



(51) International Patent Classification:

C07D 401/14 (2006.01) C07D 513/04 (2006.01)
 C07D 401/12 (2006.01) A61K 31/44 (2006.01)
 C07D 417/12 (2006.01) A61P 29/00 (2006.01)
 C07D 417/14 (2006.01) A61P 35/00 (2006.01)
 C07D 491/107 (2006.01)

(21) International Application Number:

PCT/EP2015/065052

(22) International Filing Date:

2 July 2015 (02.07.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/020,705 3 July 2014 (03.07.2014) US

(71) Applicant (for all designated States except US): **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH).

(71) Applicant (for US only): **GENENTECH, INC.** [US/US]; 1 DNA Way, South San Francisco, California 94080 (US).

(72) Inventors: **BROMIDGE, Steven**; 114 Milton Park, Abingdon Oxfordshire OX14 4SA (GB). **BURCH, Jason**; c/o Genentech Inc., 1 DNA Way, South San Francisco, California 94070 (US). **HEIFETZ, Alexander**; 114 Milton Park, Abingdon Oxfordshire OX14 4SA (GB). **KRULLE, Thomas**; 114 Milton Park, Abingdon Oxfordshire OX14 4SA (GB). **MONTALBETTI, Christian A.G.N.**; 114 Milton Park, Abingdon Oxfordshire OX14 4SA (GB). **PEI, Zhonghua**; c/o Genentech Inc., 1 DNA Way, South San Francisco, California 94070 (US).

PÉREZ-FUERTES, Yolanda; 114 Milton Park, Abingdon Oxfordshire OX14 4SA (GB). **TRANI, Giancarlo**; 114 Milton Park, Abingdon Oxfordshire OX14 4SA (GB).

(74) Agent: **SAUER, Frank**; Grenzacherstrasse 124, CH-4070 Basel (CH).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

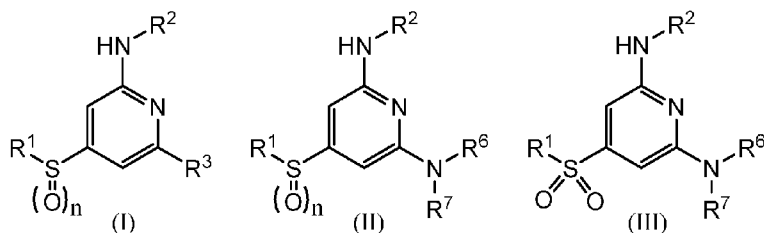
Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

— with international search report (Art. 21(3))

(54) Title: SULFONYLAMINOPYRIDINE COMPOUNDS, COMPOSITIONS AND METHODS OF USE



(57) Abstract: Provided are sulfonylaminopyridine compounds that are inhibitors of ITK kinase, compositions containing these compounds and methods for treating diseases mediated by ITK kinase. In particular, provided are compounds of Formula (I), (II) or (III), stereoisomers, tautomers, solvates, prodrugs or pharmaceutically acceptable salts thereof, where n, R¹, R², R³, R⁶ and R⁷ are defined herein, pharmaceutical compositions comprising the compound and a pharmaceutically acceptable carrier, adjuvant or vehicle, methods of using the compound or composition in therapy, for example, for treating a disease or condition mediated by ITK kinase in a patient.

SULFONYLAMINOPYRIDINE COMPOUNDS, COMPOSITIONS AND
METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of priority to U.S. Provisional Application Serial
5 Number 62/020,705 filed July 3, 2014, which is incorporated herein by reference in its
entirety.

FIELD OF THE INVENTION

The present invention relates to organic compounds useful for therapy and/or
prophylaxis in a patient, and in particular to inhibitors of ITK kinase useful for treating
10 diseases mediated by ITK kinase.

BACKGROUND OF THE INVENTION

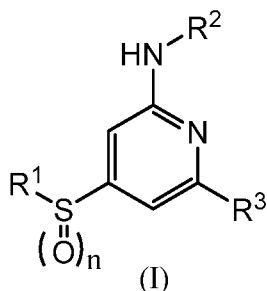
Interleukin-2-inducible T-cell kinase (ITK) is a Tec family kinase that is expressed in
T cells, NKT cells, NK cells, and mast cells. ITK is activated downstream of antigen
engagement of the T cell receptor (TCR) and mediates TCR signals through the
15 phosphorylation and activation of PLC γ . Mice in which ITK is deleted showed defective
differentiation of T cells towards the Th2 subset, but not the Th1 subset. Additional studies
indicate that Th2 cytokine production, but not early Th2 lineage commitment, is defective in
ITK-deficient mouse T cells. Th2 cells promote allergic inflammation, and ITK knock-out
mice have reduced lung inflammation, mucus production, and airway hyperreactivity in
20 models of allergic asthma. The reduction in lung pathology in ITK knock-out asthma models
is not rescued by a kinase-deficient ITK transgene, indicating that the kinase activity of ITK
is necessary for asthma pathology. Human patients with immunological and inflammatory
disorders, such as the allergic disease atopic dermatitis, express higher levels of ITK in
peripheral blood T cells.

25 There exists a need for inhibitors of ITK kinase and treatments of diseases and
disorders mediated by ITK kinase.

BRIEF SUMMARY OF THE INVENTION

Disclosed are sulfonylaminopyridine compounds that are inhibitors of ITK kinase,
compositions containing these compounds and methods for treating diseases mediated by ITK
30 kinase.

In one aspect, provided is a compound of Formula I:



or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein:

R^1 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, C_6 - C_{14} aryl, 5-10-membered heteroaryl, 3-10-membered heterocyclyl or $-NR^4R^5$, wherein R^1 is optionally substituted by R^{10} ;

n is 1 or 2;

R^2 is 5-10-membered heteroaryl optionally substituted by R^{10} ;

R^3 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, 3-10-membered heterocyclyl or $-NR^6R^7$, wherein R^3 is optionally substituted by R^{10} ;

R^4 and R^5 are each independently C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_6 - C_{14} aryl or $-(C_1$ - C_3 alkylene) NR^8R^9 ; or

R^4 and R^5 are taken together with the nitrogen to which they attached to form 3-10-membered heterocyclyl optionally substituted by R^{10} ;

R^6 and R^7 are each independently hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and heterocyclyl are independently optionally substituted by halogen, oxo, $-OR^8$, $-NR^8R^9$, $-S(O)R^9$, $-S(O)_2R^9$ or 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1 - C_6 alkyl optionally substituted by oxo or halogen; or

R^6 and R^7 are taken together with the nitrogen to which they attached to form 3-10-membered heterocyclyl optionally substituted by R^{10} ;

R^8 and R^9 are each independently hydrogen or C_1 - C_6 alkyl optionally substituted by oxo or halogen;

each R^{10} is independently hydrogen, oxo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, halogen, $-CN$, $-OR^{11}$, $-SR^{11}$, $-NR^{11}R^{12}$, $-NO_2$, $-C=NH(OR^{11})$, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)NR^{11}R^{12}$, $-NR^{11}C(O)R^{12}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-NR^{11}S(O)R^{12}$, $-NR^{11}S(O)_2R^{12}$, $-S(O)NR^{11}R^{12}$, $-S(O)_2NR^{11}R^{12}$, C_3 - C_6 cycloalkyl, 3-10-membered heterocyclyl, 5-10-

5 membered heteroaryl, C₆-C₁₄ aryl, -(C₁-C₃ alkylene)CN, -(C₁-C₃ alkylene)OR¹¹, -(C₁-C₃ alkylene)SR¹¹, -(C₁-C₃ alkylene)NR¹¹R¹², -(C₁-C₃ alkylene)CF₃, -(C₁-C₃ alkylene)NO₂,
 -C=NH(OR¹¹), -(C₁-C₃ alkylene)C(O)R¹¹, -(C₁-C₃ alkylene)C(O)OR¹¹, -(C₁-C₃ alkylene)C(O)NR¹¹R¹², -(C₁-C₃ alkylene)NR¹¹C(O)R¹², -(C₁-C₃ alkylene)S(O)R¹¹, -(C₁-
 10 C₃ alkylene)S(O)₂R¹¹, -(C₁-C₃ alkylene)NR¹¹S(O)R¹², -(C₁-C₃ alkylene)NR¹¹S(O)₂R¹², -(C₁-C₃ alkylene)S(O)NR¹¹R¹², -(C₁-C₃ alkylene)S(O)₂NR¹¹R¹², -(C₁-C₃ alkylene)(C₃-C₆
 cycloalkyl), -(C₁-C₃ alkylene)(3-10-membered heterocyclyl), -(C₁-C₃ alkylene)(5-10-
 membered heteroaryl) or -(C₁-C₃ alkylene)(C₆-C₁₄ aryl), wherein each R¹⁰ is independently
 optionally substituted by halogen, oxo, -OR¹³, -NR¹³R¹⁴, -C(O)R¹³, -S(O)R¹³, -S(O)₂R¹³, -(C₁-
 10 C₃ alkylene)OR¹³, -(C₁-C₃ alkylene)NR¹³R¹⁴, -(C₁-C₃ alkylene)C(O)R¹³, -(C₁-
 C₃ alkylene)S(O)R¹³, -(C₁-C₃ alkylene)S(O)₂R¹³ or C₁-C₆ alkyl optionally substituted by oxo,
 -CN or halogen;

15 R¹¹ and R¹² are each independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆
 alkynyl, C₃-C₆ cycloalkyl, C₆-C₁₄ aryl, 5-6 membered heteroaryl or 3-6 membered
 heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl
 are independently optionally substituted by halogen, oxo, -CN, -OR¹⁶, -NR¹⁶R¹⁷ or C₁-C₆
 alkyl optionally substituted by halogen, -CN or oxo; or

20 R¹¹ and R¹² are taken together with the atom to which they attached to form a 3-6
 membered heterocyclyl optionally substituted by halogen, oxo, -OR¹⁶, -NR¹⁶R¹⁷ or C₁-C₆
 alkyl optionally substituted by halogen, oxo or OH;

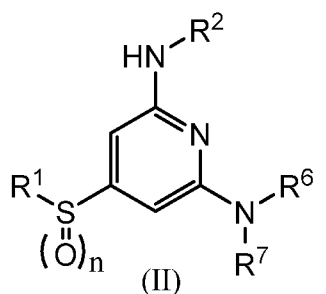
R¹³ and R¹⁴ are each independently hydrogen, C₁-C₆ alkyl optionally substituted by
 halogen or oxo, C₂-C₆ alkenyl optionally substituted by halogen or oxo, or C₂-C₆ alkynyl
 optionally substituted by halogen or oxo; or

25 R¹³ and R¹⁴ are taken together with the atom to which they attached to form a 3-6
 membered heterocyclyl optionally substituted by halogen, oxo or C₁-C₆ alkyl optionally
 substituted by halogen or oxo; and

R¹⁶ and R¹⁷ are each independently hydrogen, C₁-C₆ alkyl optionally substituted by
 halogen or oxo, C₂-C₆ alkenyl optionally substituted by halogen or oxo, or C₂-C₆ alkynyl
 optionally substituted by halogen or oxo; or

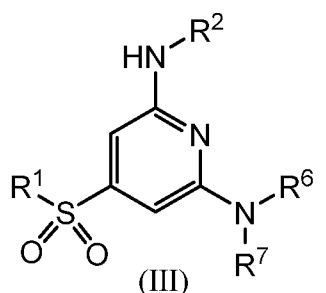
30 R¹⁶ and R¹⁷ are taken together with the atom to which they attached to form a 3-6
 membered heterocyclyl optionally substituted by halogen, oxo or C₁-C₆ alkyl optionally
 substituted by oxo or halogen.

In some embodiments, provided is a compound of Formula II:



or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 , R^2 , R^6 , R^7 and n are as defined for Formula (I).

5 In some embodiments, provided is a compound of Formula III:



or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 , R^2 , R^6 and R^7 are as defined for Formula (I).

10 Further provided is a pharmaceutical composition comprising a compound of Formula I, II, III or any variations described herein (e.g., a compound of Examples 1-98), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof; and optionally further comprising a pharmaceutically acceptable carrier, adjuvant, and/or vehicle.

15 In another aspect, provided is a method of inhibiting ITK kinase activity in a cell, comprising introducing into said cell an amount effective to inhibit said kinase of a compound of Formula I, II, III, or any variations described herein (e.g., a compound of Examples 1-98), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof.

20 Further provided is a method of treating a disease responsive to the inhibition of ITK kinase activity in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula I, II, III, or any variations described herein (e.g., a compound of Examples 1-98), or a stereoisomer, tautomer, solvate or prodrug thereof, or a

pharmaceutically acceptable salt thereof. In some embodiments, the disease is an immunological or inflammatory disease, such as asthma, inflammatory bowel disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriasis, allergic rhinitis, atopic dermatitis, contact dermatitis, delayed hypersensitivity reactions, lupus and multiple sclerosis.

5 In some embodiments, the disease is cancer, such as T-cell related cancer.

In another aspect, provided is the use of a compound of Formula I, II, III, or any variations described herein (e.g., a compound of Examples 1-98), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof, in therapy.

10 In one embodiment, provided is the use of a compound of Formula I, II, III, or any variations described herein (e.g., a compound of Examples 1-98), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof, in the treatment of a disease responsive to the inhibition of ITK kinase activity, such as an immunological or inflammatory disease or cancer (e.g., T-cell related cancer).

15 In one embodiment, provided is a compound of Formula I, II, III, or any variations described herein (e.g., a compound of Examples 1-98), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof, for use in a method of treating a disease responsive to the inhibition of ITK kinase activity, such as an immunological or inflammatory disease or cancer (e.g., T-cell related cancer).

20 Further provided is the use of a compound of Formula I, II, III, or any variations described herein (e.g., a compound of Examples 1-98), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof, in the manufacturing of a medicament for the treatment of a disease responsive to the inhibition of ITK kinase activity in a patient, such as an immunological or inflammatory disease or cancer (e.g., T-cell related cancer).

25 Also provided is a kit for treating a disease or disorder responsive to the inhibition of ITK kinase, comprising a compound of Formula I, II, III, or any variations described herein (e.g., a compound of Examples 1-98), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

30 The invention provides, *inter alia*, sulfonylaminopyridine compounds, and stereoisomers, tautomers, salts (e.g., pharmaceutically acceptable salts), solvates and prodrugs thereof. Compositions (e.g., pharmaceutical compositions) comprising the sulfonylaminopyridine compounds, and pharmaceutical formulations thereof, are useful in

inhibiting ITK kinase activity in a cell, and in the treatment of diseases, conditions and/or disorders responsive to the inhibition of ITK kinase activity in a patient.

Definition

The term “a” or “an” as used herein, unless clearly indicated otherwise, refers to one or more.

Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X”.

“Alkyl” as used herein refers to and includes, unless otherwise stated, a saturated linear (i.e. unbranched) or branched-chain monovalent hydrocarbon radical, wherein the alkyl radical may be optionally substituted independently with one or more substituents described herein. In one example, the alkyl radical has one to eighteen carbon atoms (“C₁-C₁₈ alkyl”). In other examples, the alkyl radical is C₁-C₁₂, C₁-C₁₀, C₁-C₈, C₁-C₆, C₁-C₅, C₁-C₄ or C₁-C₃ alkyl. Examples of alkyl groups include, but are not limited to, groups such as methyl (Me, -CH₃), ethyl (Et, -CH₂CH₃), 1-propyl (n-Pr, n-propyl, -CH₂CH₂CH₃), 2-propyl (i-Pr, i-propyl, -CH(CH₃)₂), 1-butyl (n-Bu, n-butyl, -CH₂CH₂CH₂CH₃), 2-methyl-1-propyl (i-Bu, i-butyl, -CH₂CH(CH₃)₂), 2-butyl (s-Bu, s-butyl, -CH(CH₃)CH₂CH₃), 2-methyl-2-propyl (t-Bu, t-butyl, -C(CH₃)₃), 1-pentyl (n-pentyl, -CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), 3-pentyl (-CH(CH₂CH₃)₂), 2-methyl-2-butyl (-C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl (-CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl (-CH₂CH(CH₃)CH₂CH₃), 1-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl (-CH(CH₃)CH₂CH₂CH₂CH₃), 3-hexyl (-CH(CH₂CH₃)(CH₂CH₂CH₃)), 2-methyl-2-pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (-C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-butyl (-C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃), 1-heptyl and 1-octyl.

“Alkenyl” as used herein refers to a linear or branched-chain monovalent hydrocarbon radical with at least one site of unsaturation, i.e., a carbon-carbon double bond, wherein the alkenyl radical may be optionally substituted independently with one or more substituents described herein, and includes radicals having “cis” and “trans” orientations, or alternatively, “E” and “Z” orientations. In one example, the alkenyl radical has two to eighteen carbon atoms (“C₂-C₁₈ alkenyl”). In other examples, the alkenyl radical is C₂-C₁₂, C₂-C₁₀, C₂-C₈, C₂-C₆ or C₂-C₃ alkenyl. Examples of alkenyl groups include, but are not limited to, groups such as ethenyl or vinyl (-CH=CH₂), prop-1-enyl (-CH=CHCH₃), prop-2-enyl (-CH₂CH=CH₂), 2-

methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, 2-methylbuta-1,3-diene, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl and hexa-1,3-dienyl.

“Alkynyl” as used herein refers to a linear or branched monovalent hydrocarbon radical with at least one site of unsaturation, i.e., a carbon-carbon triple bond, wherein the alkynyl radical may be optionally substituted independently with one or more substituents described herein. In one example, the alkynyl radical has two to eighteen carbon atoms (“C₂-C₁₈ alkynyl”). In other examples, the alkynyl radical is C₂-C₁₂, C₂-C₁₀, C₂-C₈, C₂-C₆ or C₂-C₃ alkynyl. Examples of alkynyl groups include, but are not limited to, groups such as ethynyl (-C≡CH), prop-1-ynyl (-C≡CCH₃), prop-2-ynyl (propargyl, -CH₂C≡CH), but-1-ynyl, but-2-ynyl and but-3-ynyl.

“Alkylene” as used herein refers to a saturated, branched or straight chain hydrocarbon group having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. In one example, the divalent alkylene group has one to eighteen carbon atoms (“C₁-C₁₈ alkylene”). In other examples, the divalent alkylene group is C₁-C₁₂, C₁-C₁₀, C₁-C₈, C₁-C₆, C₁-C₅, C₁-C₄ or C₁-C₃ alkylene. Examples of alkylene groups include, but are not limited to, groups such as methylene (-CH₂-), 1,1-ethylene (-CH(CH₃)-), 1,2-ethylene (-CH₂CH₂-), 1,1-propylene (-CH(CH₂CH₃)-), 2,2-propylene (-C(CH₃)₂-), 1,2-propylene (-CH(CH₃)CH₂-), 1,3-propylene (-CH₂CH₂CH₂-), 1,1-dimethyl-1,2-ethylene (-C(CH₃)₂CH₂-), 1,4-butylene (-CH₂CH₂CH₂CH₂-), and the like.

“Cycloalkyl” as used herein refers to a non-aromatic, saturated or partially unsaturated hydrocarbon ring group wherein the cycloalkyl group may be optionally substituted independently with one or more substituents described herein. In one example, the cycloalkyl group has 3 to 12 carbon atoms (“C₃-C₁₂ cycloalkyl”). In other examples, cycloalkyl is C₃-C₅, C₃-C₆, C₃-C₇, C₃-C₈, C₃-C₁₀, C₅-C₆, C₅-C₇, C₅-C₈ or C₅-C₁₀ cycloalkyl. In other examples, the cycloalkyl group, as a monocycle, is C₃-C₄, C₃-C₆ or C₅-C₆ cycloalkyl. In another example, the cycloalkyl group, as a bicycle, is C₇-C₁₂ cycloalkyl. Examples of monocyclic cycloalkyl groups include, but are not limited to, groups such as cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl and cyclododecyl. Exemplary arrangements of bicyclic cycloalkyl groups having 7 to 12 ring atoms include, but are not limited to, [4,4], [4,5], [5,5], [5,6] or [6,6] ring systems. Exemplary bridged bicyclic cycloalkanes include, but are not limited to, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane and bicyclo[3.2.2]nonane. In another example, the cycloalkyl group is a spiro cycloalkyl group, e.g. a C₅-C₁₂ spiro cycloalkyl. Examples of

spiro cycloalkanes include, but are not limited to, spiro[2.2]pentane, spiro[2.3]hexane, spiro[2.4]heptane, spiro[2.5]octane, spiro[3.3]heptane, spiro[3.4]octane, spiro[3.5]nonane, spiro[4.4]nonane and spiro[4.5]decane.

