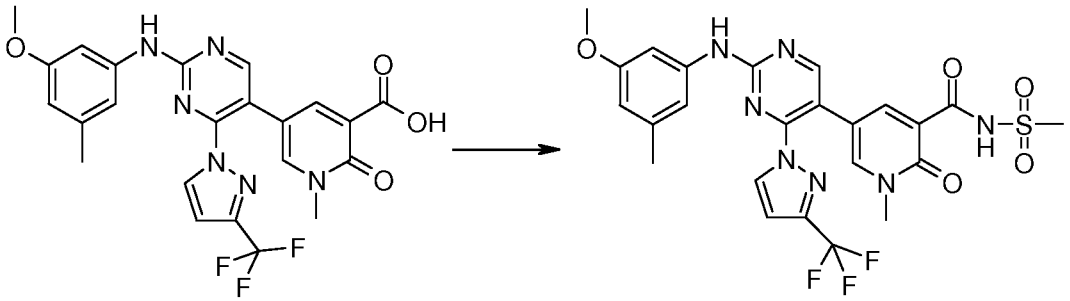
Example 1172: 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-oxo-1,2-dihydropyridine-3-carboxylic acid



To 350 mg of ethyl 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-oxo-1,2-dihydropyridine-3-carboxylate (**Example 1171**, 0.65 mmol) taken in a mixture of THF (10 mL) /H_2O (10 mL), was added NaOH (1.1 mmol, 46 mg) and stirred at rt for 2 h. The solvent was removed *in vacuo* and the mixture was then carefully acidified with 1 N HCl and the solid that precipitate was filtered and dried to obtain 200 mg of the title compound.

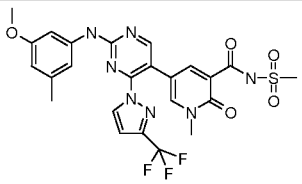
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1172	 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-oxo-1,2-dihydropyridine-3-carboxylic acid	MS(ES): 515 (M+1) for $C_{24}H_{21}F_3N_6O_4$. 400 MHz, DMSO-d_6: δ 1.31 (t, J = 7.12 Hz, 3H), 2.28 (s, 3H), 3.74 (s, 3H), 4.14 (q, J = 6.92 Hz, 2H), 6.46 (s, 1H), 7.08 (d, J = 2.44 Hz, 1H), 7.14 (s, 1H), 7.32 (s, 1H), 8.10 (d, J = 2.40 Hz, 1H), 8.38 (s, 1H), 8.58 (s, 1H), 8.74 (s, 1H), 10.15 (s, 1H) .	**Example 1171** ethyl 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-oxo-1,2-dihydropyridine-3-carboxylate

Example 1173: 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-*N*-(methylsulfonyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

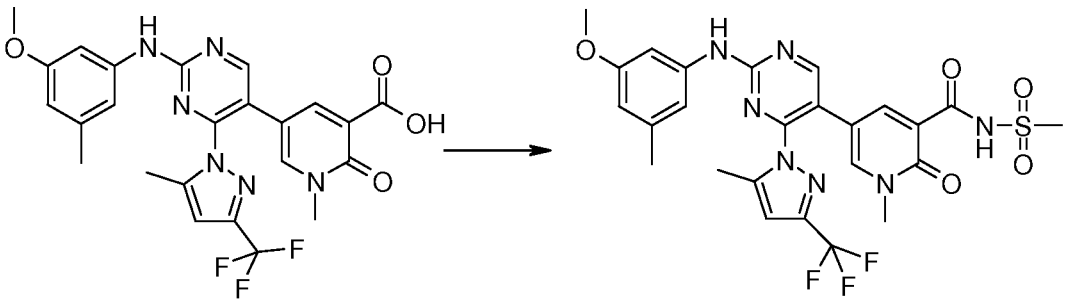


To a solution of 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (**Example 859**, 0.19 mmol, 100 mg) in CH_2Cl_2 (10 mL), were added methanesulfonamide (0.29 mmol, 28 mg), triethylamine (0.57 mmol, 0.08 mL), 2-chloro-1-methylpyridinium iodide (0.2 mmol, 58 mg) and 4-(Dimethylamino)pyridine (0.04 mmol, 4 mg) and stirred at RT for 2 h. The reaction mixture was diluted with dichloromethane (20 mL) and further washed with 10% citric acid solution (2 x

15 mL), water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by flash chromatography (product eluted with 2 % MeOH in $CHCl_3$) to afford 85 mg of the title compound.

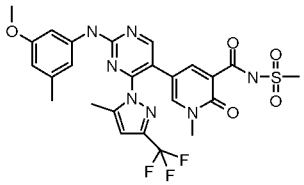
Compound	Structure	Mass spectrum and ^1H NMR	SM
Example 1173	 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-*N*-(methylsulfonyl)-2-oxo-1,2-dihydropyridine-3-carboxamide	MS(ES): 578 (M+1) for $C_{24}H_{22}F_3N_7O_5S$. 400 MHz, DMSO-d_6: δ 2.29 (s, 3H), 3.36 (s, 3H), 3.66 (s, 3H), 3.75 (s, 3H), 6.48 (s, 1H), 7.10 (d, *J* = 2.64 Hz, 1H), 7.15 (s, 1H), 7.34 (s, 1H), 8.09 (d, *J* = 2.64 Hz, 1H), 8.45 (d, *J* = 2.68 Hz, 1H), 8.59 (d, *J* = 1.76 Hz, 1H), 8.73 (s, 1H), 10.16 (s, 1H), 12.82 (s, 1H).	**Example 859** 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

Example 1174: 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-*N*-(methylsulfonyl)-2-oxo-1,2-dihydropyridine-3-carboxamide

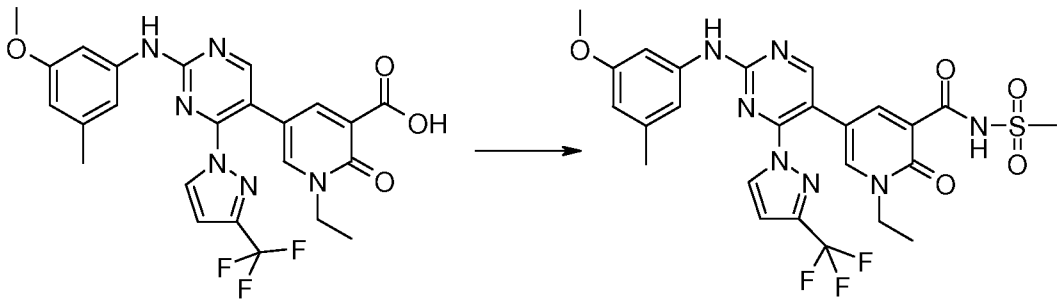


To a solution of 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (**Example 861**, 0.49 mmol, 250 mg) in CH_2Cl_2 (20 mL), was added methanesulfonamide (0.97 mmol, 92

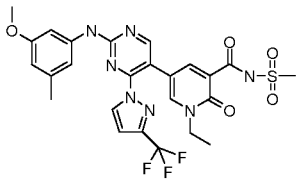
mg), triethylamine (1.45 mmol, 0.21 mL), 2-chloro-1-methylpyridinium iodide (0.58 mmol, 150 mg) and 4-(Dimethylamino)pyridine (0.097 mmol, 12 mg) and stirred at RT for 4 h. The reaction mixture was diluted with dichloromethane (20 mL) and further washed with 1.5 N HCl (2 x 15 mL), water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by flash chromatography (product eluted with 1 % MeOH in $CHCl_3$) to afford 120 mg of the title compound.

Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1174	 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-*N*-(methylsulfonyl)-2-oxo-1,2-dihydropyridine-3-carboxamide	MS(ES): 592 (M+1) for $C_{25}H_{24}F_3N_7O_5S$. 400 MHz, DMSO-d_6: δ 2.26 (s, 3H), 2.47-2.50 (m, 6H), 3.62 (s, 3H), 3.71 (s, 3H), 6.46 (s, 1H), 6.81 (s, 1H), 7.11 (s, 1H), 7.25 (s, 1H), 7.70 (d, J = 2.68 Hz, 1H), 8.40 (d, J = 2.68 Hz, 1H), 8.86 (s, 1H), 10.15 (s, 1H).	**Example 861** 5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