“Aryl” as used herein refers to a cyclic aromatic hydrocarbon group optionally substituted independently with one or more substituents described herein. In one example, the aryl group has 6 to 20 annular carbon atoms (“C₆-C₂₀ aryl”). In another example, the aryl group has 6 to 14 annular carbon atoms (“C₆-C₁₄ aryl”). In another example, the aryl group has 6 to 10 annular carbon atoms (“C₆-C₁₀ aryl”). In another example, the aryl group is a C₆ aryl group. Aryl includes bicyclic groups comprising an aromatic ring with a fused non-aromatic or partially saturated ring. Examples of aryl groups include, but are not limited to, phenyl, naphthalenyl, anthracenyl, indenyl, indanyl, 1,2-dihydronaphthalenyl and 1,2,3,4-tetrahydronaphthyl. In one example, aryl includes phenyl. Substituted phenyl or substituted aryl means a phenyl group or aryl group substituted with one, two, three, four or five, for example 1-2, 1-3 or 1-4 substituents chosen from groups specified herein. In one example, optional substituents on aryl are selected from halogen (F, Cl, Br, I), hydroxy, protected hydroxy, cyano, nitro, alkyl (for example C₁-C₆ alkyl), alkoxy (for example C₁-C₆ alkoxy), benzyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, aminomethyl, protected aminomethyl, trifluoromethyl, alkylsulfonylamino, alkylsulfonylaminoalkyl, arylsulfonylamino, arylsulfonylaminoalkyl, heterocyclysulfonylamino, heterocyclysulfonylaminoalkyl, heterocyclyl, aryl, or other groups specified. One or more methine (CH) and/or methylene (CH₂) groups in these substituents may in turn be substituted with a similar group as those denoted above. Examples of the term “substituted phenyl” include a mono- or di(halo)phenyl group such as 2-chlorophenyl, 2-bromophenyl, 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 3-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2-fluorophenyl and the like; a mono- or di(hydroxy)phenyl group such as 4-hydroxyphenyl, 3-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives thereof and the like; a nitrophenyl group such as 3- or 4-nitrophenyl; a cyanophenyl group, for example, 4-cyanophenyl; a mono- or di(lower alkyl)phenyl group such as 4-methylphenyl, 2,4-dimethylphenyl, 2-methylphenyl, 4-(isopropyl)phenyl, 4-ethylphenyl, 3-(n-propyl)phenyl and the like; a mono or di(alkoxy)phenyl group, for example, 3,4-dimethoxyphenyl, 3-methoxy-4-benzyloxyphenyl, 3-ethoxyphenyl, 4-(isopropoxy)phenyl, 4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl and the like; 3- or 4- trifluoromethylphenyl; a mono- or dicarboxyphenyl or (protected carboxy)phenyl group such 4-carboxyphenyl, a mono- or di(hydroxymethyl)phenyl or

(protected hydroxymethyl)phenyl such as 3-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl; a mono- or di(aminomethyl)phenyl or (protected aminomethyl)phenyl such as 2-(aminomethyl)phenyl or 2,4-(protected aminomethyl)phenyl; or a mono- or di(N-(methylsulfonylamino))phenyl such as 3-(N-methylsulfonylamino))phenyl. Also, the term “substituted phenyl” represents disubstituted phenyl groups where the substituents are different, for example, 3-methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy-4-chlorophenyl, and the like, as well as trisubstituted phenyl groups where the substituents are different, for example 3-methoxy-4-benzyloxy-6-methyl sulfonylamino, 3-methoxy-4-benzyloxy-6-phenyl sulfonylamino, and tetrasubstituted phenyl groups where the substituents are different such as 3-methoxy-4-benzyloxy-5-methyl-6-phenyl sulfonylamino. Particular substituted phenyl groups include the 2-chlorophenyl, 2-aminophenyl, 2-bromophenyl, 3-methoxyphenyl, 3-ethoxy-phenyl, 4-benzyloxyphenyl, 4-methoxyphenyl, 3-ethoxy-4-benzyloxyphenyl, 3,4-diethoxyphenyl, 3-methoxy-4-benzyloxyphenyl, 3-methoxy-4-(1-chloromethyl)benzyloxy-6-methyl sulfonyl aminophenyl groups. Fused aryl rings may also be substituted with any, for example 1, 2 or 3, of the substituents specified herein in the same manner as substituted alkyl groups.

“Heterocycle”, “heterocyclic”, or “heterocyclyl” as used herein refers to a saturated or partially unsaturated cyclic group (i.e., having one or more double and/or triple bonds within the ring), having at least one annular heteroatom independently selected from nitrogen, oxygen, phosphorus and sulfur, the remaining annular atoms being carbon. The heterocyclyl group may be optionally substituted with one or more substituents described below. In one embodiment, heterocyclyl includes monocycles or bicycles having 1 to 9 annular carbon atoms (C_1 - C_9) with the remaining ring atoms being heteroatoms selected from N, O, S and P. In other examples, heterocyclyl includes monocycles or bicycles having 1 to 5 annular carbon atoms (C_1 - C_5), 3 to 5 annular carbon atoms (C_3 - C_5) or 4 to 5 annular carbon atoms (C_4 - C_5), with the remaining ring atoms being heteroatoms selected from N, O, S and P. In another embodiment, heterocyclyl includes 3-10-membered rings, 3-8-membered rings, 3-7-membered rings, 3-6-membered rings, 5-8-membered rings, 5-7-membered rings or 5-6-membered rings, containing one or more heteroatoms independently selected from N, O, S and P. In other examples, heterocyclyl includes monocyclic 3-, 4-, 5-, 6- or 7-membered rings, containing one or more heteroatoms independently selected from N, O, S and P. In another embodiment, heterocyclyl includes bi- or polycyclic, spiro or bridged 4-, 5-, 6-, 7-, 8- and 9- membered ring systems, containing one or more heteroatoms independently selected from N, O, S and P. Examples of bicycle systems include, but are not limited to, [3,5], [4,5],

[5,5], [3,6], [4,6], [5,6] or [6,6] systems. Examples of bridged ring systems include, but are not limited to [2.2.1], [2.2.2], [3.2.2] and [4.1.0] arrangements, and having 1 to 3 heteroatoms selected from N, O, S and P. In another embodiment, heterocyclyl includes spiro cyclic groups having 1 to 4 heteroatoms selected from N, O, S and P. The heterocyclyl group may be a carbon-linked group or heteroatom-linked group. "Heterocyclyl" includes a heterocyclyl group fused to a cycloalkyl group.

Exemplary heterocyclyl groups include, but are not limited to, groups such as oxiranyl, aziridinyl, thiiranyl, azetidiny, oxetanyl, thietanyl, 1,2-dithietanyl, 1,3-dithietanyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, homopiperazinyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, oxazepanyl, diazepanyl, 1,4-diazepanyl, diazepinyl, thiazepinyl, thiazepanyl, dihydrothienyl, dihydropyranyl, dihydrofuranyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, pyrazolidinyl, dithianyl, dithiolanyl, pyrazolidinylimidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3,6-diazabicyclo[3.1.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[4.1.0]heptanyl and azabicyclo[2.2.2]hexanyl. Examples of a heterocyclyl group wherein a ring atom is substituted with oxo (=O) are pyrimidinonyl and 1,1-dioxo-thiomorpholinyl. The heterocyclyl groups herein are optionally substituted independently with one or more substituents described herein. Heterocycles are described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566.

"Heteroaryl" as used herein refers to an aromatic cyclic radical in which at least one ring atom is a heteroatom independently selected from nitrogen, oxygen and sulfur, the remaining ring atoms being carbon. Heteroaryl groups may be optionally substituted with one or more substituents described herein. In one example, the heteroaryl group contains 1 to 9 annular carbon atoms (C₁-C₉). In other examples, the heteroaryl group contains 1 to 5 annular carbon atoms (C₁-C₅), 3 to 5 annular carbon atoms (C₃-C₅) or 4 to 5 annular carbon atoms (C₄-C₅). In one embodiment, exemplary heteroaryl groups include 5 to 10-membered rings, 5 to 6-membered rings or monocyclic aromatic 5-, 6- and 7-membered rings containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur. In one embodiment, exemplary heteroaryl groups include 5 to 10-membered rings containing 1 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In another

embodiment, exemplary heteroaryl groups include fused ring systems of up to 9 carbon atoms wherein at least one aromatic ring contains one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur. "Heteroaryl" includes heteroaryl groups fused with an aryl, cycloalkyl or heterocyclyl group. Examples of heteroaryl groups include, but are not limited to, groups such as pyridinyl, imidazolyl, imidazopyridinyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indoliziny, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, triazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, thiazolopyridinyl, and furopyridinyl.

In certain embodiments, the heterocyclyl or heteroaryl group is C-attached. By way of example and not limitation, carbon bonded heterocyclyl groups include bonding arrangements at position 2, 3, 4, 5 or 6 of a piperidine (e.g., piperidin-2-yl, piperidin-3-yl or piperidin-4-yl), position 2, 3, 5 or 6 of a piperazine (e.g., piperizin-2-yl or piperizin-3-yl), position 2, 3, 4 or 5 of a tetrahydrofuran, tetrahydrothiophene, pyrroline or pyrrolidine, position 2, 3 or 4 of an azetidine, position 2 or 3 of an aziridine, and the like. Non-limiting examples of carbon bonded heteroaryl groups include bonding arrangements at position 2, 3, 4, 5 or 6 of a pyridine (2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl), position 3, 4, 5 or 6 of a pyridazine, position 2, 4, 5 or 6 of a pyrimidine, position 2, 3, 5 or 6 of a pyrazine, position 2, 3, 4 or 5 of a furan, thiophene or pyrrole, position 2, 4 or 5 of an oxazole, imidazole or thiazole, position 3, 4 or 5 of an isoxazole, pyrazole or isothiazole, position 2, 3, 4, 5, 6, 7 or 8 of a quinolone, position 1, 3, 4, 5, 6, 7 or 8 of an isoquinoline, and the like.

In certain embodiments, the heterocyclyl or heteroaryl group contains at least one annular nitrogen atom with is attached to the parent structure (i.e. N-attached). By way of example and not limitation, the nitrogen bonded heterocyclyl groups include bonding arrangements at position 1 of an aziridine, azetidine, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine or indoline, position 2 of an isoindoline, position 4 of a morpholine, and the like. Non-limiting examples of N-attached heteroaryl group include bonding arrangements at position 1 of a pyrrole, imidazole, pyrazole, indole or 1H-indazole, position 2 of a isoindole, position 9 of a carbazole or β -carboline, and the like.

"Halo" or "halogen" refers to fluoro (F), chloro (Cl), bromo (Br) and iodo (I). Where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached, e.g., dihaloaryl, dihaloalkyl,

trihaloaryl etc. refer to aryl and alkyl substituted with two (“di”) or three (“tri”) halo groups, which may be but are not necessarily the same halogen; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl. An alkyl group in which each hydrogen is replaced with a halo group is referred to as a “perhaloalkyl.” A preferred perhaloalkyl group is trifluoroalkyl (-CF₃). Similarly, “perhaloalkoxy” refers to an alkoxy group in which a halogen takes the place of each H in the hydrocarbon making up the alkyl moiety of the alkoxy group. An example of a perhaloalkoxy group is trifluoromethoxy (-OCF₃).

“Optionally substituted” unless otherwise specified means that a group may be unsubstituted or substituted by one or more (e.g. 1, 2, 3 or 4) of the substituents listed for that group in which said substituents may be the same or different. In an embodiment an optionally substituted group has 1 substituent. In another embodiment an optionally substituted group has 2 substituents. In another embodiment an optionally substituted group has 3 substituents.

The term “stereoisomers” refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space. Stereoisomers include diastereomers, enantiomers, conformers and the like.

“Diastereomer” refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

“Enantiomers” refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., *McGraw-Hill Dictionary of Chemical Terms* (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., “Stereochemistry of Organic Compounds”, John Wiley & Sons, Inc., New York, 1994. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or R and S, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an

enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms “racemic mixture” and “racemate” refer to an equimolar mixture of two
5 enantiomeric species, devoid of optical activity.

The term “tautomer” or “tautomeric form” refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include
10 interconversions by reorganization of some of the bonding electrons.

A “solvate” refers to an association or complex of one or more solvent molecules and a compound provided herein. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, dimethyl sulfoxide (DMSO), ethyl acetate, acetic acid, and ethanolamine. The term “hydrate” refers to the complex where the solvent
15 molecule is water.

The term “prodrug” as used in this application refers to a precursor or derivative form of a pharmaceutically active substance that is less efficacious to the patient or cytotoxic to tumor cells compared to the parent drug and is capable of being enzymatically or hydrolytically activated or converted into the more active parent form. See, *e.g.*, Wilman,
20 “Prodrugs in Cancer Chemotherapy” *Biochemical Society Transactions*, 14, pp. 375-382, 615th Meeting Belfast (1986) and Stella et al., “Prodrugs: A Chemical Approach to Targeted Drug Delivery,” *Directed Drug Delivery*, Borchardt et al., (ed.), pp. 247-267, Humana Press (1985). Examples of prodrugs include, but are not limited to, phosphate-containing prodrugs, thiophosphate-containing prodrugs, sulfate-containing prodrugs, peptide-containing prodrugs,
25 D-amino acid-modified prodrugs, glycosylated prodrugs, β -lactam-containing prodrugs, optionally substituted phenoxyacetamide-containing prodrugs or optionally substituted phenylacetamide-containing prodrugs.

“Leaving group” refers to a portion of a first reactant in a chemical reaction that is displaced from the first reactant in the chemical reaction. Examples of leaving groups
30 include, but are not limited to, halogen atoms, hydroxyl, alkoxy (for example -OR, wherein R is independently alkyl, alkenyl, alkynyl, cycloalkyl, phenyl or heterocyclyl and R is independently optionally substituted) and sulfonyloxy (for example -OS(O)₁₋₂R, wherein R is independently alkyl, alkenyl, alkynyl, cycloalkyl, phenyl or heterocyclyl and R is independently optionally substituted) groups. Exemplary sulfonyloxy groups include, but are

not limited to, alkylsulfonyloxy groups (for example methyl sulfonyloxy (mesylate group) and trifluoromethylsulfonyloxy (triflate group)) and arylsulfonyloxy groups (for example *p*-toluenesulfonyloxy (tosylate group) and *p*-nitrosulfonyloxy (nosylate group)).

The term “protecting group” or “Pg” refers to a substituent that is commonly employed to block or protect a particular functionality while reacting other functional groups on the compound. For example, an “amino-protecting group” is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, phthalimido, *t*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a “hydroxy-protecting group” refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable hydroxy-protecting groups include acetyl, trialkylsilyl, dialkylphenylsilyl, benzoyl, benzyl, benzyloxymethyl, methyl, methoxymethyl, triarylmethyl, and tetrahydropyranyl. A “carboxy-protecting group” refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include -CH₂CH₂SO₂Ph, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(*p*-toluenesulfonyl)ethyl, 2-(*p*-nitrophenylsulfenyl)ethyl, 2-(diphenylphosphino)-ethyl, nitroethyl and the like. For a general description of protecting groups and their use, see T. W. Greene and P. Wuts, *Protective Groups in Organic Synthesis*, Third Ed., John Wiley & Sons, New York, 1999; and P. Kocienski, *Protecting Groups*, Third Ed., Verlag, 2003.

The term “individual” or “patient” includes human patients and animal patients. The term “animal” includes companion animals (e.g., dogs, cats and horses), food-source animals, zoo animals, marine animals, birds and other similar animal species. In one example, patient is a mammal. In one example, patient is a human.

“Treat” and “treatment” includes therapeutic treatment, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (*i.e.*, not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, remission (whether partial or total), whether detectable or undetectable, sustaining remission and suppressing reoccurrence. “Treatment” can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder, (for example, through a genetic mutation) or those in which the condition or disorder is to be prevented. In some embodiments, a method may comprise prophylactic and/or preventative treatment.

The phrase “therapeutically effective amount” means an amount of a compound of the present invention that (i) treats or prevents the particular disease, condition or disorder, (ii) attenuates, ameliorates or eliminates one or more symptoms of the particular disease, condition or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition or disorder described herein. In the case of immunological disorders, the therapeutic effective amount is an amount sufficient to decrease or alleviate an allergic disorder, the symptoms of an autoimmune and/or inflammatory disease, or the symptoms of an acute inflammatory reaction (e.g. asthma). In some embodiments, a therapeutically effective amount is an amount of a chemical entity described herein sufficient to significantly decrease the activity or number of B-cells. In the case of cancer, the therapeutically effective amount of the drug may reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and alternatively stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and alternatively stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. To the extent the drug may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic. For cancer therapy, efficacy can, for example, be measured by assessing the time to disease progression (TTP) and/or determining the response rate (RR).

The phrase “pharmaceutically acceptable” indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

The phrase “pharmaceutically acceptable salt,” as used herein, refers to pharmaceutically acceptable organic or inorganic salts of a compound provided herein. “Pharmaceutically acceptable salts” include both acid and base addition salts. Exemplary salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. A pharmaceutically acceptable salt may involve the inclusion of another molecule such as an acetate ion, a succinate ion or other counter ion. The counter ion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a pharmaceutically acceptable salt may have more than one charged atom in its structure. Instances where multiple charged atoms are part of the pharmaceutically acceptable salt can have multiple counter ions. Hence, a

pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counter ion, for example a dihydrochloride or diformate salt.

“Pharmaceutically acceptable acid addition salt” refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid and the like, and organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

“Pharmaceutically acceptable base addition salts” include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly base addition salts are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, tromethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly organic non-toxic bases are isopropylamine, diethylamine, ethanolamine, tromethamine, dicyclohexylamine, choline, and caffeine.

The terms “cancer” and “cancerous” refer to or describe the physiological condition in patients that is typically characterized by unregulated cell growth. A “tumor” comprises one or more cancerous cells. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (*e.g.*, epithelial squamous cell cancer), lung cancer including small- cell lung cancer, non-small cell lung cancer (“NSCLC”), adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder

cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, as well as head and neck cancer.

5 A “chemotherapeutic agent” is an agent useful in the treatment of a given disorder, for example, cancer or inflammatory disorders. Examples of chemotherapeutic agents include NSAIDs; hormones such as glucocorticoids; corticosteroids such as hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisolone, methylprednisolone, prednisone, triamcinolone acetonide, triamcinolone alcohol,
 10 mometasone, amcinonide, budesonide, desonide, fluocinonide, fluocinolone acetonide, halcinonide, betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, fluocortolone, hydrocortisone-17-butyrate, hydrocortisone-17-valerate, aclometasone dipropionate, betamethasone valerate, betamethasone dipropionate, prednicarbate, clobetasone-17-butyrate, clobetasol-17-
 15 propionate, fluocortolone caproate, fluocortolone pivalate and fluprednidene acetate; immune selective anti-inflammatory peptides (ImSAIDs) such as phenylalanine-glutamine-glycine (FEG) and its D-isomeric form (feG) (IMULAN BioTherapeutics, LLC); anti-rheumatic drugs such as azathioprine, ciclosporin (cyclosporine A), D-penicillamine, gold salts, hydroxychloroquine, leflunomide, methotrexate (MTX), minocycline, sulfasalazine,
 20 cyclophosphamide, tumor necrosis factor alpha (TNF α) blockers such as etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi), Interleukin 1 (IL-1) blockers such as anakinra (Kineret), monoclonal antibodies against B cells such as rituximab (RITUXAN®), T cell costimulation blockers such as abatacept (Orencia), Interleukin 6 (IL-6) blockers such as tocilizumab; hormone antagonists,
 25 such as tamoxifen, finasteride or LHRH antagonists; radioactive isotopes (e.g., At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹², P³², Pb²¹² and radioactive isotopes of Lu); miscellaneous investigational agents such as thioplatin, PS-341, phenylbutyrate, ET-18- OCH₃, or farnesyl transferase inhibitors (L-739749, L-744832); polyphenols such as quercetin, resveratrol, piceatannol, epigallocatechine gallate, theaflavins, flavanols, procyanidins, betulinic acid and
 30 derivatives thereof; autophagy inhibitors such as chloroquine; alkylating agents such as thiotepa and cyclophosphamide (CYTOXAN®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate and trimethylmelamine;
 35 acetogenins (especially bullatacin and bullatacinone); delta-9-tetrahydrocannabinol

(dronabinol, MARINOL®); beta-lapachone; lapachol; colchicines; betulinic acid; a camptothecin (including the synthetic analogue topotecan (HYCAMTIN®), CPT-11 (irinotecan, CAMPTOSAR®), acetylcamptothecin, scopoletin, and 9-aminocamptothecin); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); podophyllotoxin; podophyllinic acid; teniposide; cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e. g., calicheamicin, especially calicheamicin gammaII and calicheamicin omegaII (see, e.g., Nicolaou *et al.*, *Angew. Chem Intl. Ed. Engl.*, 33: 183-186 (1994))); CDP323, an oral alpha-4 integrin inhibitor; dynemicin, including dynemicin A; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabycin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including ADRIAMYCIN®, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, doxorubicin HCl liposome injection (DOXIL®), liposomal doxorubicin TLC D-99 (MYOCET®), pegylated liposomal doxorubicin (CAELYX®), and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate, gemcitabine (GEMZAR®), tegafur (UFTORAL®), capecitabine (XELODA®), an epothilone, and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitioestanol, mepitioestane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone;

mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2'-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine (ELDISINE®, FILDESIN®); dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); thiotepa; taxoid, *e.g.*, paclitaxel (TAXOL®), albumin-engineered nanoparticle formulation of paclitaxel (ABRAXANE™), and docetaxel (TAXOTERE®); chloranbucil; 6-thioguanine; mercaptopurine; methotrexate; platinum agents such as cisplatin, oxaliplatin (*e.g.*, ELOXATIN®), and carboplatin; vincas, which prevent tubulin polymerization from forming microtubules, including vinblastine (VELBAN®), vincristine (ONCOVIN®), vindesine (ELDISINE®, FILDESIN®), and vinorelbine (NAVELBINE®); etoposide (VP-16); ifosfamide; mitoxantrone; leucovorin; novantrone; edatrexate; daunomycin; aminopterin; ibandronate; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as fenretinide, retinoic acid, including bexarotene (TARGRETIN®); bisphosphonates such as clodronate (for example, BONEFOS® or OSTAC®), etidronate (DIDROCAL®), NE-58095, zoledronic acid/zoledronate (ZOMETA®), alendronate (FOSAMAX®), pamidronate (AREDIA®), tiludronate (SKELID®), or risedronate (ACTONEL®); troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); antisense oligonucleotides, particularly those that inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as, for example, PKC-alpha, Raf, H-Ras, and epidermal growth factor receptor (EGF-R); vaccines such as THERATOPE® vaccine and gene therapy vaccines, for example, ALLOVECTIN® vaccine, LEUVECTIN® vaccine, and VAXID® vaccine; topoisomerase 1 inhibitor (*e.g.*, LURTOTECAN®); rmRH (*e.g.*, ABARELIX®); BAY439006 (sorafenib; Bayer); SU-11248 (sunitinib, SUTENT®, Pfizer); perifosine, COX-2 inhibitor (*e.g.* celecoxib or etoricoxib), proteosome inhibitor (*e.g.* PS341); bortezomib (VELCADE®); CCI-779; tipifarnib (R11577); orafenib, ABT510; Bcl-2 inhibitor such as oblimersen sodium (GENASENSE®); pixantrone; EGFR inhibitors (see definition below); farnesyltransferase inhibitors such as lonafarnib (SCH 6636, SARASAR™); and pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above such as CHOP, an abbreviation for a combined therapy of cyclophosphamide, doxorubicin, vincristine, and prednisolone; and FOLFOX, an abbreviation for a treatment regimen with oxaliplatin (ELOXATIN™) combined with 5-FU and leucovorin.