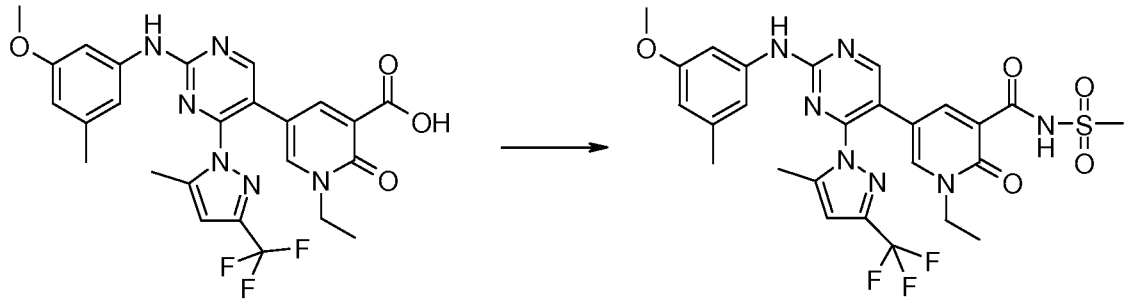
Example 1175: 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(methylsulfonyl)-2-oxo-1,2-dihydropyridine-3-carboxamide



A mixture of 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-oxo-1,2-dihydropyridine-3-carboxylic acid (**Example 1172**, 0.53 mmol, 270 mg), methanesulfonamide (0.78 mmol, 74 mg), triethylamine (1.5 mmol, 0.21 mL), 2-chloro-1-methylpyridinium iodide (0.6 mmol, 153 mg) and 4-(Dimethylamino)pyridine (0.097 mmol, 12 mg) in CH_2Cl_2 (10 mL), was stirred at RT for 2 h. The reaction mixture was diluted with dichloromethane (20 mL) and further washed with 10% citric acid solution (2 x 15 mL), water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by flash chromatography (product eluted with 2 % MeOH in $CHCl_3$) to afford 170 mg of the title compound.

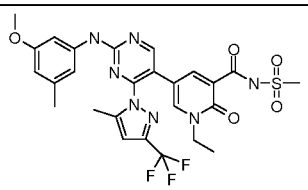
Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1175	 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(methylsulfonyl)-2-oxo-1,2-dihydropyridine-3-carboxamide	MS(ES): 592 (M+1) for $C_{25}H_{24}F_3N_7O_5S$. 400 MHz, DMSO-d_6: δ 1.29 (t, J = 7.12 Hz, 3H), 2.28 (s, 3H), 3.36 (s, 3H), 3.74 (s, 3H), 4.10 (q, J = 6.28 Hz, 2H), 6.46 (s, 1H), 7.08 (d, J = 2.52 Hz, 1H), 7.14 (s, 1H), 7.33 (s, 1H), 8.15 (d, J = 2.64 Hz, 1H), 8.38 (d, J = 2.60 Hz, 1H), 8.58 (d, J = 1.60 Hz, 1H), 8.75 (s, 1H), 10.16 (s, 1H), 12.84 (s, 1H).	**Example 1172** 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-oxo-1,2-dihydropyridine-3-carboxylic acid

Example 1176: 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(methylsulfonyl)-2-oxo-1,2-dihydropyridine-3-carboxamide



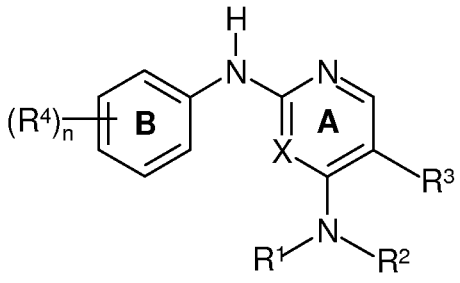
A mixture of 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-oxo-1,2-dihydropyridine-3-carboxylic acid (**Example 863**, 0.59 mmol, 310 mg) methanesulfonamide (0.87 mmol, 83 mg), triethylamine (1.5 mmol, 0.21 mL), 2-chloro-1-methylpyridinium iodide (0.6 mmol, 153 mg) and 4-(Dimethylamino)pyridine (0.097 mmol, 12 mg) in CH_2Cl_2 (10 mL) was stirred at RT for 2 h. The reaction mixture was diluted with dichloromethane (20 mL) and further washed with 10% citric acid (2 x 15 mL), water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude mass was purified by flash chromatography (product eluted with 3 % MeOH in $CHCl_3$) to afford 120 mg of the title compound.

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Compound	Structure	Mass spectrum and ^{1}H NMR	SM
Example 1176	 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-*N*-(methylsulfonyl)-2-oxo-1,2-dihydropyridine-3-carboxamide	MS(ES): 606 (M+1) for $C_{26}H_{26}F_3N_7O_5S$. 400 MHz, DMSO-d_6: δ 1.25 (t, *J* = 7.20 Hz, 3H), 2.27 (s, 3H), 2.45 (s, 3H), 3.35 (s, 3H), 3.72 (s, 3H), 4.07 (q, *J* = 7.00 Hz, 2H), 6.47 (s, 1H), 6.80 (s, 1H), 7.12 (s, 1H), 7.25 (s, 1H), 7.88 (d, *J* = 2.60 Hz, 1H), 8.26 (d, *J* = 2.52 Hz, 1H), 8.89 (s, 1H), 10.15 (s, 1H), 12.73 (s, 1H).	**Example 863** 1-ethyl-5-{2-[(3-methoxy-5-methylphenyl)amino]-4-[5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]pyrimidin-5-yl}-2-oxo-1,2-dihydropyridine-3-carboxylic acid

Claims

1. A compound of formula **(I)**:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X is CH or N;

R^1 is hydrogen, a C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-14}carbocyclyl, or a heterocyclyl, wherein R^1 may be optionally substituted on carbon by one or more R^6; and wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^7; provided that R^1 is not a substituted or unsubstituted phenyl;

R^2 is hydrogen or a C_{1-6}alkyl; or

R^1 and R^2, together with the nitrogen to which they are attached, form a heterocyclyl, wherein said heterocyclyl may be optionally substituted on carbon by one or more R^8; wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^3 is a C_{6-14}aryl or a heteroaryl; wherein R^3 may be optionally substituted on carbon by one or more R^{14}; and wherein if said heteraryl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heteroaryl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{15}; provided that R^3 is not an unsubstituted phenyl or an unsubstituted thiophenyl;

R^4, for each occurrence, is independently selected from the group consisting of halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, carbamoyl, N-C_{1-6}alkylcarbamoyl, N-C_{1-6}alkoxycarbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl, N-(SO_2R')carbamoyl, N-C_{1-6}alkyl, C_{1-6}alkyl-$S(O)_a$-, $R^{17}R^{18}$N-$S(O)_a$-, C_{3-14}carbocyclyl, and heterocyclyl; or two R^4 taken together with the carbon atoms to which they are attached form a C_{3-14}carbocyclyl or a heterocyclyl, wherein each R^4 may be optionally substituted on carbon by one or more R^{16}, wherein if either of said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{26}; provided that ring B together with $-(R^4)_n$ is not 3,4,5-trimethoxyphenyl;

n is an integer from 1 to 5;

a is 0, 1, or 2;

R^6, R^8, and R^{14}, for each occurrence, are each independently selected from the group consisting of hydroxy, halo, cyano, nitro, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, mercapto, C_{1-6}alkoxy, C_{1-6}alkyl$S(O)_a$ wherein a is 0 to 2, -C(=N-OH)NH_2, -C(O)$NHNH_2$, phenoxy, carboxy, oxo, amino, N-C_{1-6}alkylamino, N,N-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonyl, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkanoylamino, C_{1-6}alkoxycarbonylamino, carbamoyl, N-C_{1-6}alkylcarbamoyl, N-C_{1-6}alkoxycarbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl, N-C_{1-6}alkyl-N-alkoxycarbamoyl, N-(SO_2R')carbamoyl, N-C_{1-6}alkyl-N-(SO_2R')carbamoyl, C_{1-6}alkylsulphonylamino, sulphamoyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, sulphamoylamino, *N*-(C_{1-6}alkyl)sulphamoylamino, *N,N*-(C_{1-6}alkyl)$_2$sulphamoylamino, C_{3-14}carbocyclyl-L- and heterocyclyl-L-; or two R^{14} taken together with the carbon atoms to which they are attached form a C_{3-14}carbocyclyl or a heterocyclyl; wherein R^6, R^8, and R^{14} may be each independently optionally substituted on carbon by one or more R^{10}; and wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if either of said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{11};