Additional chemotherapeutic agents as defined herein include “anti-hormonal agents” or “endocrine therapeutics” which act to regulate, reduce, block, or inhibit the effects of hormones that can promote the growth of cancer. They may be hormones themselves, including, but not limited to: anti-estrogens with mixed agonist/antagonist profile, including, 5 tamoxifen (NOLVADEX®), 4-hydroxytamoxifen, toremifene (FARESTON®), idoxifene, droloxifene, raloxifene (EVISTA®), trioxifene, keoxifene, and selective estrogen receptor modulators (SERMs) such as SERM3; pure anti-estrogens without agonist properties, such as fulvestrant (FASLODEX®), and EM800 (such agents may block estrogen receptor (ER) dimerization, inhibit DNA binding, increase ER turnover, and/or suppress ER levels); 10 aromatase inhibitors, including steroidal aromatase inhibitors such as formestane and exemestane (AROMASIN®), and nonsteroidal aromatase inhibitors such as anastrozole (ARIMIDEX®), letrozole (FEMARA®) and aminoglutethimide, and other aromatase inhibitors include vorozole (RIVISOR®), megestrol acetate (MEGASE®), fadrozole, and 4(5)-imidazoles; lutenizing hormone-releasing hormone agonists, including leuprolide 15 (LUPRON® and ELIGARD®), goserelin, buserelin, and triptorelin; sex steroids, including progestines such as megestrol acetate and medroxyprogesterone acetate, estrogens such as diethylstilbestrol and premarin, and androgens/retinoids such as fluoxymesterone, all transretinoic acid and fenretinide; onapristone; anti-progesterones; estrogen receptor down-regulators (ERDs); anti-androgens such as flutamide, nilutamide and bicalutamide.

20 Additional chemotherapeutic agents include therapeutic antibodies such as alemtuzumab (Campath), bevacizumab (AVASTIN®, Genentech); cetuximab (ERBITUX®, Imclone); panitumumab (VECTIBIX®, Amgen), rituximab (RITUXAN®, Genentech/Biogen Idec), pertuzumab (OMNITARG®, 2C4, Genentech), trastuzumab (HERCEPTIN®, Genentech), tositumomab (Bexxar, Corixa), and the antibody drug conjugate, gemtuzumab 25 ozogamicin (MYLOTARG®, Wyeth). Additional humanized monoclonal antibodies with therapeutic potential as agents in combination with the compounds of the invention include: apolizumab, aselizumab, atlizumab, bapineuzumab, bivatuzumab mertansine, cantuzumab mertansine, cedelizumab, certolizumab pegol, cidfusituzumab, cidtuzumab, daclizumab, eculizumab, efalizumab, epratuzumab, erlizumab, felvizumab, fontolizumab, gemtuzumab 30 ozogamicin, inotuzumab ozogamicin, ipilimumab, labetuzumab, lintuzumab, matuzumab, mepolizumab, motavizumab, motovizumab, natalizumab, nimotuzumab, nolovizumab, numavizumab, ocrelizumab, omalizumab, palivizumab, pascolizumab, pecfusituzumab, pectuzumab, pexelizumab, ralivizumab, ranibizumab, reslivizumab, reslizumab, resyvizumab, rovelizumab, ruplizumab, sibrotuzumab, sipilizumab, sontuzumab, tacatuzumab tetraxetan, 35 tadocizumab, talizumab, tefibazumab, tocilizumab, toralizumab, tucotuzumab celmoleukin,

tucusituzumab, umavizumab, urtoxazumab, ustekinumab, visilizumab, and the anti-interleukin-12 (ABT-874/J695, Wyeth Research and Abbott Laboratories) which is a recombinant exclusively human-sequence, full-length IgG₁ λ antibody genetically modified to recognize interleukin-12 p40 protein.

5 Chemotherapeutic agents also include “EGFR inhibitors,” which refers to compounds that bind to or otherwise interact directly with EGFR and prevent or reduce its signaling activity, and is alternatively referred to as an “EGFR antagonist.” Examples of such agents include antibodies and small molecules that bind to EGFR. Examples of antibodies which
 10 bind to EGFR include MAb 579 (ATCC CRL HB 8506), MAb 455 (ATCC CRL HB8507), MAb 225 (ATCC CRL 8508), MAb 528 (ATCC CRL 8509) (see, US Patent No. 4,943, 533, Mendelsohn *et al.*) and variants thereof, such as chimerized 225 (C225 or Cetuximab; ERBUTIX[®]) and reshaped human 225 (H225) (see, WO 96/40210, Imclone Systems Inc.); IMC-11F8, a fully human, EGFR-targeted antibody (Imclone); antibodies that bind type II mutant EGFR (US Patent No. 5,212,290); humanized and chimeric antibodies that bind
 15 EGFR as described in US Patent No. 5,891,996; and human antibodies that bind EGFR, such as ABX-EGF or Panitumumab (see WO98/50433, Abgenix/Amgen); EMD 55900 (Stragliotto *et al. Eur. J. Cancer* 32A:636-640 (1996)); EMD7200 (matuzumab) a humanized EGFR antibody directed against EGFR that competes with both EGF and TGF- α for EGFR binding (EMD/Merck); human EGFR antibody, HuMax-EGFR (GenMab); fully human
 20 antibodies known as E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6. 3 and E7.6. 3 and described in US 6,235,883; MDX-447 (Medarex Inc); and mAb 806 or humanized mAb 806 (Johns *et al., J. Biol. Chem.* 279(29):30375-30384 (2004)). The anti-EGFR antibody may be conjugated with a cytotoxic agent, thus generating an immunoconjugate (see, *e.g.*, EP659,439A2, Merck Patent GmbH). EGFR antagonists include small molecules such as compounds described in
 25 US Patent Nos: 5,616,582, 5,457,105, 5,475,001, 5,654,307, 5,679,683, 6,084,095, 6,265,410, 6,455,534, 6,521,620, 6,596,726, 6,713,484, 5,770,599, 6,140,332, 5,866,572, 6,399,602, 6,344,459, 6,602,863, 6,391,874, 6,344,455, 5,760,041, 6,002,008, and 5,747,498, as well as the following PCT publications: WO98/14451, WO98/50038, WO99/09016, and WO99/24037. Particular small molecule EGFR antagonists include OSI-774 (CP-358774, erlotinib, TARCEVA[®] Genentech/OSI Pharmaceuticals); PD 183805 (CI 1033, 2-propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride, Pfizer Inc.); ZD1839, gefitinib (IRESSA[™]) 4-(3'-Chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline, AstraZeneca); ZM 105180 ((6-amino-4-(3-methylphenyl-amino)-quinazoline, Zeneca); BIBX-1382 (N8-(3-chloro-4-fluoro-phenyl)-N2-(1-methyl-piperidin-4-yl)-pyrimido[5,4-d]pyrimidine-2,8-diamine,
 35

Boehringer Ingelheim); PKI-166 ((R)-4-[4-[(1-phenylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-6-yl]-phenol); (R)-6-(4-hydroxyphenyl)-4-[(1-phenylethyl)amino]-7H-pyrrolo[2,3-d]pyrimidine); CL-387785 (N-[4-[(3-bromophenyl)amino]-6-quinazoliny]-2-butyramide); EKB-569 (N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-7-ethoxy-6-quinoliny]-4-(dimethylamino)-2-butenamide) (Wyeth); AG1478 (Pfizer); AG1571 (SU 5271; Pfizer); dual EGFR/HER2 tyrosine kinase inhibitors such as lapatinib (TYKERB®, GSK572016 or N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6[5[[[2methylsulfonyl)ethyl]amino]methyl]-2-furanyl]-4-quinazolinamine).

Chemotherapeutic agents also include “tyrosine kinase inhibitors” including the EGFR-targeted drugs noted in the preceding paragraph; small molecule HER2 tyrosine kinase inhibitor such as TAK165 available from Takeda; CP-724,714, an oral selective inhibitor of the ErbB2 receptor tyrosine kinase (Pfizer and OSI); dual-HER inhibitors such as EKB-569 (available from Wyeth) which preferentially binds EGFR but inhibits both HER2 and EGFR-overexpressing cells; lapatinib (GSK572016; available from Glaxo-SmithKline), an oral HER2 and EGFR tyrosine kinase inhibitor; PKI-166 (available from Novartis); pan-HER inhibitors such as canertinib (CI-1033; Pharmacia); Raf-1 inhibitors such as antisense agent ISIS-5132 available from ISIS Pharmaceuticals which inhibit Raf-1 signaling; non-HER targeted TK inhibitors such as imatinib mesylate (GLEEVEC®, available from Glaxo SmithKline); multi-targeted tyrosine kinase inhibitors such as sunitinib (SUTENT®, available from Pfizer); VEGF receptor tyrosine kinase inhibitors such as vatalanib (PTK787/ZK222584, available from Novartis/Schering AG); MAPK extracellular regulated kinase I inhibitor CI-1040 (available from Pharmacia); quinazolines, such as PD 153035, 4-(3-chloroanilino) quinazoline; pyridopyrimidines; pyrimidopyrimidines; pyrrolopyrimidines, such as CGP 59326, CGP 60261 and CGP 62706; pyrazolopyrimidines, 4-(phenylamino)-7H-pyrrolo[2,3-d] pyrimidines; curcumin (diferuloyl methane, 4,5-bis (4-fluoroanilino)phthalimide); tyrphostines containing nitrothiophene moieties; PD-0183805 (Warner-Lambert); antisense molecules (*e.g.* those that bind to HER-encoding nucleic acid); quinoxalines (US Patent No. 5,804,396); tryphostins (US Patent No. 5,804,396); ZD6474 (Astra Zeneca); PTK-787 (Novartis/Schering AG); pan-HER inhibitors such as CI-1033 (Pfizer); Affinitac (ISIS 3521; Isis/Lilly); imatinib mesylate (GLEEVEC®); PKI 166 (Novartis); GW2016 (Glaxo SmithKline); CI-1033 (Pfizer); EKB-569 (Wyeth); Semaxinib (Pfizer); ZD6474 (AstraZeneca); PTK-787 (Novartis/Schering AG); INC-1C11 (Imclone), rapamycin (sirolimus, RAPAMUNE®); or as described in any of the following patent publications: US Patent No. 5,804,396; WO 1999/09016 (American Cyanamid); WO 1998/43960 (American Cyanamid); WO 1997/38983 (Warner Lambert); WO 1999/06378

(Warner Lambert); WO 1999/06396 (Warner Lambert); WO 1996/30347 (Pfizer, Inc); WO 1996/33978 (Zeneca); WO 1996/3397 (Zeneca) and WO 1996/33980 (Zeneca).

Chemotherapeutic agents also include asthma treatment agents, including inhaled corticosteroids such as fluticasone, budesonide, mometasone, flunisolide and beclomethasone; leukotriene modifiers, such as montelukast, zafirlukast and zileuton; long-acting beta agonists, such as salmeterol and formoterol; combinations of the above such as combinations of fluticasone and salmeterol, and combinations of budesonide and formoterol; theophylline; short-acting beta agonists, such as albuterol, levalbuterol and pirbuterol; ipratropium; oral and intravenous corticosteroids, such as prednisone and methylprednisolone; omalizumab; lebrikizumab; antihistamines; and decongestants; cromolyn; and ipratropium.

The term “NSAID” is an acronym for “non-steroidal anti-inflammatory drug” and is a therapeutic agent with analgesic, antipyretic (lowering an elevated body temperature and relieving pain without impairing consciousness) and, in higher doses, with anti-inflammatory effects (reducing inflammation). The term “non-steroidal” is used to distinguish these drugs from steroids, which (among a broad range of other effects) have a similar eicosanoid-depressing, anti-inflammatory action. As analgesics, NSAIDs are unusual in that they are non-narcotic. NSAIDs include aspirin, ibuprofen, and naproxen. NSAIDs are usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present. NSAIDs are generally indicated for the symptomatic relief of the following conditions: rheumatoid arthritis, osteoarthritis, inflammatory arthropathies (e.g. ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, acute gout, dysmenorrhoea, metastatic bone pain, headache and migraine, postoperative pain, mild-to-moderate pain due to inflammation and tissue injury, pyrexia, ileus, and renal colic. Most NSAIDs act as non-selective inhibitors of the enzyme cyclooxygenase, inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. Cyclooxygenase catalyzes the formation of prostaglandins and thromboxane from arachidonic acid (itself derived from the cellular phospholipid bilayer by phospholipase A₂). Prostaglandins act (among other things) as messenger molecules in the process of inflammation. COX-2 inhibitors include celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, rofecoxib, and valdecoxib.

“Combination therapy” as used herein means a therapy that includes two or more different compounds. Thus, in one aspect, a combination therapy comprising a compound detailed herein and another compound is provided. In some variations, the combination therapy optionally includes one or more pharmaceutically acceptable carriers or excipients, non-pharmaceutically active compounds, and/or inert substances.

The term “package insert” is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

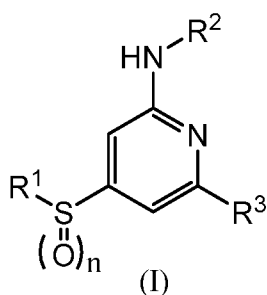
5 The terms “compound of this invention,” and “compounds of the present invention”, unless otherwise indicated, include compounds of Formulae I, II, III, any variations thereof described herein, stereoisomers, tautomers, solvates, prodrugs and salts (e.g., pharmaceutically acceptable salts) thereof. Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more
10 isotopically enriched atoms. For example, compounds of Formulae I, II, III, and variations described herein, wherein one or more hydrogen atoms are replaced deuterium or tritium, or one or more carbon atoms are replaced by a ¹³C or ¹⁴C carbon atom, or one or more nitrogen atoms are replaced by a ¹⁵N nitrogen atom, or one or more sulfur atoms are replaced by a ³³S, ³⁴S or ³⁶S sulfur atom, or one or more oxygen atoms are replaced by a ¹⁷O or ¹⁸O oxygen
15 atom are within the scope of this invention.

Disclosed are materials, compositions, and components that can be used for, can be used in conjunction with, can be used in preparation for, or are products of the disclosed methods and compositions. These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc., of these materials are
20 disclosed that while specific reference of each various individual and collective combinations and permutations of these compounds may not be explicitly disclosed, each is specifically contemplated and described herein. For example, if a method is disclosed and discussed and a number of modifications that can be made to a number of molecules including the method are discussed, each and every combination and permutation of the method, and the modifications
25 that are possible, are specifically contemplated unless specifically indicated to the contrary. Likewise, any subset or combination of these is also specifically contemplated and disclosed. This concept applies to all aspects of this disclosure including, but not limited to, steps in methods using the disclosed compounds and compositions. Thus, if there are a variety of additional steps that can be performed, it is understood that each of these additional steps can
30 be performed with any specific method steps or combination of method steps of the disclosed methods, and that each such combination or subset of combinations is specifically contemplated and should be considered disclosed. It is therefore contemplated that any embodiment discussed in this specification can be implemented with respect to any method, compound, kit, or composition, etc., described herein, and *vice versa*.

ITK Inhibitor Compounds

Compounds according to the invention are detailed herein, including in the Brief Summary of the Invention and the appended claims. The invention includes the use of all of the compounds described herein, including any and all stereoisomers, including geometric isomers (cis/trans), salts (including pharmaceutically acceptable salts) and solvates of the compounds described herein, as well as methods of making such compounds.

In one aspect, provided is a compound of Formula I:



or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein:

R^1 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, C_6 - C_{14} aryl, 5-10-membered heteroaryl, 3-10-membered heterocyclyl or $-NR^4R^5$, wherein R^1 is optionally substituted by R^{10} ;

n is 1 or 2;

R^2 is 5-10-membered heteroaryl optionally substituted by R^{10} ;

R^3 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, 3-10-membered heterocyclyl or $-NR^6R^7$, wherein R^3 is optionally substituted by R^{10} ;

R^4 and R^5 are each independently C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_6 - C_{14} aryl or $-(C_1-C_3 \text{ alkylene})NR^8R^9$; or

R^4 and R^5 are taken together with the nitrogen to which they attached to form 3-10-membered heterocyclyl optionally substituted by R^{10} ;

R^6 and R^7 are each independently hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and heterocyclyl are independently optionally substituted by halogen, oxo, $-OR^8$, $-NR^8R^9$, $-S(O)R^9$, $-S(O)_2R^9$ or 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1 - C_6 alkyl optionally substituted by oxo or halogen; or

R⁶ and R⁷ are taken together with the nitrogen to which they attached to form 3-10-membered heterocyclyl optionally substituted by R¹⁰;

R⁸ and R⁹ are each independently hydrogen or C₁-C₆ alkyl optionally substituted by oxo or halogen;

5 each R¹⁰ is independently hydrogen, oxo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, -CN, -OR¹¹, -SR¹¹, -NR¹¹R¹², -NO₂, -C=NH(OR¹¹), -C(O)R¹¹, -C(O)OR¹¹, -C(O)NR¹¹R¹², -NR¹¹C(O)R¹², -S(O)R¹¹, -S(O)₂R¹¹, -NR¹¹S(O)R¹², -NR¹¹S(O)₂R¹², -S(O)NR¹¹R¹², -S(O)₂NR¹¹R¹², C₃-C₆ cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, C₆-C₁₄ aryl, -(C₁-C₃ alkylene)CN, -(C₁-C₃ alkylene)OR¹¹, -(C₁-C₃ alkylene)SR¹¹, -(C₁-C₃ alkylene)NR¹¹R¹², -(C₁-C₃ alkylene)CF₃, -(C₁-C₃ alkylene)NO₂, -C=NH(OR¹¹), -(C₁-C₃ alkylene)C(O)R¹¹, -(C₁-C₃ alkylene)C(O)OR¹¹, -(C₁-C₃ alkylene)C(O)NR¹¹R¹², -(C₁-C₃ alkylene)NR¹¹C(O)R¹², -(C₁-C₃ alkylene)S(O)R¹¹, -(C₁-C₃ alkylene)S(O)₂R¹¹, -(C₁-C₃ alkylene)NR¹¹S(O)R¹², -(C₁-C₃ alkylene)NR¹¹S(O)₂R¹², -(C₁-C₃ alkylene)S(O)NR¹¹R¹², -(C₁-C₃ alkylene)S(O)₂NR¹¹R¹², -(C₁-C₃ alkylene)(C₃-C₆ cycloalkyl), -(C₁-C₃ alkylene)(3-10-membered heterocyclyl), -(C₁-C₃ alkylene)(5-10-membered heteroaryl) or -(C₁-C₃ alkylene)(C₆-C₁₄ aryl), wherein each R¹⁰ is independently optionally substituted by halogen, oxo, -OR¹³, -NR¹³R¹⁴, -C(O)R¹³, -S(O)R¹³, -S(O)₂R¹³, -(C₁-C₃ alkylene)OR¹³, -(C₁-C₃ alkylene)NR¹³R¹⁴, -(C₁-C₃ alkylene)C(O)R¹³, -(C₁-C₃ alkylene)S(O)R¹³, -(C₁-C₃ alkylene)S(O)₂R¹³ or C₁-C₆ alkyl optionally substituted by oxo, -CN or halogen;

R¹¹ and R¹² are each independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₆-C₁₄ aryl, 5-6 membered heteroaryl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are independently optionally substituted by halogen, oxo, -CN, -OR¹⁶, -NR¹⁶R¹⁷ or C₁-C₆ alkyl optionally substituted by halogen, -CN or oxo; or

R¹¹ and R¹² are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, -OR¹⁶, -NR¹⁶R¹⁷ or C₁-C₆ alkyl optionally substituted by halogen, oxo or OH;

R¹³ and R¹⁴ are each independently hydrogen, C₁-C₆ alkyl optionally substituted by halogen or oxo, C₂-C₆ alkenyl optionally substituted by halogen or oxo, or C₂-C₆ alkynyl optionally substituted by halogen or oxo; or

R¹³ and R¹⁴ are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C₁-C₆ alkyl optionally substituted by halogen or oxo; and

R^{16} and R^{17} are each independently hydrogen, C_1 - C_6 alkyl optionally substituted by halogen or oxo, C_2 - C_6 alkenyl optionally substituted by halogen or oxo, or C_2 - C_6 alkynyl optionally substituted by halogen or oxo; or

5 R^{16} and R^{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1 - C_6 alkyl optionally substituted by oxo or halogen.

In some embodiments, n is 1. In some embodiments, n is 2.

In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 -
10 C_8 cycloalkyl, C_6 - C_{14} aryl, 5-10-membered heteroaryl, 3-10-membered heterocyclyl or $-NR^4R^5$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl of R^1 are independently optionally substituted by R^{10} . In some embodiments, R^1 is C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{14} aryl, 5-10-membered heteroaryl, 3-10-membered heterocyclyl or $-NR^4R^5$, where the alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl of R^1 are independently
15 optionally substituted by R^{10} . In some embodiments, R^1 is C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{14} aryl, 5-10-membered heteroaryl, 3-10-membered heterocyclyl or $-NR^4R^5$.

In some embodiments, R^1 is C_1 - C_6 alkyl optionally substituted by R^{10} . In some embodiments, R^1 is C_3 - C_8 cycloalkyl optionally substituted by R^{10} . In some embodiments, R^1 is C_1 - C_6 alkyl (e.g., 2-propyl) or C_3 - C_8 cycloalkyl (e.g., cyclohexyl).

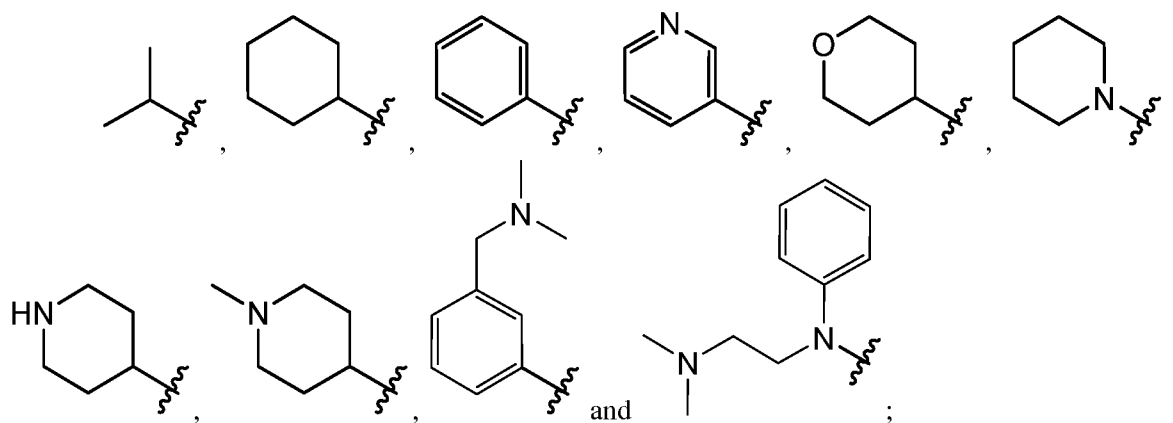
20 In some embodiments, R^1 is C_6 - C_{14} aryl optionally substituted by R^{10} . In some embodiments, R^1 is phenyl optionally substituted by R^{10} . In some embodiments, R^1 is phenyl. In some embodiments, R^1 is phenyl optionally substituted by C_1 - C_6 alkyl or $-(C_1$ - C_3 alkylene) $NR^{11}R^{12}$. In some embodiments, R^1 is phenyl substituted by $-(C_1$ - C_3 alkylene) $NR^{11}R^{12}$ where R^{11} and R^{12} are independently hydrogen or C_1 - C_6 alkyl. In some
25 embodiments, R^1 is dimethylaminomethylphenyl (e.g., 3-(dimethylaminomethyl)phenyl).

In some embodiments, R^1 is 3-10-membered heterocyclyl optionally substituted by R^{10} . In some embodiments, R^1 is 5-6-membered heterocyclyl optionally substituted by R^{10} . In some embodiments, R^1 is 5-6-membered heterocyclyl optionally substituted by C_1 - C_6 alkyl. In some embodiments, R^1 is 6-membered heterocyclyl optionally substituted by C_1 - C_6
30 alkyl. In some embodiments, R^1 is tetrahydropyranyl (e.g., tetrahydropyran-4-yl). In some embodiments, R^1 is piperidinyl optionally substituted by C_1 - C_6 alkyl (e.g., piperidin-1-yl, piperidin-4-yl and 1-methylpiperidin-4-yl).

In some embodiments, R^1 is 5-10-membered heteroaryl optionally substituted by R^{10} . In some embodiments, R^1 is 5-6-membered heteroaryl optionally substituted by R^{10} . In some embodiments, R^1 is 5-6-membered heteroaryl. In some embodiments, R^1 is pyridyl (e.g., pyridin-3-yl). In some embodiments, R^1 is phenyl, cyclohexyl, pyridyl (e.g., pyridin-3-yl) or piperidinyl (e.g., piperidin-4-yl).

In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, where R^1 is $-NR^4R^5$. In some of these embodiments, R^4 is C_6 - C_{14} aryl (e.g., phenyl). In some of these embodiments, R^5 is $-(C_1-C_3 \text{ alkylene})NR^8R^9$. In some of these embodiments, R^5 is $-(C_1-C_3 \text{ alkylene})NR^8R^9$ where R^8 and R^9 are independently hydrogen or C_1 - C_6 alkyl. In one variation, R^8 and R^9 are independently C_1 - C_6 alkyl (e.g., methyl and ethyl). In some of these embodiments, R^4 is phenyl and R^5 is $-(CH_2)_2N(CH_3)_2$. In some of these embodiments, R^4 and R^5 are taken together with the nitrogen to which they attached to form 3-10-membered heterocyclyl optionally substituted by R^{10} . In some of these embodiments, R^4 and R^5 are taken together with the nitrogen to which they attached to form 5-6-membered heterocyclyl optionally substituted by R^{10} . In some of these embodiments, R^4 and R^5 are taken together with the nitrogen to which they attached to form piperidinyl optionally substituted by R^{10} or pyrrolidinyl optionally substituted by R^{10} . In some of these embodiments, the $-NR^4R^5$ moiety is piperidin-1-yl or pyrrolidin-1-yl.

In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, where R^1 is selected from the group consisting of:



wherein the wavy line represents the point of attachment of R^1 in Formula I.

In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, where R^2 is 5-10-membered heteroaryl optionally substituted by R^{10} . In some embodiments, R^2 is 5-9-membered heteroaryl optionally substituted by R^{10} .

In some embodiments, R^2 is 5, 6, 7, 8, 9 or 10-membered heteroaryl optionally substituted by one or more (e.g., 1, 2, 3 or 4) substituents independently selected from (i) C_1 - C_6 alkyl which is optionally substituted by halogen, oxo, $-OR^{13}$, $-NR^{13}R^{14}$, C_3 - C_6 cycloalkyl or phenyl; (ii) C_3 - C_6 cycloalkyl which is optionally substituted by halogen, oxo, $-OR^{13}$, $-NR^{13}R^{14}$, phenyl or C_1 - C_6 alkyl optionally substituted by halo; (iii) phenyl which is optionally substituted by halogen, $-OR^{13}$, $-NR^{13}R^{14}$, C_3 - C_6 cycloalkyl or C_1 - C_6 alkyl optionally substituted by halo; (iv) 3-10-membered heterocyclyl which is optionally substituted by halogen, $-OR^{13}$, $-NR^{13}R^{14}$, C_3 - C_6 cycloalkyl or C_1 - C_6 alkyl optionally substituted by halo; and (v) 5-10-membered heteroaryl which is optionally substituted by halogen, $-OR^{13}$, $-NR^{13}R^{14}$, C_3 - C_6 cycloalkyl or C_1 - C_6 alkyl optionally substituted by halo.

In some embodiments, R^2 is 5-6-membered heteroaryl optionally substituted by R^{10} . In some embodiments, R^2 is 5-6-membered monocyclic heteroaryl optionally substituted by R^{10} . In some embodiments, R^2 is 5-6-membered monocyclic heteroaryl optionally substituted by C_1 - C_6 alkyl which is optionally substituted by halogen, oxo, $-OR^{13}$, $-NR^{13}R^{14}$, C_3 - C_6 cycloalkyl or phenyl. In some embodiments, R^2 is 5-6-membered monocyclic heteroaryl optionally substituted by C_3 - C_6 cycloalkyl which is optionally substituted by halogen, oxo, $-OR^{13}$, $-NR^{13}R^{14}$, phenyl or C_1 - C_6 alkyl optionally substituted by halo. In some embodiments, R^2 is 5-6-membered monocyclic heteroaryl optionally substituted by phenyl which is optionally substituted by halogen, $-OR^{13}$, $-NR^{13}R^{14}$, C_3 - C_6 cycloalkyl or C_1 - C_6 alkyl optionally substituted by halo. In some embodiments, R^2 is 5-6-membered monocyclic heteroaryl optionally substituted by 3-10-membered heterocyclyl which is optionally substituted by halogen, $-OR^{13}$, $-NR^{13}R^{14}$, C_3 - C_6 cycloalkyl or C_1 - C_6 alkyl optionally substituted by halo. In some embodiments, R^2 is 5-6-membered monocyclic heteroaryl optionally substituted by 5-10-membered heteroaryl which is optionally substituted by halogen, $-OR^{13}$, $-NR^{13}R^{14}$, C_3 - C_6 cycloalkyl or C_1 - C_6 alkyl optionally substituted by halo. In some embodiments, R^2 is pyridyl (e.g., pyridin-2-yl) optionally substituted by R^{10} . In some embodiments, R^2 is pyrazolyl (e.g., pyrazol-3-yl) optionally substituted by R^{10} . In some embodiments, R^2 is imidazolyl (e.g., imidazol-4-yl) optionally substituted by R^{10} . In some embodiments, R^2 is thiazolyl (e.g., thiazol-2-yl) optionally substituted by R^{10} . In some embodiments, R^2 is thiadiazolyl (e.g., [1,2,4]thiadiazol-5-yl) optionally substituted by R^{10} .

In some embodiments, R^2 is 5-10-membered fused heteroaryl optionally substituted by R^{10} . In some embodiments, R^2 is 5-10-membered heteroaryl fused with an aryl, cycloalkyl or heterocyclyl group. In some embodiments, R^2 is 5- or 6-membered heteroaryl fused with phenyl, C_5 - C_6 cycloalkyl or 5-6-membered heterocyclyl, where in the fused heteroaryl is optionally substituted by R^{10} . In some embodiments, R^2 is 5-membered heteroaryl fused with

phenyl, C₅-C₆ cycloalkyl or 5-6-membered heterocyclyl, where in the fused heteroaryl is optionally substituted by R¹⁰. In some embodiments, R² is thiazolyl fused with phenyl, C₅-C₆ cycloalkyl or 5-6-membered heterocyclyl, where in the fused heteroaryl is optionally substituted by R¹⁰. In some embodiments, R² is benzothiazolyl optionally substituted by R¹⁰.

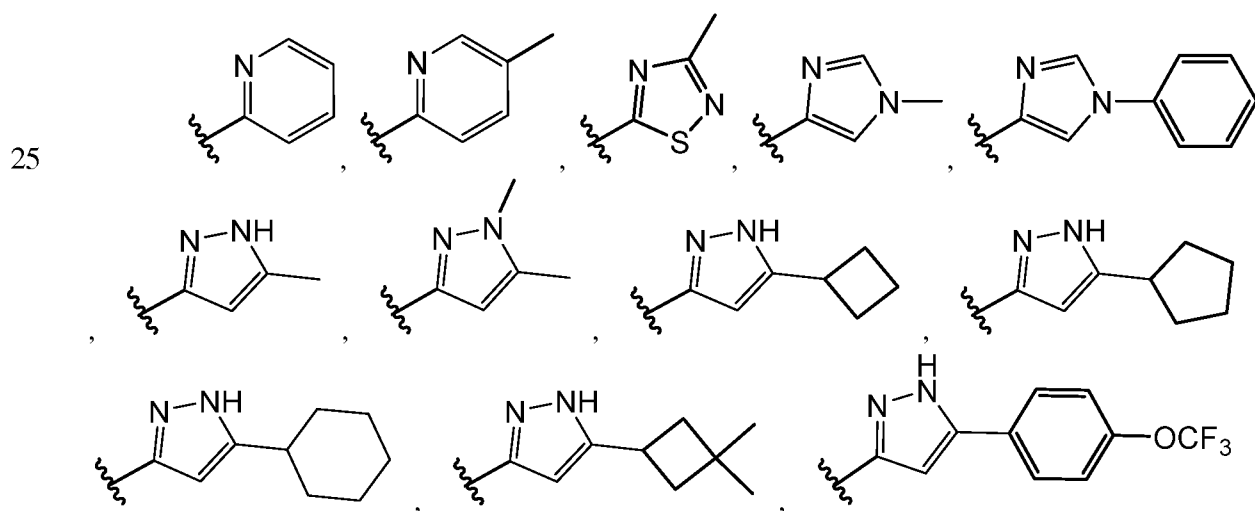
5 In some embodiments, R² is thiazolyl fused with C₅-C₆ cycloalkyl optionally substituted by R¹⁰. In certain embodiments, R² is 4,5,6,7-tetrahydro-benzothiazol-2-yl optionally substituted by R¹⁰. In certain embodiments, R² is 4,5,6,7-tetrahydro-benzothiazol-2-yl optionally substituted by C₁-C₆ alkyl (e.g., 4,5,6,7-tetrahydro-benzothiazol-2-yl; and 6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-yl). In certain embodiments, R² is 5,6-dihydro-4H-

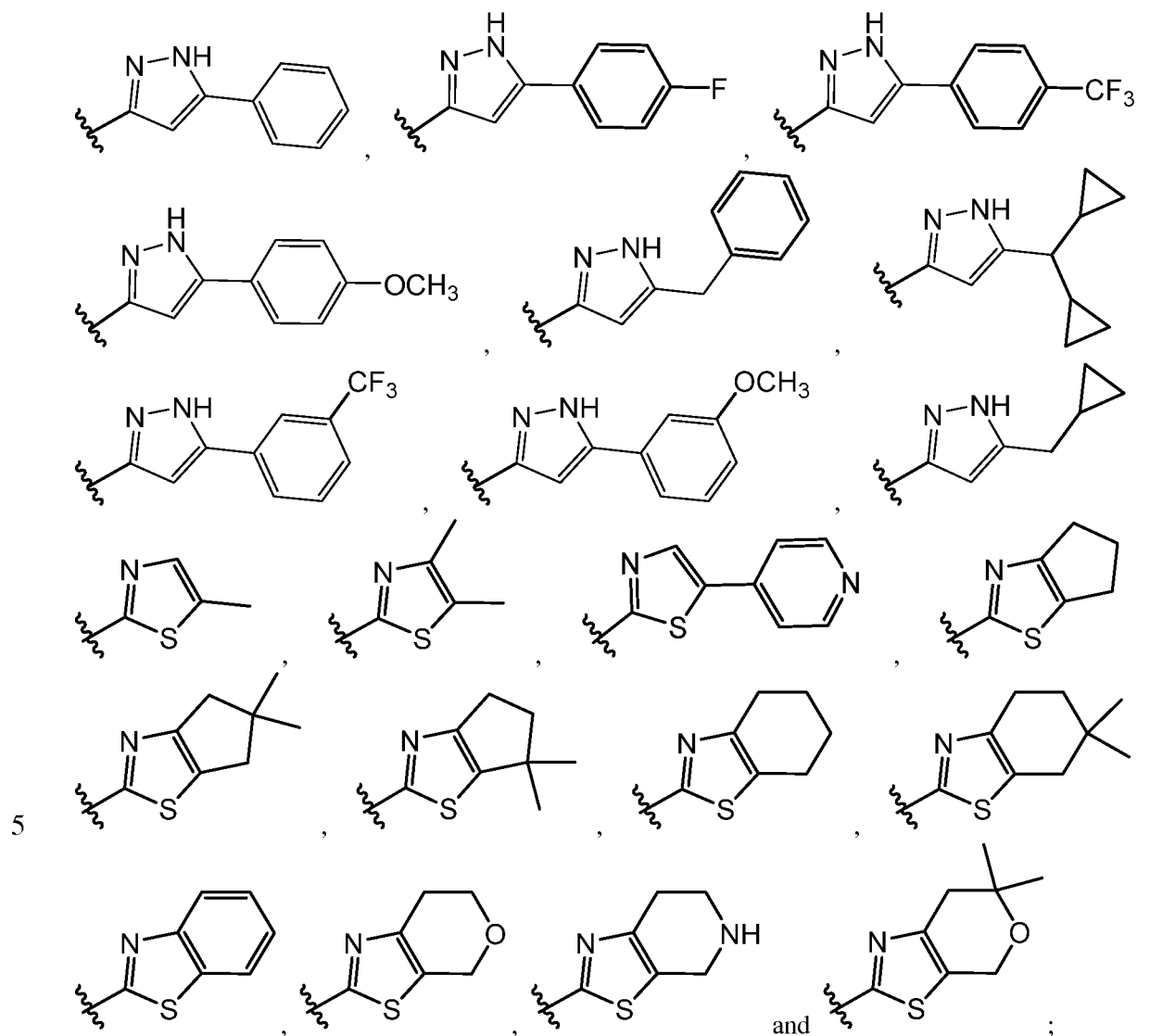
10 cyclopentathiazol-2-yl optionally substituted by R¹⁰. In certain embodiments, R² is 5,6-dihydro-4H-cyclopentathiazol-2-yl optionally substituted by C₁-C₆ alkyl (e.g., 5,6-dihydro-4H-cyclopentathiazol-2-yl; 5,5-dimethyl-5,6-dihydro-4H-cyclopentathiazol-2-yl; and 6,6-dimethyl-5,6-dihydro-4H-cyclopentathiazol-2-yl). In some embodiments, R² is thiazolyl fused with 5-6-membered heterocyclyl optionally substituted by R¹⁰. In certain embodiments,

15 R² is 6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-yl optionally substituted by R¹⁰. In certain embodiments, R² is 6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-yl optionally substituted by C₁-C₆ alkyl (e.g., 6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-yl; and 6,6-dimethyl-6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-yl). In certain embodiments, R² is 4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-yl optionally substituted by R¹⁰. In certain embodiments, R² is 4,5,6,7-

20 tetrahydro-thiazolo[5,4-c]pyridin-2-yl optionally substituted by C₁-C₆ alkyl. In some embodiments, R² is pyrazolyl (e.g., pyrazol-3-yl) optionally substituted by R¹⁰ or thiazolyl fused with C₅-C₆ cycloalkyl optionally substituted by R¹⁰.

In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, where R² is selected from the group consisting of:





wherein the wavy line represents the point of attachment of R^2 in Formula I.