R' and R", for each occurrence, are independently selected from the group consisting of C_{1-6}alkyl, C_{6-14}aryl and heterocyclyl, wherein R' and R"may be optionally substituted on carbon by one or more R^{22} and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{23};

R^7, R^9, R^{15} and R^{23}, for each occurrence, are each independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkanoyl, carbamoyl, N-C_{1-6}alkylcarbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl, C_{3-14}carbocyclyl-C(O)-, heterocyclyl-C(O)-, (C_{1-6}alkyl)$_3$silyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, wherein R^7, R^9, and R^{15} may be each independently optionally substituted on carbon by one or more R^{12}; and wherein if said hetercyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

L, for each occurrence, is independent selected from a direct bond, -O-, -N(R^{25})-, -C(O)-, -N(R^{25})C(O)-, -C(O)N(R^{25})-, -S(O)$_s$-, -SO$_2$N(R^{25})- or -N(R^{25})SO$_2$-; wherein R^{25}, for each occurrence, is independently selected from hydrogen or C_{1-6}alkyl and s is 0, 1 or 2;

R^{10} and R^{12}, for each occurrence, are independently selected from the group consisting of C_{1-6}alkyl, phenyl, halo, cyano, nitro, oxo, carboxy, hydroxy, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, amino, N-C_{1-6}alkylamino, N,N-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, C_{1-6}alkylSO$_2$NH-, carbamoyl, N-C_{1-6}alkylcarbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl, N-C_{1-6}alkyloxycarbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, and heterocyclyl, wherein said R^{10} and R^{12} are independently optionally substituted on carbon by one or more C_{1-6}alkyl and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from $R^{13'}$;

R^{11}, R^{13}, $R^{13'}$, and R^{26}, for each occurrence, are each independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkanoyl, C_{3-6}cycloalkanoyl, carbamoyl, C_{1-6}alkanoyloxy, C_{1-6}alkylS(O)$_a$, arylS(O)$_a$ wherein a is 0 to 2, carboxy, sulphamoyl and urea wherein said R^{11}, R^{13}, $R^{13'}$, and R^{26} are independently optionally substituted on carbon by one or more amino, C_{1-6}alkyl, C_{1-6}alkoxy or heterocyclyl;

R^{16}, for each occurrence, is independently, a halo, hydroxy, a C_{1-6}alkyl, or a C_{1-6}alkoxy;

R^{17} and R^{18}, for each occurrence, are independently hydrogen or a C_{1-6}alkyl; or R^{17} and R^{18}, together with the nitrogen to which they are attached form a heterocyclyl;

R^{22}, for each occurrence, is independently selected from the group consisting of halo, C_{1-6}alkyl, S(O)$_a$R" wherein a is 0 to 2, C_{1-6}alkanoyl, C_{1-6}alkanoylamino and heterocyclyl wherein R^{22} may be optionally substituted on carbon by one or more R^{24};

R^{24} is selected from halo, C_{1-6}alkanoylamino, and heterocyclyl;

provided that $-NR^1R^2$ is not $-NHCH_3$ or $-N(CH_3)_2$.

2. A compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein X is N.

3. A compound according to Claims 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2, together with the nitrogen to which they are attached, form a heterocyclyl, wherein said heterocyclyl may be optionally substituted on carbon by one or more R^8; wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9.

4. A compound according to Claim 3, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2, together with the nitrogen to which they are attached, form a 1*H*-pyrazol-1-yl, wherein said 1*H*-pyrazol-1-yl may be optionally substituted on carbon by one or more R^8.