It is intended and understood that each and every variation of R^2 described for Formula I may be combined with each and every variation of n and R^1 described for Formula I as if each and every combination is individually described. For example, in some embodiments, R^1 is C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{14} aryl, 5-10-membered heteroaryl, 3-10-membered heterocyclyl or $-NR^4R^5$ and R^2 is 5-9-membered heteroaryl optionally substituted by R^{10} . In some embodiments, R^1 is phenyl, cyclohexyl, pyridyl (e.g., pyridin-3-yl) or piperidinyl (e.g., piperidin-4-yl) and R^2 is pyrazolyl (e.g., pyrazol-3-yl) optionally substituted by R^{10} or thiazolyl fused with C_5 - C_6 cycloalkyl optionally substituted by R^{10} . In some embodiments, n is 2, R^1 is phenyl and R^2 is pyrazolyl (e.g., pyrazol-3-yl) optionally

substituted by R^{10} . In some embodiments, n is 2, R^1 is phenyl and R^2 is thiazolyl fused with C_5 - C_6 cycloalkyl optionally substituted by R^{10} .

In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^3 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, 3-10-membered heterocyclyl or $-NR^6R^7$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and heterocyclyl of R^3 are independently optionally substituted by R^{10} . In some embodiments, R^3 is C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, 3-10-membered heterocyclyl or $-NR^6R^7$, wherein the alkyl, cycloalkyl and heterocyclyl of R^3 are independently optionally substituted by R^{10} .

In certain embodiments, R^3 is C_1 - C_6 alkyl optionally substituted by R^{10} or C_3 - C_8 cycloalkyl optionally substituted by R^{10} . In certain embodiments, R^3 is C_1 - C_6 alkyl optionally substituted by R^{10} or $-NR^6R^7$. In certain embodiments, R^3 is C_1 - C_6 alkyl optionally substituted by hydroxyl, oxo or halo. In one embodiment, R^3 is 4-hydroxybutyl.

In certain embodiments, R^3 is 3-10-membered heterocyclyl optionally substituted by R^{10} . In certain embodiments, R^3 is 3-6-membered heterocyclyl optionally substituted by R^{10} . In certain embodiments, R^3 is 5- or 6-membered heterocyclyl optionally substituted by R^{10} . In certain embodiments, R^3 is 4-membered heterocyclyl (e.g., azetidiny) optionally substituted by R^{10} . In certain embodiments, R^3 is 5-membered heterocyclyl (e.g., pyrrolidiny) optionally substituted by R^{10} . In certain embodiments, R^3 is 6-membered heterocyclyl (e.g., piperidiny, morpholiny or piperaziny) optionally substituted by R^{10} . In certain embodiments, R^3 is 7-10-membered bicyclic or spirocyclic heterocyclyl (e.g., 2-oxa-6-aza-spiro[3,4]octyl) optionally substituted by R^{10} .

In some embodiments, R^3 is $-NR^6R^7$. In some of these embodiments, R^6 and R^7 are each independently hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and heterocyclyl are independently optionally substituted by halogen, oxo, $-OR^8$, $-NR^8R^9$, $-S(O)R^9$, $-S(O)_2R^9$ or 3-6 membered heterocyclyl which is optionally substituted by halogen, oxo or C_1 - C_6 alkyl which is optionally further substituted by oxo or halogen. In some embodiments, R^6 and R^7 are each independently hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl or 3-6 membered heterocyclyl, wherein the alkyl, cycloalkyl and heterocyclyl are independently optionally substituted by halogen, oxo, $-OR^8$, $-NR^8R^9$, $-S(O)R^9$, $-S(O)_2R^9$ or 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1 - C_6 alkyl optionally substituted by oxo or halogen. In some embodiments, R^6 and R^7 are independently hydrogen or C_1 - C_6 alkyl optionally substituted by $-OR^8$, $-NR^8R^9$, $-S(O)R^9$, $-S(O)_2R^9$ or 3-6 membered heterocyclyl

optionally substituted by C₁-C₆ alkyl. In some embodiments, R⁶ and R⁷ are independently hydrogen or C₃-C₆ cycloalkyl optionally substituted by -OR⁸, -NR⁸R⁹ or 3-6 membered heterocyclyl. In some embodiments, R⁶ and R⁷ are independently hydrogen or 3-6 membered heterocyclyl optionally substituted by oxo or C₁-C₆ alkyl. In some of these embodiments, each R⁸ and R⁹ is independently hydrogen or C₁-C₆ alkyl optionally substituted by oxo or halogen. In some of these embodiments, each R⁸ and R⁹ is independently hydrogen or C₁-C₆ alkyl (e.g., methyl). In some of these embodiments, each R⁸ is hydrogen and each R⁹ is C₁-C₆ alkyl (e.g., methyl). In some embodiments, R⁶ and R⁷ are each independently hydrogen, C₃-C₆ cycloalkyl optionally substituted by -OR⁸ where R⁸ is hydrogen. In some embodiments, R⁶ and R⁷ are each independently hydrogen, C₁-C₆ alkyl optionally substituted by -OR⁸ where R⁸ is hydrogen.

In some embodiments, R⁶ is C₁-C₆ alkyl, C₃-C₆ cycloalkyl or 3-6 membered heterocyclyl, wherein the alkyl, cycloalkyl and heterocyclyl are independently optionally substituted by halogen, oxo, -OR⁸, -NR⁸R⁹, -S(O)R⁹, -S(O)₂R⁹ or 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C₁-C₆ alkyl optionally substituted by oxo or halogen. In some embodiments, R⁶ is C₁-C₆ alkyl optionally substituted by -OR⁸, -NR⁸R⁹, -S(O)R⁹, -S(O)₂R⁹ or 3-6 membered heterocyclyl optionally substituted by C₁-C₆ alkyl. In some embodiments, R⁶ is C₃-C₆ cycloalkyl optionally substituted by -OR⁸, -NR⁸R⁹ or 3-6 membered heterocyclyl. In some embodiments, R⁶ is 3-6 membered heterocyclyl optionally substituted by oxo or C₁-C₆ alkyl. In some of these embodiments, each R⁸ and R⁹ is independently hydrogen or C₁-C₆ alkyl optionally substituted by oxo or halogen. In some of these embodiments, each R⁸ and R⁹ is independently hydrogen or C₁-C₆ alkyl (e.g., methyl). In some of these embodiments, each R⁸ is hydrogen and each R⁹ is C₁-C₆ alkyl (e.g., methyl).

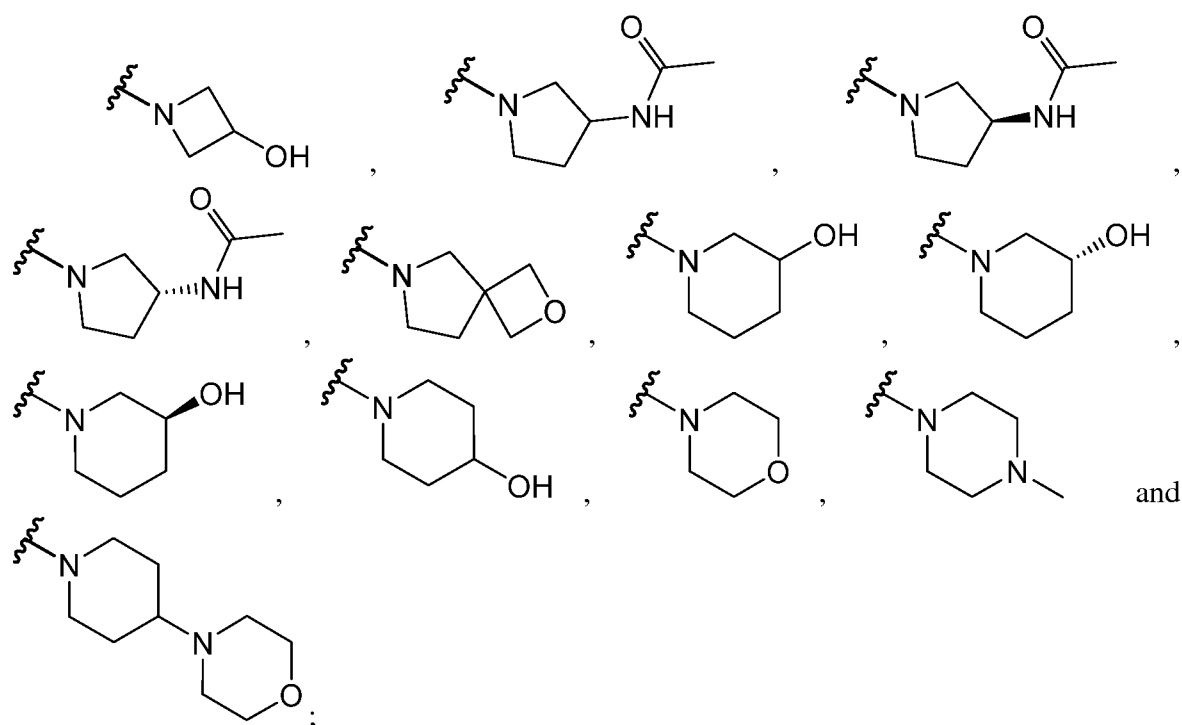
In some embodiments, R⁶ is C₁-C₆ alkyl (e.g., ethyl, propyl or butyl) optionally substituted by -OH, -NH₂, -S(O)CH₃, -S(O)₂CH₃, morpholin-4-yl or 4-methylpiperazin-1-yl. In some embodiments, R⁶ is C₁-C₆ alkyl optionally substituted by -OR⁸ where R⁸ is hydrogen. In some embodiments, R⁶ is C₃-C₆ cycloalkyl (e.g., cyclopentyl or cyclohexyl) optionally substituted by -OH or -NH₂. In some embodiments, R⁶ is C₃-C₆ cycloalkyl optionally substituted by -OR⁸ where R⁸ is hydrogen. In some embodiments, R⁶ is 3-6 membered heterocyclyl optionally substituted by oxo or C₁-C₆ alkyl. In some embodiments, R⁶ is 3-6 membered heterocyclyl (e.g., tetrahydropyranyl, tetrahydrothiophenyl or tetrahydrothiopyranyl) optionally substituted by oxo. In some embodiments, R⁷ is hydrogen or C₁-C₆ alkyl optionally substituted by -OR⁸ where R⁸ is hydrogen (e.g., 3-hydroxypropyl). In some embodiments, R⁷ is hydrogen or C₁-C₆ alkyl (e.g., methyl). In some embodiments, R⁷ is hydrogen.

It is intended and understood that each and every variation of R^6 described may be combined with each and every variation of R^7 describe as if each and every combination is individually described. For example, in certain embodiments, R^6 is C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl or 3-6 membered heterocyclyl, wherein the alkyl, cycloalkyl and heterocyclyl are independently optionally substituted by halogen, oxo, $-OR^8$, $-NR^8R^9$, $-S(O)R^9$, $-S(O)_2R^9$ or 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1 - C_6 alkyl optionally substituted by oxo or halogen and R^7 is hydrogen or C_1 - C_6 alkyl optionally substituted by $-OR^8$ where R^8 is hydrogen. In certain embodiments, R^6 is C_1 - C_6 alkyl optionally substituted by $-OR^8$, $-NR^8R^9$, $-S(O)R^9$, $-S(O)_2R^9$ or 3-6 membered heterocyclyl optionally substituted by C_1 - C_6 alkyl and R^7 is hydrogen or C_1 - C_6 alkyl optionally substituted by $-OR^8$ where R^8 is hydrogen. In certain embodiments, R^6 is C_3 - C_6 cycloalkyl optionally substituted by $-OR^8$, $-NR^8R^9$ or 3-6 membered heterocyclyl and R^7 is hydrogen. In certain embodiments, R^6 is C_3 - C_6 cycloalkyl optionally substituted by $-OR^8$ where R^8 is hydrogen and R^7 is hydrogen. In certain embodiments, R^6 is 3-6 membered heterocyclyl optionally substituted by oxo or C_1 - C_6 alkyl and R^7 is hydrogen. In certain embodiments, R^6 is C_1 - C_6 alkyl (e.g., ethyl, propyl or butyl) optionally substituted by $-OH$, $-NH_2$, $-S(O)CH_3$, $-S(O)_2CH_3$, morpholin-4-yl or 4-methylpiperazin-1-yl; C_3 - C_6 cycloalkyl (e.g., cyclopentyl or cyclohexyl) optionally substituted by $-OH$ or $-NH_2$; 3-6 membered heterocyclyl (e.g., tetrahydropyranyl, tetrahydrothiophenyl or tetrahydrothiopyranyl) optionally substituted by oxo; and R^7 is hydrogen, C_1 - C_6 alkyl (e.g., methyl) or C_1 - C_6 alkyl substituted by hydroxyl (e.g., 3-hydroxypropyl).

In some embodiments, R^3 is $-NR^6R^7$ where R^6 and R^7 are taken together with the nitrogen to which they attached to form 3-10-membered heterocyclyl optionally substituted by R^{10} . In some embodiments, R^6 and R^7 are taken together with the nitrogen to which they are attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, $-OR^{11}$, $-NR^{11}R^{12}$ or C_1 - C_6 alkyl optionally substituted by halogen. In some embodiments, R^6 and R^7 are taken together with the nitrogen to which they are attached to form a 3-6-membered heterocyclyl optionally substituted by $-OH$, $-NHC(O)CH_3$, 3-6 membered heterocyclyl or C_1 - C_6 alkyl. In some embodiments, R^6 and R^7 are taken together with the nitrogen to which they are attached to form a 4-membered heterocyclyl (e.g., azetidiny) optionally substituted by $-OH$ or C_1 - C_6 alkyl. In some embodiments, R^6 and R^7 are taken together with the nitrogen to which they are attached to form a 5-membered heterocyclyl (e.g., pyrrolidiny) optionally substituted by $-OH$, $-NHC(O)CH_3$, 3-6 membered heterocyclyl or C_1 - C_6 alkyl. In some embodiments, R^6 and R^7 are taken together with the nitrogen to which they are attached to form a 6-membered heterocyclyl (e.g., piperidiny, morpholinyl or

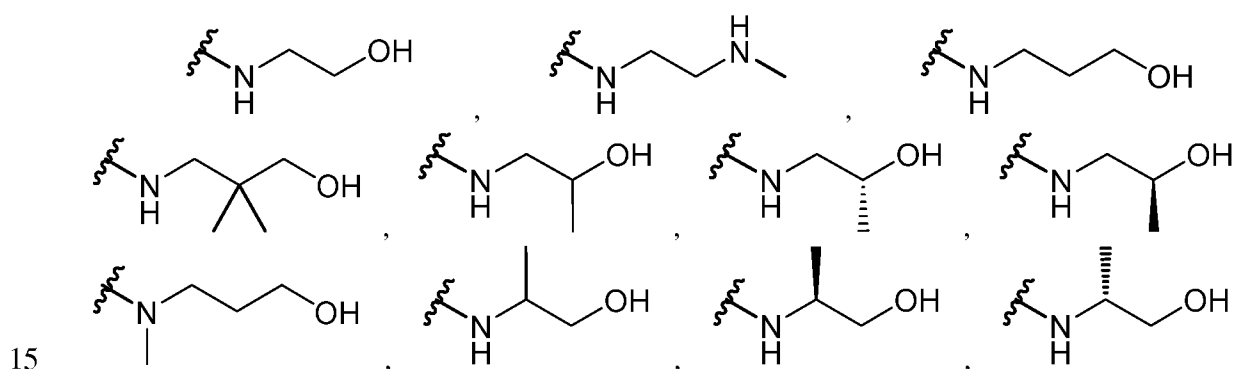
piperazinyl) optionally substituted by R¹⁰. In some embodiments, R⁶ and R⁷ are taken together with the nitrogen to which they are attached to form a 7-10-membered bicyclic or spirocyclic heterocyclyl (e.g., 2-oxa-6-aza-spiro[3,4]octyl) optionally substituted by R¹⁰.

In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, 5 solvate, prodrug or salt thereof, where R³ is selected from the group consisting of:



10 wherein the wavy line represents the point of attachment of R³ in Formula I.

In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, where R³ is selected from the group consisting of:





wherein the wavy line represents the point of attachment of R^3 in Formula I.

10

15

3-yl) optionally substituted by R^{10} or thiazolyl fused with C_5 - C_6 cycloalkyl optionally substituted by R^{10} ; and R^3 is C_1 - C_6 alkyl optionally substituted by R^{10} or $-NR^6R^7$. In some embodiments, n is 2; R^1 is phenyl; R^2 is pyrazolyl (e.g., pyrazol-3-yl) optionally substituted by R^{10} or thiazolyl fused with C_5 - C_6 cycloalkyl optionally substituted by R^{10} ; and R^3 is $-NR^6R^7$, where R^6 is C_1 - C_6 alkyl (e.g., ethyl, propyl or butyl) optionally substituted by -OH, -NH₂, -S(O)CH₃, -S(O)₂CH₃, morpholin-4-yl or 4-methylpiperazin-1-yl, C_3 - C_6 cycloalkyl (e.g., cyclopentyl or cyclohexyl) optionally substituted by -OH or -NH₂, or 3-6 membered heterocyclyl (e.g., tetrahydropyranyl, tetrahydrothiophenyl or tetrahydrothiopyranyl) optionally substituted by oxo; and R^7 is hydrogen, C_1 - C_6 alkyl (e.g., methyl) or C_1 - C_6 alkyl substituted by hydroxyl (e.g., 3-hydroxypropyl). In some embodiments, n is 2; R^1 is phenyl; R^2 is pyrazolyl (e.g., pyrazol-3-yl) optionally substituted by R^{10} or thiazolyl fused with C_5 - C_6 cycloalkyl optionally substituted by R^{10} ; and R^3 is $-NR^6R^7$, where R^6 and R^7 are taken together with the nitrogen to which they are attached to form a 3-6-membered heterocyclyl optionally substituted by -OH, -NHC(O)CH₃, 3-6 membered heterocyclyl or C_1 - C_6 alkyl.

In some of these embodiments, each R^{10} is independently hydrogen, oxo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, halogen, -CN, -OR¹¹, -SR¹¹, -NR¹¹R¹², -NO₂, -C=NH(OR¹¹), -C(O)R¹¹, -C(O)OR¹¹, -C(O)NR¹¹R¹², -NR¹¹C(O)R¹², -S(O)R¹¹, -S(O)₂R¹¹, -NR¹¹S(O)R¹², -NR¹¹S(O)₂R¹², -S(O)NR¹¹R¹², -S(O)₂NR¹¹R¹², C_3 - C_6 cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, C_6 - C_{14} aryl, -(C_1 - C_3 alkylene)CN, -(C_1 - C_3 alkylene)OR¹¹, -(C_1 - C_3 alkylene)SR¹¹, -(C_1 - C_3 alkylene)NR¹¹R¹², -(C_1 - C_3 alkylene)CF₃, -(C_1 - C_3 alkylene)NO₂, -C=NH(OR¹¹), -(C_1 - C_3 alkylene)C(O)R¹¹, -(C_1 - C_3 alkylene)C(O)OR¹¹, -(C_1 - C_3 alkylene)C(O)NR¹¹R¹², -(C_1 - C_3 alkylene)NR¹¹C(O)R¹², -(C_1 - C_3 alkylene)S(O)R¹¹, -(C_1 - C_3 alkylene)S(O)₂R¹¹, -(C_1 - C_3 alkylene)NR¹¹S(O)R¹², -(C_1 - C_3 alkylene)NR¹¹S(O)₂R¹², -(C_1 - C_3 alkylene)S(O)NR¹¹R¹², -(C_1 - C_3 alkylene)S(O)₂NR¹¹R¹², -(C_1 - C_3 alkylene)(C_3 - C_6 cycloalkyl), -(C_1 - C_3 alkylene)(3-10-membered heterocyclyl), -(C_1 - C_3 alkylene)(5-10-membered heteroaryl) or -(C_1 - C_3 alkylene)(C_6 - C_{14} aryl), wherein each R^{10} is independently optionally substituted by halogen, oxo, -OR¹³, -NR¹³R¹⁴, -C(O)R¹³, -S(O)R¹³, -S(O)₂R¹³, -(C_1 - C_3 alkylene)OR¹³, -(C_1 - C_3 alkylene)NR¹³R¹⁴, -(C_1 - C_3 alkylene)C(O)R¹³, -(C_1 - C_3 alkylene)S(O)R¹³, -(C_1 - C_3 alkylene)S(O)₂R¹³ or C_1 - C_6 alkyl optionally substituted by oxo, -CN or halogen.

In certain embodiments, R^{10} is independently -OH. In certain embodiments, R^{10} is independently -N(CH₃)₂. In certain embodiments, R^{10} is independently -NHC(O)CH₃. In certain embodiments, R^{10} is independently halogen (e.g., fluoro).

In certain embodiments, R^{10} is independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl or C_2 - C_6 alkynyl, wherein said alkyl, alkenyl and alkynyl are independently optionally substituted by

halogen, oxo, $-\text{OR}^{13}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{S(O)}\text{R}^{11}$, $-\text{S(O)}_2\text{R}^{11}$, $\text{C}_3\text{-C}_6$ cycloalkyl, phenyl or 3-6 membered heterocyclyl optionally substituted by halogen, oxo or $\text{C}_1\text{-C}_6$ alkyl optionally substituted by oxo or halogen. In certain embodiments, R^{10} is independently $\text{C}_1\text{-C}_6$ alkyl optionally substituted by halogen, oxo, $-\text{OR}^{13}$, $-\text{NR}^{13}\text{R}^{14}$, $\text{C}_3\text{-C}_6$ cycloalkyl or phenyl. In certain embodiments, R^{10} is independently $\text{C}_1\text{-C}_6$ alkyl optionally substituted by halogen, oxo, $-\text{OR}^{13}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{S(O)}\text{R}^{11}$, $-\text{S(O)}_2\text{R}^{11}$ or 3-6 membered heterocyclyl optionally substituted by halogen, oxo or $\text{C}_1\text{-C}_6$ alkyl optionally substituted by oxo or halogen.

In certain embodiments, R^{10} is methyl, ethyl or isopropyl. In certain embodiments, R^{10} is $-\text{CH}_2\text{Ph}$, $-\text{CH}_2(\text{cyclopropyl})$ or $-\text{CH}(\text{cyclopropyl})_2$. In certain embodiments, R^{10} is $-\text{CH}_2\text{OH}$, $-\text{CH}(\text{OH})\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{OH}$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OH}$, $-(\text{CH}_2)_3\text{OH}$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{NHCH}_3$, $-\text{CH}_2\text{N}(\text{CH}_3)_2$, $-(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$, $-\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{S(O)}\text{CH}_3$ or $-\text{CH}_2\text{CH}_2\text{S(O)}_2\text{CH}_3$. In certain embodiments, R^{10} is $-(\text{CH}_2)_2(\text{morpholinyl})$, $-(\text{CH}_2)_3(\text{morpholinyl})$, $-(\text{CH}_2)_2(\text{piperazinyl})$, $-(\text{CH}_2)_2(\text{N-methylpiperazinyl})$, $-(\text{CH}_2)_3(\text{piperazinyl})$ or $-(\text{CH}_2)_3(\text{N-methylpiperazinyl})$. In certain embodiments, R^{10} is methyl.

In certain embodiments, R^{10} is independently $\text{C}_3\text{-C}_6$ cycloalkyl optionally substituted by halogen, oxo, $-\text{OR}^{13}$, $-\text{NR}^{13}\text{R}^{14}$, phenyl or $\text{C}_1\text{-C}_6$ alkyl optionally substituted by halo. In certain embodiments, R^{10} is independently $\text{C}_3\text{-C}_6$ cycloalkyl optionally substituted by halogen, oxo or $\text{C}_1\text{-C}_3$ alkyl. In certain embodiments, R^{10} is independently cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In certain embodiments, R^{10} is independently 3,3-dimethylcyclobutyl, 3,4-dihydroxycyclopentyl, 4-hydroxycyclohexyl or 4-aminocyclohexyl.

In certain embodiments, R^{10} is independently 3-10-membered heterocyclyl which is optionally substituted by halogen, $-\text{OR}^{13}$, $-\text{NR}^{13}\text{R}^{14}$, 3-6 membered heterocyclyl, $\text{C}_3\text{-C}_6$ cycloalkyl or $\text{C}_1\text{-C}_6$ alkyl optionally substituted by halo. In certain embodiments, R^{10} is independently 3-10-membered heterocyclyl which is optionally substituted by $-\text{OR}^{13}$, $-\text{NR}^{13}\text{R}^{14}$, $\text{C}_3\text{-C}_6$ cycloalkyl or $\text{C}_1\text{-C}_6$ alkyl optionally substituted by halo. In certain embodiments, R^{10} is independently morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrrolidinyl, furanyl, tetrahydrothiophenyl or aziridinyl, each of the forgoing is independently optionally substituted by $-\text{OH}$, oxo, methyl or $-\text{CF}_3$.

In certain embodiments, R^{10} is independently 3-6 membered heterocyclyl or $-\text{C(O)}(3\text{-}6\text{ membered heterocyclyl})$, wherein said heterocyclyl is independently optionally substituted by $-\text{OR}^{13}$, $-(\text{C}_1\text{-C}_3\text{ alkylene})\text{OR}^{13}$, $-\text{NR}^{13}\text{R}^{14}$, $-(\text{C}_1\text{-C}_3\text{ alkylene})\text{NR}^{13}\text{R}^{14}$, halogen, $-\text{CN}$, oxo or $\text{C}_1\text{-C}_6$ alkyl optionally substituted by oxo or halogen. In certain embodiments, said

heterocyclyl is morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl or aziridinyl, wherein said heterocyclyl is independently optionally substituted by oxo, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{OH}$, methyl or $-\text{CF}_3$.

In certain embodiments, R^{10} is independently phenyl which is optionally substituted by halogen, $-\text{OR}^{13}$, $-\text{NR}^{13}\text{R}^{14}$, $\text{C}_3\text{-C}_6$ cycloalkyl or $\text{C}_1\text{-C}_6$ alkyl optionally substituted by halo. In certain embodiments, R^{10} is independently phenyl, or phenyl substituted by halo (e.g., fluoro), $-\text{CF}_3$, $-\text{OCH}_3$ or $-\text{OCF}_3$. In certain embodiments, R^{10} is independently phenyl, 4-fluorophenyl, 4-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-(trifluoromethoxy)phenyl or 3-(trifluoromethoxy)phenyl.

In certain embodiments, R^{10} is independently 5-10-membered heteroaryl which is optionally substituted by halogen, $-\text{OR}^{13}$, $-\text{NR}^{13}\text{R}^{14}$, $\text{C}_3\text{-C}_6$ cycloalkyl or $\text{C}_1\text{-C}_6$ alkyl optionally substituted by halo.

In certain embodiments, R^{10} is independently $-\text{OR}^{11}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{OR}^{11}$, $-\text{SR}^{11}$ or $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{SR}^{11}$. In certain embodiments, R^{10} is $-\text{OH}$, $-\text{OCH}_3$ or $-\text{OCF}_3$.

In certain embodiments, R^{10} is independently $-\text{NR}^{11}\text{R}^{12}$ or $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{NR}^{11}\text{R}^{12}$. In certain embodiments, R^{10} is $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_2\text{OH})_2$, $-\text{NHCH}_2\text{CH}_2\text{OH}$, $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH}$, $-\text{NHCH}_2\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{N}(\text{CH}_3)\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$, 4-hydroxyaziridin-1-yl, morpholinyl, dioxothiomorpholinyl, piperidinyl, 4-hydroxypiperidinyl, 4-methylpiperazinyl, pyrrolidinyl or 4-(2-hydroxyethyl)piperazinyl. In certain embodiments, R^{10} is $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_2\text{CH}_2\text{OH})_2$, $-\text{NHCH}_2\text{CH}_2\text{OH}$, $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH}$, $-\text{NHCH}_2\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{N}(\text{CH}_3)\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$, 4-hydroxyaziridin-1-yl, morpholinyl, dioxothiomorpholinyl, piperidinyl, 4-hydroxypiperidinyl, 4-methylpiperazinyl, pyrrolidinyl, $-\text{CH}_2\text{thiomorpholinyl dioxide}$, $-\text{CH}_2\text{morpholinyl}$, $(R)\text{-CH}(\text{NH}_2)\text{CH}_3$, $(S)\text{-CH}(\text{NH}_2)\text{CH}_3$ or 4-(2-hydroxyethyl)piperazinyl. In certain embodiments, R^{10} is $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$.

In certain embodiments, R^{10} is independently $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$. In certain embodiments, R^{10} is $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$ or $-\text{C}(\text{O})\text{morpholinyl}$.

In certain embodiments, R^{10} is independently $\text{C}_1\text{-C}_6$ alkyl, halogen, $-\text{CN}$, $-\text{OR}^{11}$, $-\text{SR}^{11}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{CF}_3$, $-\text{C}=\text{NH}(\text{OR}^{11})$, $-\text{C}(\text{O})\text{OR}^{11}$, $\text{C}_3\text{-C}_6$ cycloalkyl, 3-6-membered heterocyclyl, 5-6-membered heteroaryl or phenyl, wherein R^{10} is independently optionally substituted by halogen, oxo, $-\text{CF}_3$, $-\text{OR}^{13}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{C}(\text{O})\text{R}^{13}$, $-\text{S}(\text{O})_{1-2}\text{R}^{13}$ or $\text{C}_1\text{-C}_3$ alkyl optionally substituted by oxo or halogen.

In some embodiments, R^{11} and R^{12} are each independently hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_6 - C_{14} aryl, 5-6 membered heteroaryl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are independently optionally substituted by halogen, oxo, -CN, -OR¹⁶, -NR¹⁶R¹⁷ or C_1 - C_6 alkyl optionally substituted by halogen, -CN or oxo. In some embodiments, R^{11} and R^{12} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, -OR¹⁶, -NR¹⁶R¹⁷ or C_1 - C_6 alkyl optionally substituted by halogen, oxo or -OH.

In certain embodiments, R^{11} and R^{12} are independently hydrogen or C_1 - C_6 alkyl optionally substituted by halogen, oxo, -CN, -OR¹⁶ or -NR¹⁶R¹⁷, or are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, -OR¹⁶, -NR¹⁶R¹⁷ or C_1 - C_3 alkyl optionally substituted by halogen, oxo or OH. In some embodiments, R^{11} and R^{12} are each independently hydrogen or C_1 - C_6 alkyl optionally substituted by halogen, oxo or -OH.

In certain embodiments, R^{11} and R^{12} are independently hydrogen, methyl, -C(O)CH₃, 2-hydroxy-2-methylpropyl or 2-hydroxyethyl, or are taken together with the atom to which they attached to form a azetidiny, pyrrolidinyl, morpholinyl, dioxothiomorpholinyl, piperazinyl or piperidinyl ring optionally substituted by halogen, oxo or C_1 - C_3 alkyl optionally substituted by oxo, halogen or OH. In certain embodiments, R^{11} and R^{12} are independently hydrogen, methyl, -C(O)CH₃, 2-hydroxy-2-methylpropyl or 2-hydroxyethyl.

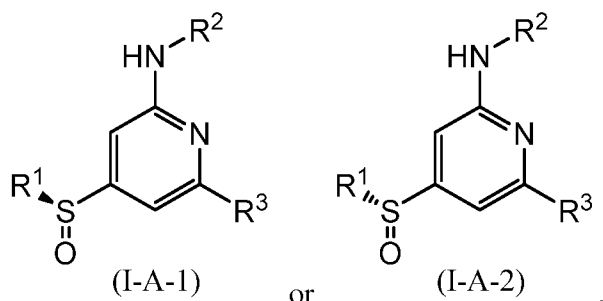
In some embodiments, R^{13} and R^{14} are each independently hydrogen or C_1 - C_6 alkyl optionally substituted by halogen or oxo. In some embodiments, R^{13} and R^{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1 - C_6 alkyl optionally substituted by halogen or oxo.

In certain embodiments, R^{13} and R^{14} are independently hydrogen or C_1 - C_3 alkyl. In certain embodiments, R^{13} and R^{14} are independently hydrogen or methyl.

In some embodiments, R^{16} and R^{17} are each independently hydrogen or C_1 - C_6 alkyl optionally substituted by halogen or oxo. In some embodiments, R^{16} and R^{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1 - C_6 alkyl optionally substituted by oxo or halogen.

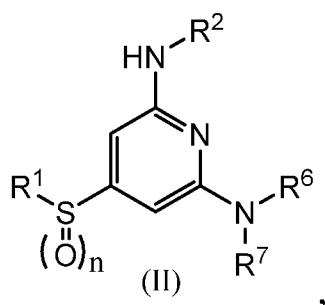
In certain embodiments, R^{16} and R^{17} are each independently hydrogen or C_1 - C_3 alkyl. In certain embodiments, R^{16} and R^{17} are each independently hydrogen or methyl.

In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein n is 1, and the compound is of the Formula (I-A-1) or (I-A-2):



5 wherein R^1 , R^2 and R^3 are as defined for Formula (I), or variations thereof detailed herein.

In some embodiments, provided are compounds of Formula II:



or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein:

10 R^1 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, C_6 - C_{14} aryl, 5-10-membered heteroaryl, 3-10-membered heterocyclyl or $-NR^4R^5$, wherein R^1 is optionally substituted by R^{10} ;

n is 1 or 2;

R^2 is 5-10-membered heteroaryl optionally substituted by R^{10} ;

15 R^4 and R^5 are each independently C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_6 - C_{14} aryl or $-(C_1$ - C_3 alkylene) NR^8R^9 ; or

R^4 and R^5 are taken together with the nitrogen to which they attached to form 3-10-membered heterocyclyl optionally substituted by R^{10} ;

20 R^6 and R^7 are each independently hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and heterocyclyl are independently optionally substituted by halogen,

oxo, $-\text{OR}^8$, $-\text{NR}^8\text{R}^9$, $-\text{S}(\text{O})\text{R}^9$, $-\text{S}(\text{O})_2\text{R}^9$ or 3-6 membered heterocyclyl optionally substituted by halogen, oxo or $\text{C}_1\text{-C}_6$ alkyl optionally substituted by oxo or halogen; or

R^6 and R^7 are taken together with the nitrogen to which they attached to form 3-10-membered heterocyclyl optionally substituted by R^{10} ;

5 R^8 and R^9 are each independently hydrogen or $\text{C}_1\text{-C}_6$ alkyl optionally substituted by oxo or halogen;

each R^{10} is independently hydrogen, oxo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, halogen, $-\text{CN}$, $-\text{OR}^{11}$, $-\text{SR}^{11}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NO}_2$, $-\text{C}=\text{NH}(\text{OR}^{11})$, $-\text{C}(\text{O})\text{R}^{11}$, $-\text{C}(\text{O})\text{OR}^{11}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{S}(\text{O})\text{R}^{11}$, $-\text{S}(\text{O})_2\text{R}^{11}$, $-\text{NR}^{11}\text{S}(\text{O})\text{R}^{12}$, $-\text{NR}^{11}\text{S}(\text{O})_2\text{R}^{12}$,
 10 $-\text{S}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{S}(\text{O})_2\text{NR}^{11}\text{R}^{12}$, $\text{C}_3\text{-C}_6$ cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, $\text{C}_6\text{-C}_{14}$ aryl, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{CN}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{OR}^{11}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{SR}^{11}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{NR}^{11}\text{R}^{12}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{CF}_3$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{NO}_2$, $-\text{C}=\text{NH}(\text{OR}^{11})$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{C}(\text{O})\text{R}^{11}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{C}(\text{O})\text{OR}^{11}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{S}(\text{O})\text{R}^{11}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{S}(\text{O})_2\text{R}^{11}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{NR}^{11}\text{S}(\text{O})\text{R}^{12}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{NR}^{11}\text{S}(\text{O})_2\text{R}^{12}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{S}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{S}(\text{O})_2\text{NR}^{11}\text{R}^{12}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})(\text{C}_3\text{-C}_6 \text{ cycloalkyl})$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})(3\text{-}10\text{-membered heterocyclyl})$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})(5\text{-}10\text{-membered heteroaryl})$ or $-(\text{C}_1\text{-C}_3 \text{ alkylene})(\text{C}_6\text{-C}_{14} \text{ aryl})$, wherein each R^{10} is independently optionally substituted by halogen, oxo, $-\text{OR}^{13}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{C}(\text{O})\text{R}^{13}$, $-\text{S}(\text{O})\text{R}^{13}$, $-\text{S}(\text{O})_2\text{R}^{13}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{OR}^{13}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{NR}^{13}\text{R}^{14}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{C}(\text{O})\text{R}^{13}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{S}(\text{O})\text{R}^{13}$, $-(\text{C}_1\text{-C}_3 \text{ alkylene})\text{S}(\text{O})_2\text{R}^{13}$ or $\text{C}_1\text{-C}_6$ alkyl optionally substituted by oxo, $-\text{CN}$ or halogen;

R^{11} and R^{12} are each independently hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_6\text{-C}_{14}$ aryl, 5-6 membered heteroaryl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are independently optionally substituted by halogen, oxo, $-\text{OR}^{16}$, $-\text{NR}^{16}\text{R}^{17}$ or $\text{C}_1\text{-C}_6$ alkyl optionally substituted by halogen, $-\text{CN}$ or oxo; or

R^{11} and R^{12} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, $-\text{OR}^{16}$, $-\text{NR}^{16}\text{R}^{17}$ or $\text{C}_1\text{-C}_6$ alkyl optionally substituted by halogen, oxo or OH;

R^{13} and R^{14} are each independently hydrogen, $\text{C}_1\text{-C}_6$ alkyl optionally substituted by halogen or oxo, $\text{C}_2\text{-C}_6$ alkenyl optionally substituted by halogen or oxo, or $\text{C}_2\text{-C}_6$ alkynyl optionally substituted by halogen or oxo; or

R^{13} and R^{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1 - C_6 alkyl optionally substituted by halogen or oxo; and

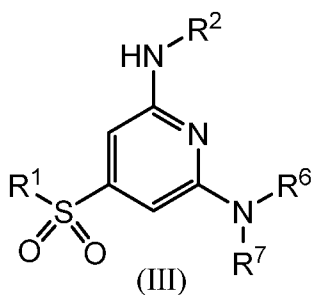
R^{16} and R^{17} are each independently hydrogen, C_1 - C_6 alkyl optionally substituted by halogen or oxo, C_2 - C_6 alkenyl optionally substituted by halogen or oxo, or C_2 - C_6 alkynyl optionally substituted by halogen or oxo; or

R^{16} and R^{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1 - C_6 alkyl optionally substituted by oxo or halogen.

In some embodiments, R^1 is C_3 - C_8 cycloalkyl, C_6 - C_{14} aryl, 5-10-membered monocyclic heteroaryl, 3-10-membered monocyclic heterocyclyl or $-NR^4R^5$, where the cycloalkyl, aryl, heteroaryl and heterocyclyl are independently optionally substituted by R^{10} .

It is further intended and understood that each and every variation of n , R^1 , R^2 , R^4 , R^5 , R^6 and R^7 described for Formula I or variations thereof may be applicable to Formula II as if each and every combination is individually described. It is further understood and intended that each and every variation of R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{16} and R^{17} described herein, where applicable, may be combined with each and every variation of n , R^1 , R^2 , R^4 , R^5 , R^6 and R^7 described for Formula II as if each and every combination is individually described.