5. A compound according to any one of Claims 1 through 4, or a pharmaceutically acceptable salt thereof, wherein R^3 is a heteroaryl; wherein R^3 may be optionally substituted on carbon by one or more R^{14}; and wherein if said heteraryl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heteroaryl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{15}; provided that R^3 is not an unsubstituted thiophenyl.

6. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein:

X is N;

R^1 and R^2, together with the nitrogen to which they are attached, form pyrazol-1-yl wherein said pyrazol-1-yl may be optionally substituted on carbon by one or more R^8;

R^3 is a 6-membered heteroaryl containing at least one nitrogen atom wherein one of the carbon atoms of said 6-membered heteroaryl ring may be optionally substituted with O to form a

–(CO)-, and further wherein said 6-membered heteroaryl may be optionally substituted on carbon by one or more R^{14} and when one of the carbon atoms of said 6-membered heteroaryl ring is substituted with O to form a –(CO)-, the nitrogen of that 6-membered heteroaryl is substituted by a group selected from R^{15};

n is 2;

R^4, for each occurrence, is independently a halo, C_{1-6}alkyl or C_{1-6}alkoxy;

R^8, for each occurrence, is independently a C_{1-6}alkyl or a C_{3-6}cycloalkyl wherein said R^8 is optionally substituted on carbon by one or more fluoro;

R^{14}, for each occurrence, is independently a carboxy, C_{1-6}alkoxy, C_{1-3}alkylsulphonylcarbamoyl, N-C_{1-3}alkylcarbamoyl, N-C_{1-3}alkoxycarbamoyl, or C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2 wherein said R^{14} may be optionally substituted on carbon by one or more hydroxy, $(C_{1-3}alkyl)_2N$, or C_{1-3}alkylsulfonyl; and

R^{15}, for each occurrence, is independently a C_{1-6}alkyl wherein said C_{1-6}alkyl is optionally substituted by C_{1-6}alkoxy or saturated heterocyclyl.

7. A pharmaceutical composition comprising a compound of any one of Claims 1-6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient or carrier.

8. A method of inhibiting bacterial DNA gyrase and/or bacterial topoisomerase IV in a warm-blooded animal in need of such treatment, comprising administering to the animal an effective amount of a compound of any one of Claims 1-6, or a pharmaceutically acceptable salt thereof.

9. A method of producing an antibacterial effect in a warm-blooded animal in need of such treatment, comprising administering to the animal an effective amount of a compound of any one of Claims 1-6, or a pharmaceutically acceptable salt thereof.

10. A method of treating a bacterial infection in a warm-blooded animal in need thereof, comprising administering to the animal an effective amount of a compound of any one of Claims 1-6, or a pharmaceutically acceptable salt thereof.

11. The method of Claim 10, wherein the bacterial infection is selected from the group consisting of community-acquired pneumoniae, hospital-acquired pneumoniae, skin and skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci.

12. A compound of formula **(I)** or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-6, for use as a medicament.

13. The use of a compound of any one of Claims 1-6, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in the production of an antibacterial effect in a warm-blooded animal.

14. The use of a compound of any one of Claims 1-6, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in inhibition of bacterial DNA gyrase and/or topoisomerase IV in a warm-blooded animal.

15. The use of a compound of any one of Claims 1-6, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in the treatment of a bacterial infection in a warm-blooded animal.

16. The use according to Claim 15, wherein the bacterial infection is selected from the group consisting of community-acquired pneumoniae, hospital-acquired pneumoniae, skin and skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections, Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci.

17. A compound of any one of Claims 1-6, or a pharmaceutically acceptable salt thereof, for use in production of an anti-bacterial effect in a warm-blooded animal.

18. A compound of any one of Claims 1-6, or a pharmaceutically acceptable salt thereof, for use in inhibition of bacterial DNA gyrase and/or topoisomerase IV in a warm-blooded animal.

19. A compound of any one of Claims 1-6, or a pharmaceutically acceptable salt thereof, for use in the treatment of a bacterial infection in a warm-blooded animal.

20. A compound of any one of Claims 1-6, or a pharmaceutically acceptable salt thereof, for use in the treatment of community-acquired pneumoniae, hospital-acquired pneumoniae, skin and skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections, Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis or Vancomycin-Resistant Enterococci.