In some embodiments, provided are compounds of Formula III:



or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein:

R^1 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, C_6 - C_{14} aryl, 5-10-membered heteroaryl, 3-10-membered heterocyclyl or $-NR^4R^5$, wherein R^1 is optionally substituted by R^{10} ;

R^2 is 5-10-membered heteroaryl optionally substituted by R^{10} ;

R^4 and R^5 are each independently C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_6 - C_{14} aryl or $-(C_1$ - C_3 alkylene) NR^8R^9 ; or

R⁴ and R⁵ are taken together with the nitrogen to which they attached to form 3-10-membered heterocyclyl optionally substituted by R¹⁰;

R⁶ and R⁷ are each independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and heterocyclyl are independently optionally substituted by halogen, oxo, -OR⁸, -NR⁸R⁹, -S(O)R⁹, -S(O)₂R⁹ or 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C₁-C₆ alkyl optionally substituted by oxo or halogen; or

R⁶ and R⁷ are taken together with the nitrogen to which they attached to form 3-10-membered heterocyclyl optionally substituted by R¹⁰;

R⁸ and R⁹ are each independently hydrogen or C₁-C₆ alkyl optionally substituted by oxo or halogen;

each R¹⁰ is independently hydrogen, oxo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, halogen, -CN, -OR¹¹, -SR¹¹, -NR¹¹R¹², -NO₂, -C=NH(OR¹¹), -C(O)R¹¹, -C(O)OR¹¹, -C(O)NR¹¹R¹², -NR¹¹C(O)R¹², -S(O)R¹¹, -S(O)₂R¹¹, -NR¹¹S(O)R¹², -NR¹¹S(O)₂R¹², -S(O)NR¹¹R¹², -S(O)₂NR¹¹R¹², C₃-C₆ cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, C₆-C₁₄ aryl, -(C₁-C₃ alkylene)CN, -(C₁-C₃ alkylene)OR¹¹, -(C₁-C₃ alkylene)SR¹¹, -(C₁-C₃ alkylene)NR¹¹R¹², -(C₁-C₃ alkylene)CF₃, -(C₁-C₃ alkylene)NO₂, -C=NH(OR¹¹), -(C₁-C₃ alkylene)C(O)R¹¹, -(C₁-C₃ alkylene)C(O)OR¹¹, -(C₁-C₃ alkylene)C(O)NR¹¹R¹², -(C₁-C₃ alkylene)NR¹¹C(O)R¹², -(C₁-C₃ alkylene)S(O)R¹¹, -(C₁-C₃ alkylene)S(O)₂R¹¹, -(C₁-C₃ alkylene)NR¹¹S(O)R¹², -(C₁-C₃ alkylene)NR¹¹S(O)₂R¹², -(C₁-C₃ alkylene)S(O)NR¹¹R¹², -(C₁-C₃ alkylene)S(O)₂NR¹¹R¹², -(C₁-C₃ alkylene)(C₃-C₆ cycloalkyl), -(C₁-C₃ alkylene)(3-10-membered heterocyclyl), -(C₁-C₃ alkylene)(5-10-membered heteroaryl) or -(C₁-C₃ alkylene)(C₆-C₁₄ aryl), wherein each R¹⁰ is independently optionally substituted by halogen, oxo, -OR¹³, -NR¹³R¹⁴, -C(O)R¹³, -S(O)R¹³, -S(O)₂R¹³, -(C₁-C₃ alkylene)OR¹³, -(C₁-C₃ alkylene)NR¹³R¹⁴, -(C₁-C₃ alkylene)C(O)R¹³, -(C₁-C₃ alkylene)S(O)R¹³, -(C₁-C₃ alkylene)S(O)₂R¹³ or C₁-C₆ alkyl optionally substituted by oxo, -CN or halogen;

R¹¹ and R¹² are each independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₆-C₁₄ aryl, 5-6 membered heteroaryl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are independently optionally substituted by halogen, oxo, -CN, -OR¹⁶, -NR¹⁶R¹⁷ or C₁-C₆ alkyl optionally substituted by halogen, -CN or oxo; or

R^{11} and R^{12} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, $-OR^{16}$, $-NR^{16}R^{17}$ or C_1-C_6 alkyl optionally substituted by halogen, oxo or OH;

R^{13} and R^{14} are each independently hydrogen, C_1-C_6 alkyl optionally substituted by halogen or oxo, C_2-C_6 alkenyl optionally substituted by halogen or oxo, or C_2-C_6 alkynyl optionally substituted by halogen or oxo; or

R^{13} and R^{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by halogen or oxo; and

R^{16} and R^{17} are each independently hydrogen, C_1-C_6 alkyl optionally substituted by halogen or oxo, C_2-C_6 alkenyl optionally substituted by halogen or oxo, or C_2-C_6 alkynyl optionally substituted by halogen or oxo; or

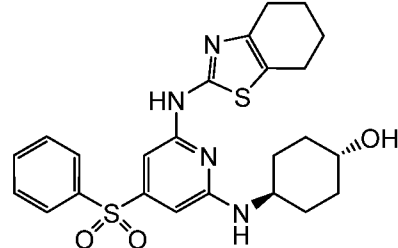
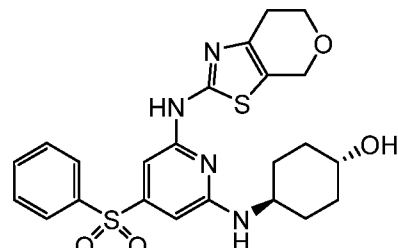
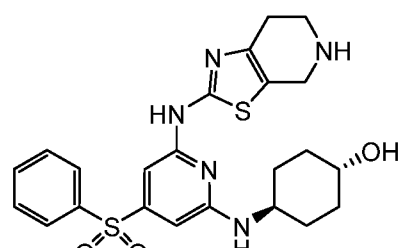
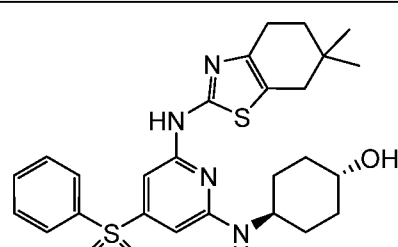
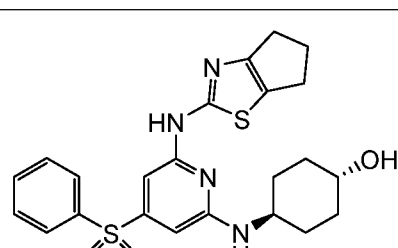
R^{16} and R^{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by oxo or halogen.

It is further intended and understood that each and every variation of R^1 , R^2 , R^4 , R^5 , R^6 and R^7 described for Formula I or variations thereof may be applicable to Formula III as if each and every combination is individually described. It is further understood and intended that each and every variation of R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{16} and R^{17} described herein, where applicable, may be combined with each and every variation of R^1 , R^2 , R^4 , R^5 , R^6 and R^7 described for Formula III as if each and every combination is individually described.

Representative compounds of the invention, and their stereoisomers, are listed in Table 1.

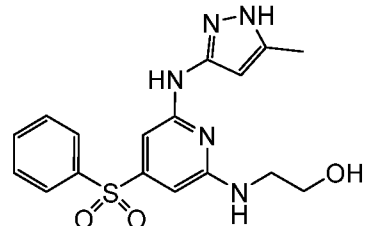
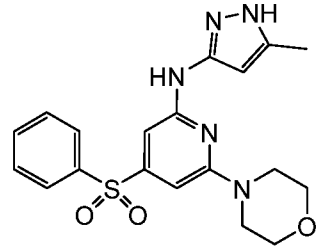
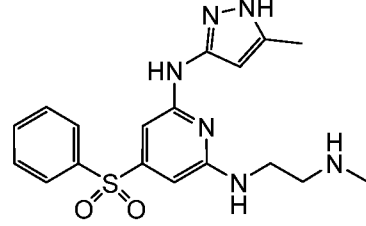
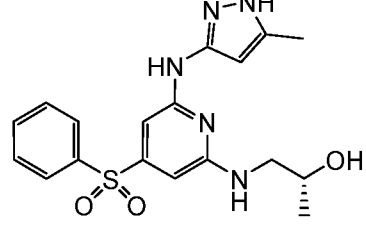
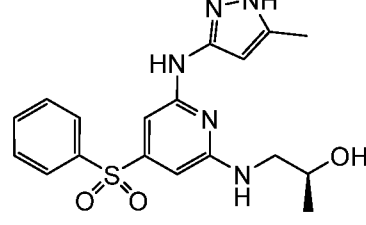
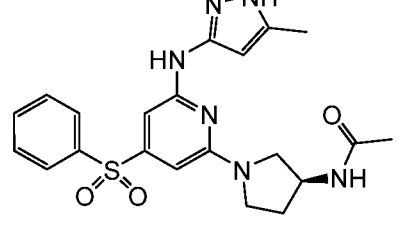
Table 1

Example No.	Structure	Name
1		(<i>trans</i>)-4-[4-Benzenesulfonyl-6-(benzothiazol-2-ylamino)-pyridin-2-ylamino]-cyclohexanol

2		(<i>trans</i>)-4-[4-Benzenesulfonyl-6-(4,5,6,7-tetrahydro-benzothiazol-2-ylamino)-pyridin-2-ylamino]-cyclohexanol
3		(<i>trans</i>)-4-[4-Benzenesulfonyl-6-(6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-ylamino)-pyridin-2-ylamino]-cyclohexanol
4		(<i>trans</i>)-4-[4-Benzenesulfonyl-6-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-ylamino)-pyridin-2-ylamino]-cyclohexanol
5		(<i>trans</i>)-4-[4-Benzenesulfonyl-6-(6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-ylamino)-pyridin-2-ylamino]-cyclohexanol
6		(<i>trans</i>)-4-[4-Benzenesulfonyl-6-(5,6-dihydro-4H-cyclopentathiazol-2-ylamino)-pyridin-2-ylamino]-cyclohexanol

7		(<i>trans</i>)-4-[4-Benzenesulfonyl-6-(5-methyl-thiazol-2-ylamino)-pyridin-2-ylamino]-cyclohexanol
8		4-Benzenesulfonyl-N-(2-methanesulfonyl-ethyl)-N'-pyridin-2-yl-pyridine-2,6-diamine
9		3-[4-Benzenesulfonyl-6-(pyridin-2-ylamino)-pyridin-2-ylamino]-propan-1-ol
10		3-[4-Benzenesulfonyl-6-(5-methyl-pyridin-2-ylamino)-pyridin-2-ylamino]-propan-1-ol
11		4-Benzenesulfonyl-N-(2-methanesulfonyl-ethyl)-N'-(5-methyl-1H-pyrazol-3-yl)-pyridine-2,6-diamine
12		4-Benzenesulfonyl-N-[2-(4-methyl-piperazin-1-yl)-ethyl]-N'-(5-methyl-1H-pyrazol-3-yl)-pyridine-2,6-diamine

13		4-Benzenesulfonyl-N-(5-methyl-1H-pyrazol-3-yl)-N'-(2-morpholin-4-yl-ethyl)-pyridine-2,6-diamine
14		4-Benzenesulfonyl-N-(5-methyl-1H-pyrazol-3-yl)-N'-(3-morpholin-4-yl-propyl)-pyridine-2,6-diamine
15		4-Benzenesulfonyl-N-[3-(4-methyl-piperazin-1-yl)-propyl]-N'-(5-methyl-1H-pyrazol-3-yl)-pyridine-2,6-diamine
16		4-Benzenesulfonyl-N-(1-methyl-piperidin-4-yl)-N'-(5-methyl-1H-pyrazol-3-yl)-pyridine-2,6-diamine
17		[4-Benzenesulfonyl-6-(4-methyl-piperazin-1-yl)-pyridin-2-yl]-(5-methyl-1H-pyrazol-3-yl)-amine
18		3-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-1-ol

19		2-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-ethanol
20		(4-Benzenesulfonyl-6-morpholin-4-yl-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine
21		4-Benzenesulfonyl-N-(2-methylamino-ethyl)-N'-(5-methyl-1H-pyrazol-3-yl)-pyridine-2,6-diamine
22		(<i>R</i>)-1-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-2-ol
23		(<i>S</i>)-1-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-2-ol
24		N-[(<i>S</i>)-1-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-yl]-pyrrolidin-3-yl]-acetamide

25		N-((<i>R</i>)-1-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-yl]-pyrrolidin-3-yl)-acetamide
26		[4-Benzenesulfonyl-6-(2-oxa-6-azaspiro[3.4]oct-6-yl)-pyridin-2-yl]-(5-methyl-1H-pyrazol-3-yl)-amine
27		(4'-Benzenesulfonyl-4-morpholin-4-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl)-(5-methyl-1H-pyrazol-3-yl)-amine
28		1-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-yl]-azetidin-3-ol
29		4-Benzenesulfonyl-N-(5-methyl-1H-pyrazol-3-yl)-N'-(tetrahydro-pyran-4-yl)-pyridine-2,6-diamine
30		(<i>S</i>)-2-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-1-ol

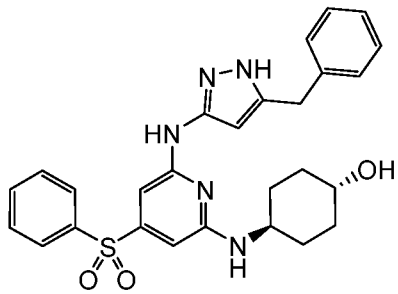
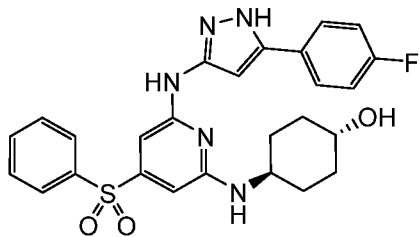
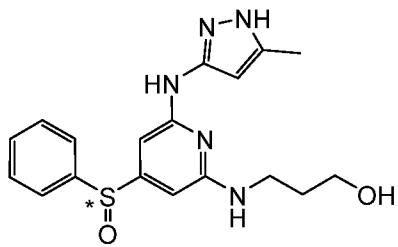
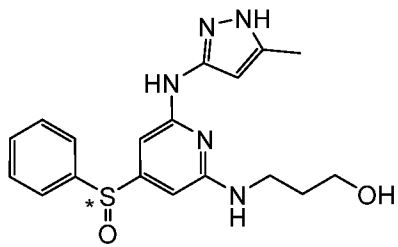
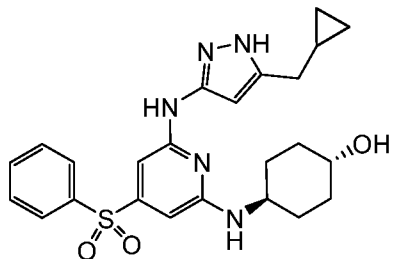
31		(R)-2-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-1-ol
32		3-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-2,2-dimethyl-propan-1-ol
33		(±)-4-Benzenesulfonyl-N-(2-methanesulfonyl-ethyl)-N'-(5-methyl-1H-pyrazol-3-yl)-pyridine-2,6-diamine
34		4-Benzenesulfonyl-N-(2-methanesulfonyl-ethyl)-N-methyl-N'-(5-methyl-1H-pyrazol-3-yl)-pyridine-2,6-diamine
35		3-{[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-yl]-methylamino}-propan-1-ol
36		1-[4-(benzenesulfonyl)-6-[(5-methyl-1H-pyrazol-3-yl)amino]pyridin-2-yl]piperidin-4-ol

37		(3S)-1-[4-(benzenesulfonyl)-6-[(5-methyl-1H-pyrazol-3-yl)amino]pyridin-2-yl]piperidin-3-ol
38		(3R)-1-[4-(benzenesulfonyl)-6-[(5-methyl-1H-pyrazol-3-yl)amino]pyridin-2-yl]piperidin-3-ol
39		(trans)-4-{4-Benzenesulfonyl-6-[5-(4-methoxy-phenyl)-1H-pyrazol-3-ylamino]-pyridin-2-ylamino}-cyclohexanol
40		(trans)-4-[4-Benzenesulfonyl-6-(5-phenyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-cyclohexanol
41		3-{4-Benzenesulfonyl-6-[5-(4-methoxy-phenyl)-1H-pyrazol-3-ylamino]-pyridin-2-ylamino}-propan-1-ol
42		(trans)-4-[4-Benzenesulfonyl-6-(5-cyclopentyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-cyclohexanol,formatesalt

43		(<i>trans</i>)-4-{4-Benzenesulfonyl-6-[5-(3-methoxy-phenyl)-1H-pyrazol-3-ylamino]-pyridin-2-ylamino}-cyclohexanol
44		(<i>trans</i>)-4-{4-Benzenesulfonyl-6-[5-(3-trifluoromethyl-phenyl)-1H-pyrazol-3-ylamino]-pyridin-2-ylamino}-cyclohexanol
45		(<i>trans</i>)-4-[4-Benzenesulfonyl-6-(5-cyclobutyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-cyclohexanol
46		(<i>trans</i>)-4-[4-Benzenesulfonyl-6-(6,6-dimethyl-6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-ylamino)-pyridin-2-ylamino]-cyclohexanol,formatesalt
47		(<i>trans</i>)-4-[6-(5-Cyclopentyl-1H-pyrazol-3-ylamino)-4-(pyridine-3-sulfonyl)-pyridin-2-ylamino]-cyclohexanol

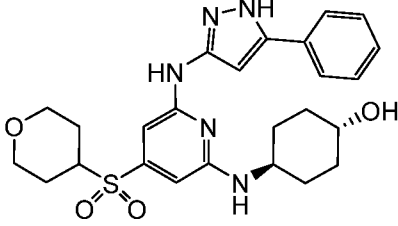
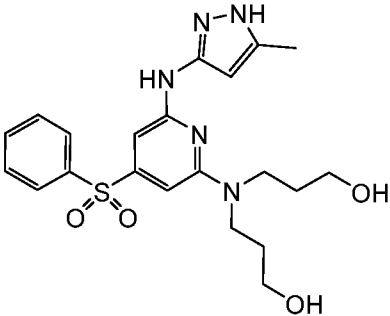
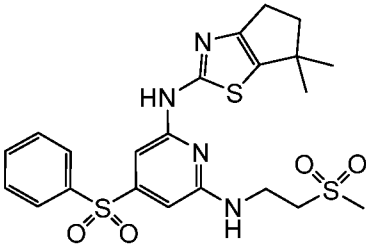
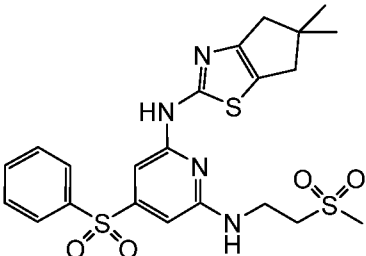
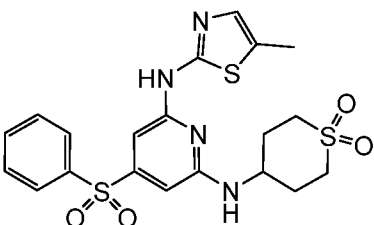
48		3-[4-Benzenesulfonyl-6-(5-dicyclopropylmethyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-1-ol,formatesalt
49		3-[6-(5-Cyclopentyl-1H-pyrazol-3-ylamino)-4-(pyridine-3-sulfonyl)-pyridin-2-ylamino]-propan-1-ol,formatesalt
50		3-[6-(5-Phenyl-1H-pyrazol-3-ylamino)-4-(pyridine-3-sulfonyl)-pyridin-2-ylamino]-propan-1-ol],formatesalt
51		N-(6,6-Dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-yl)-N'-(2-methanesulfonyl-ethyl)-4-(pyridine-3-sulfonyl)-pyridine-2,6-diamine,formatesalt
52		3-[6-(6,6-Dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-ylamino)-4-(pyridine-3-sulfonyl)-pyridin-2-ylamino]-propan-1-ol

53		(±)-N-(6,6-Dimethyl-4,5,6,7-tetrahydrobenzothiazol-2-yl)-N'-(2-methanesulfinylethyl)-4-(pyridine-3-sulfonyl)-pyridine-2,6-diamine,formatesalt
54		(trans)-4-[4-Cyclohexanesulfonyl-6-(5-cyclopentyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-cyclohexanol
55		3-[4-Cyclohexanesulfonyl-6-(5-cyclopentyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-1-ol
56		(trans)-4-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-cyclohexanol,formatesalt
57		(trans)-4-[4-Benzenesulfonyl-6-(5-cyclohexyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-cyclohexanol
58		3-[4-Benzenesulfonyl-6-(5-cyclohexyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-1-ol

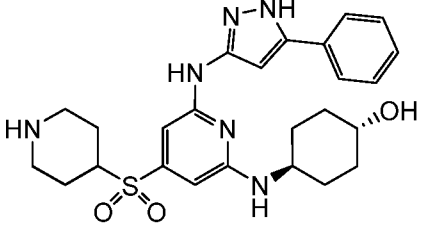
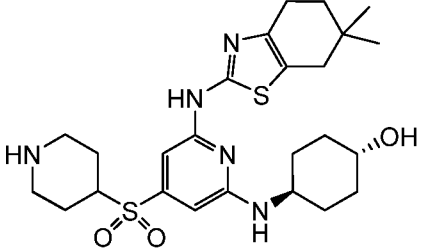
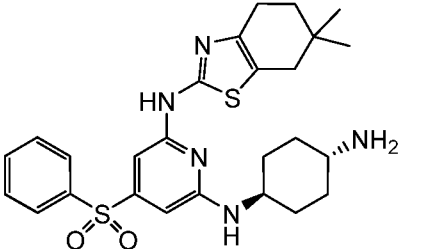
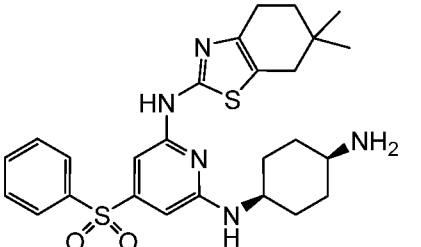
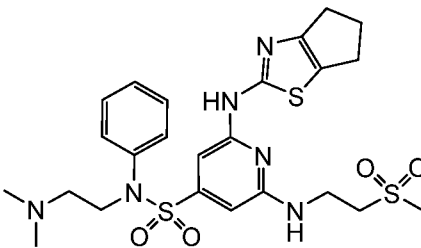
59		(<i>trans</i>)-4-[4-Benzenesulfonyl-6-(5-benzyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-cyclohexanol
60		(<i>trans</i>)-4-{4-Benzenesulfonyl-6-[5-(4-fluoro-phenyl)-1H-pyrazol-3-ylamino]-pyridin-2-ylamino}-cyclohexanol
61	 <p>(Enantiomer 1)</p>	3-[4-Benzenesulfinyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-1-ol; Enantiomer 1
62	 <p>(Enantiomer 2)</p>	3-[4-Benzenesulfinyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-1-ol; Enantiomer 2
63		(<i>trans</i>)-4-[4-Benzenesulfonyl-6-(5-cyclopropylmethyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-cyclohexanol

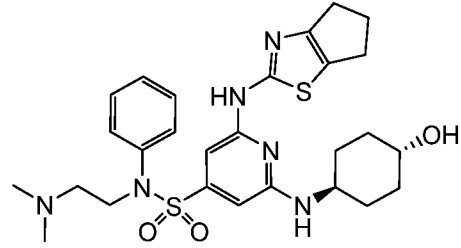
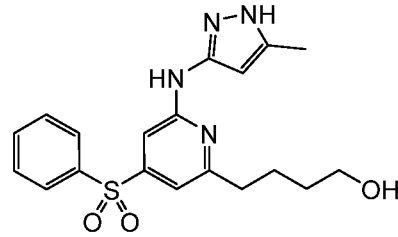
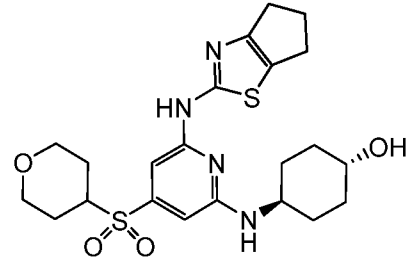
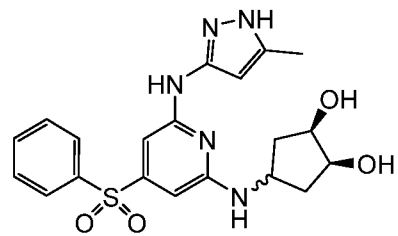
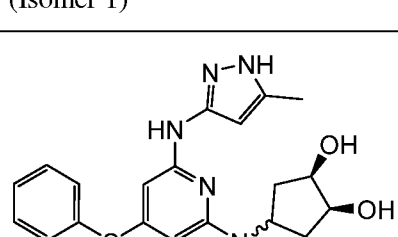
64		(<i>trans</i>)-4-{4-Benzenesulfonyl-6-[5-(4-trifluoromethyl-phenyl)-1 <i>H</i> -pyrazol-3-ylamino]-pyridin-2-ylamino}-cyclohexanol,formatesalt
65		(<i>trans</i>)-4-{4-Benzenesulfonyl-6-[5-(4-trifluoromethoxy-phenyl)-1 <i>H</i> -pyrazol-3-ylamino]-pyridin-2-ylamino}-cyclohexanol,formatesalt
66		(<i>trans</i>)-4-[4-Benzenesulfonyl-6-(1-methyl-1 <i>H</i> -imidazol-4-ylamino)-pyridin-2-ylamino]-cyclohexanol
67		3-[4-Benzenesulfonyl-6-(4,5-dimethyl-thiazol-2-ylamino)-pyridin-2-ylamino]-propan-1-ol,formatesalt
68		3-[4-Benzenesulfonyl-6-(3-methyl-[1,2,4]thiadiazol-5-ylamino)-pyridin-2-ylamino]-propan-1-ol

69		3-[4-Benzenesulfonyl-6-(1,5-dimethyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-1-ol
70		3-{4-Benzenesulfonyl-6-[5-(3,3-dimethyl-cyclobutyl)-1H-pyrazol-3-ylamino]-pyridin-2-ylamino}-propan-1-ol, formates salt
71		(trans)-4-[4-(3-Dimethylaminomethyl-benzenesulfonyl)-6-(6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-ylamino)-pyridin-2-ylamino]-cyclohexanol
72		3-[6-(5-Phenyl-1H-pyrazol-3-ylamino)-4-(piperidine-1-sulfonyl)-pyridin-2-ylamino]-propan-1-ol
73		2-(5,6-Dihydro-4H-cyclopentathiazol-2-ylamino)-6-(3-hydroxy-propylamino)-pyridine-4-sulfonic acid(2-dimethylamino-ethyl)-phenyl-amide
74		4-Benzenesulfonyl-N-(2-methanesulfonyl-ethyl)-N'-(1-phenyl-1H-imidazol-4-yl)-pyridine-2,6-diamine, formates salt

75		(<i>trans</i>)-4-[6-(5-Phenyl-2 <i>H</i> -pyrazol-3-ylamino)-4-(tetrahydro-pyran-4-sulfonyl)-pyridin-2-ylamino]-cyclohexanol
76		3-{[4-Benzenesulfonyl-6-(5-methyl-2 <i>H</i> -pyrazol-3-ylamino)-pyridin-2-yl]-(3-hydroxy-propyl)-amino}-propan-1-ol, formate salt
77		4-Benzenesulfonyl-N-(6,6-dimethyl-5,6-dihydro-4 <i>H</i> -cyclopentathiazol-2-yl)-N'-(2-methanesulfonyl-ethyl)-pyridine-2,6-diamine
78		4-Benzenesulfonyl-N-(5,5-dimethyl-5,6-dihydro-4 <i>H</i> -cyclopentathiazol-2-yl)-N'-(2-methanesulfonyl-ethyl)-pyridine-2,6-diamine
79		4-Benzenesulfonyl-N-(1,1-dioxo-hexahydro-1λ6-thiopyran-4-yl)-N'-(5-methyl-thiazol-2-yl)-pyridine-2,6-diamine

80		(±)-4-Benzenesulfonyl-N-(1,1-dioxo-tetrahydro-1λ6-thiophen-3-yl)-N'-(5-methyl-thiazol-2-yl)-pyridine-2,6-diamine
81		(<i>trans</i>)-4-[6-(5,6-Dihydro-4H-cyclopentathiazol-2-ylamino)-4-(piperidine-4-sulfonyl)-pyridin-2-ylamino]-cyclohexanol
82		N-(5,6-Dihydro-4H-cyclopentathiazol-2-yl)-N'-(2-methanesulfonyl-ethyl)-4-(piperidine-4-sulfonyl)-pyridine-2,6-diamine
83		4-Benzenesulfonyl-N-(2-methanesulfonyl-ethyl)-N'-(5-pyridin-4-yl-thiazol-2-yl)-pyridine-2,6-diamine
84		3-[6-(5-Phenyl-1H-pyrazol-3-ylamino)-4-(propane-2-sulfonyl)-pyridin-2-ylamino]-propan-1-ol
85		(<i>trans</i>)-4-[6-(5,6-Dihydro-4H-cyclopentathiazol-2-ylamino)-4-(propane-2-sulfonyl)-pyridin-2-ylamino]-cyclohexanol

86		(<i>trans</i>)-4-[4-(4-Methyl-piperidine-4-sulfonyl)-6-(5-phenyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-cyclohexanol
87		(<i>trans</i>)-4-[6-(6,6-Dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-ylamino)-4-(4-methyl-piperidine-4-sulfonyl)-pyridin-2-ylamino]-cyclohexanol
88		2-N-(6,6-dimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)-4-(1-methylidenecyclohexa-2,4-diene-1-sulfonyl)-6-N-[(<i>trans</i>)-4-aminocyclohexyl]pyridine-2,6-diamine
89		4-(benzenesulfonyl)-2-N-(6,6-dimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)-6-N-[(<i>cis</i>)-4-aminocyclohexyl]pyridine-2,6-diamine
90		2-(5,6-Dihydro-4H-cyclopentathiazol-2-ylamino)-6-(2-methanesulfonyl-ethylamino)-pyridine-4-sulfonicacid(2-dimethylamino-ethyl)-phenyl-amide,formatesalt

91		2-({4H,5H,6H-cyclopenta[d][1,3]thiazol-2-yl}amino)-N-[2-(dimethylamino)ethyl]-N-phenyl-6-{{(trans)-4-hydroxycyclohexyl}amino}pyridine-4-sulfonamide,formatesalt
92		4-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-yl]-butan-1-ol
93		(trans)-4-[6-(5,6-Dihydro-4H-cyclopentathiazol-2-ylamino)-4-(tetrahydro-pyran-4-sulfonyl)-pyridin-2-ylamino]-cyclohexanol,formatesalt
94	 <p>(Isomer 1)</p>	(1R,2S)-4-{{[4-(benzenesulfonyl)-6-[(5-methyl-1H-pyrazol-3-yl)amino]pyridin-2-yl]amino}cyclopentane-1,2-diol; Isomer 1
95	 <p>(Isomer 2)</p>	(1R,2S)-4-{{[4-(benzenesulfonyl)-6-[(5-methyl-1H-pyrazol-3-yl)amino]pyridin-2-yl]amino}cyclopentane-1,2-diol; Isomer 2

96		(1R,2R)-4-([4-(benzenesulfonyl)-6-[(5-methyl-1H-pyrazol-3-yl)amino]pyridin-2-yl]amino)cyclopentane-1,2-diol
97		(1S,2S)-4-([4-(benzenesulfonyl)-6-[(5-methyl-1H-pyrazol-3-yl)amino]pyridin-2-yl]amino)cyclopentane-1,2-diol
98		(trans)-4-({6-[(6,6-dimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)amino]-4-(1-methylpiperidine-4-sulfonyl)pyridin-2-yl}amino)cyclohexan-1-ol

In some embodiments, the invention relates to one or more of the compounds depicted in Table 1 (e.g., compounds of Example Nos. 1-98), and uses thereof. In one embodiment, the invention relates to one or more of the compounds in Example Nos. 5, 6, 42, 47, 54, 56, 57, 86 and 87, and uses thereof.

The compounds provided herein may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds provided herein, including but not limited to: diastereomers, enantiomers, and atropisomers as well as mixtures thereof such as racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Both the single positional isomers and mixture of positional isomers, e.g., resulting from the N-oxidation of the pyrimidinyl and pyrazolyl rings, or the E and Z forms of the compound (for example oxime moieties), are also within the scope of the present invention.

In the structures shown herein, where the stereochemistry of any particular chiral atom is not specified, then all stereoisomers are contemplated and included as the compounds of

the invention. Where stereochemistry is specified by a solid wedge or dashed line representing a particular configuration, then that stereoisomer is so specified and defined.

The compounds of the present invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention, as defined by the claims, embrace both solvated and unsolvated forms.

In an embodiment, compounds provided herein may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention, as defined by the claims. The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

The present invention also embraces isotopically-labeled compounds of Formulae I, II, III, and variations described herein, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. All isotopes of any particular atom or element as specified are contemplated within the scope of the invention. Exemplary isotopes that can be incorporated into compounds of Formula I include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I , and ^{125}I , respectively. Certain isotopically-labeled compounds of Formulae I, II, III, and variations described herein (e.g., those labeled with ^3H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. tritiated (i.e., ^3H) and carbon-14 (i.e., ^{14}C) isotopes are useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). Positron emitting isotopes such as ^{15}O , ^{13}N , ^{11}C , and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds provided herein can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

A compound as detailed herein may in one aspect be in a purified form and compositions comprising a compound in purified forms are detailed herein. Compositions

comprising a compound as detailed herein or a salt thereof are provided, such as compositions of substantially pure compounds. In some embodiments, a composition containing a compound as detailed herein or a salt thereof is in substantially pure form. In some embodiments, substantially pure” intends a composition that contains no more than 35%, 30%, 25%, 20%, 15%, 10%, 5%, 2% or 1% impurity, wherein the impurity denotes a compound other than the compound comprising the majority of the composition or a salt thereof.

In one variation, the compounds herein are synthetic compounds prepared for administration to an individual. In another variation, compositions are provided containing a compound in substantially pure form. In another variation, the invention embraces pharmaceutical compositions comprising a compound detailed herein and a pharmaceutically acceptable carrier. In another variation, methods of administering a compound are provided. The purified forms, pharmaceutical compositions and methods of administering the compounds are suitable for any compound or form thereof detailed herein.

General Synthetic Methods

The invention includes methods of making the compounds (as well as compositions comprising the compounds) described herein. The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process descriptions, the symbols when used in the formulae depicted are to be understood to represent those groups described above in relation to the formulae herein.

Compounds described herein (e.g., Formulae I, II, III and variations thereof) may be synthesized by synthetic routes described herein. In certain embodiments, processes well-known in the chemical arts can be used, in addition to, or in light of, the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wis.) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-19, Wiley, N.Y. (1967-1999 ed.), Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available via the Beilstein online database)), or *Comprehensive Heterocyclic Chemistry*, Editors Katrizky and Rees, Pergamon Press, 1984.

Compounds described herein (e.g., Formulae I, II, III and variations thereof) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, or 10 to 100 compounds described herein (e.g., Formulae I, II, III and variations

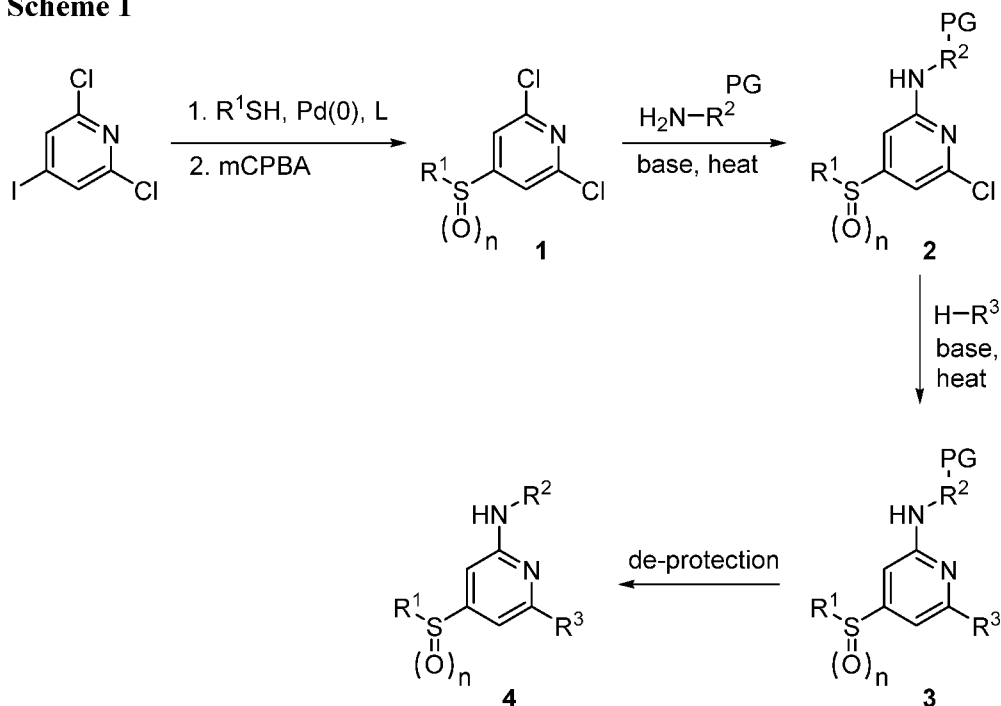
thereof). Libraries of compounds described herein may be prepared by a combinatorial `split and mix` approach or by multiple parallel syntheses using either solution phase or solid phase chemistry, by procedures known to those skilled in the art. Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds described herein (e.g., Formulae I, II, III and variations thereof), enantiomers, diastereomers or pharmaceutically acceptable salts thereof.

In the preparation of compounds of the present invention, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups (NH-Pg) include acetyl, trifluoroacetyl, t-butoxycarbonyl (Boc), benzyloxycarbonyl (CBz) and 9-fluorenylmethylenoxycarbonyl (Fmoc). The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

Compounds of the invention may be prepared from commercially available starting materials using the general methods illustrated herein.

For illustrative purposes, reaction Scheme 1 depicted below provide a route for synthesizing the compounds of Formulae I, II, III and variations thereof, as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be available and used. Although specific starting materials and reagents are depicted in the Scheme and discussed below, other starting materials and reagents may be available for substitution to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the method described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

Scheme 1



The general synthesis of target **4** is outlined in Scheme 1. 4-Iodo-2,6-dichloropyridine is treated with thiol R^1SH in the presence of the appropriate palladium catalyst and ligand (L) that provides 4-mercapto-2,6-dichloropyridine, which undergoes oxidation with *m*-chloroperbenzoic acid (*m*CPBA) that provides compound **1** sulfoxide (n is 1) or sulfone (n is 2) or a mixture thereof. Coupling of compound **1** with optionally protected amine H_2N-R^2 (PG) provides compound **2**, which is coupled with reagent R^3-H to give compound **3**. Depending on the nature of R^3-H , this final coupling can be performed using transition metal catalysts (such as, but not limited to, palladium(0) catalysts) or can be direct nucleophilic coupling. Removal of the optional protecting group affords target compound **4**.

It will be appreciated that where appropriate functional groups exist, compounds of various formulae or any intermediates used in their preparation may be further derivatized by one or more standard synthetic methods employing condensation, substitution, oxidation, reduction, or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, sulfonylation, halogenation, nitration, formylation and coupling procedures.

In the exemplary Schemes it may be advantageous to separate reaction products from one another and/or from starting materials. Diastereomeric mixtures can be separated into their individual diastereoisomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional

crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereoisomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Also, some of the compounds of the present invention may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of a chiral HPLC column.

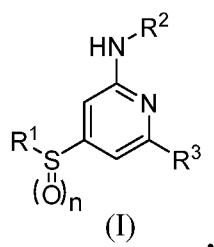
A single stereoisomer, e.g. an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Eliel, E. and Wilen, S., *Stereochemistry of Organic Compounds*, John Wiley & Sons, Inc., New York, 1994; Lochmuller, C. H., *J. Chromatogr.*, 113(3):283-302 (1975)). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions. See: *Drug Stereochemistry, Analytical Methods and Pharmacology*, Irving W. Wainer, Ed., Marcel Dekker, Inc., New York (1993).

Diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α -methyl- β -phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid or lactic acid can result in formation of the diastereomeric salts.

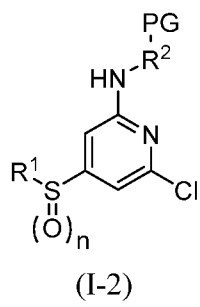
Alternatively, the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S., *Stereochemistry of Organic Compounds*, John Wiley & Sons, Inc., New York, 1994, p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the pure or enriched enantiomer. A method of determining optical purity involves making chiral esters, such as a menthyl ester, e.g. (-)-menthyl chloroformate in the presence of base, or Mosher ester (α -methoxy- α -

(trifluoromethyl)phenyl acetate) (Jacob, *J. Org. Chem.* 47:4165 (1982)), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric enantiomers or diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase (*Chiral Liquid Chromatography* W. J. Lough, Ed., Chapman and Hall, New York, (1989); Okamoto, *J. of Chromatogr.* 513:375-378 (1990)). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

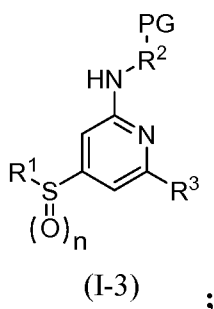
In one aspect, provided is a method of manufacturing a compound of Formula (I):



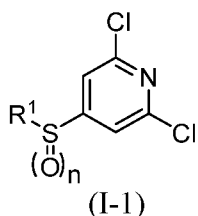
or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein n, R¹, R² and R³ are as defined for Formula I, comprising (a) reacting a compound of formula (I-2):



wherein R¹ and R² are as defined for formula (I) and PG is an optional protecting group (for example, an amine protecting group where the R² moiety contains an amino group requiring protection), with a compound of formula R³-H to form a compound of formula (I-3):



and (b) optionally removing the optional protecting group PG to afford the compound of formula (I). In some embodiments, the method further comprises reacting a compound of formula (I-1):



5

with a compound of formula $\text{H}_2\text{N-R}^2(\text{PG})$ to form a compound of formula (I-2). In some embodiments, the method further comprises reacting a compound of formula R^1SH with 4-iodo-2,6-dichloropyridine to form a 4-mercapto-2,6-dichloropyridine compound, and subsequently reacting the 4-mercapto-2,6-dichloropyridine compound with an oxidizing agent (e.g., mCPBA) to form the compound of formula (I-2). In some embodiments, the compound of formula R^1SH reacts with 4-iodo-2,6-dichloropyridine in the presence of a palladium catalyst (e.g., a Pd(0) catalyst with ligand L) to form the 4-mercapto-2,6-dichloropyridine compound. In some embodiments, the compound of formula (I-1) reacts with $\text{H}_2\text{N-R}^2(\text{PG})$ in the presence of a base and heat to produce the compound of formula (I-2). In some

10

15

embodiments, the compound of formula (I-2) reacts with a compound of $\text{R}^3\text{-H}$ in the presence of a base and heat to produce the compound of formula (I-3). Transition metal catalysis, including but not limited to palladium(0) catalysts, of this final coupling may also be necessary.

Pharmaceutical Compositions and Administration

20

Pharmaceutical compositions of any of the compounds detailed herein are embraced by this invention. Thus, the invention includes pharmaceutical compositions comprising a compound of the invention or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient. In one aspect, the pharmaceutically acceptable salt is an acid addition salt, such as a salt formed with an inorganic or organic acid.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration or a form suitable for administration by inhalation.

Another embodiment provides pharmaceutical compositions or medicaments
5 containing the compounds of the invention and a therapeutically inert carrier, diluent or excipient, as well as methods of using the compounds of the invention to prepare such compositions and medicaments. In one example, compounds of described herein (e.g., Formulae I, II, III and variations thereof) may be formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically
10 acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends on the particular use and the concentration of compound, and can range anywhere from about 3 to about 8. In one example, a compound described herein (e.g., Formulae I, II, III and variations thereof) is formulated in an acetate buffer, at pH 5. In another embodiment,
15 the compounds described herein (e.g., Formulae I, II, III and variations thereof) are sterile. The compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular
20 disorder being treated, the particular patient being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The “effective amount” of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to inhibit ITK kinase activity.
25 For example, such amount may be below the amount that is toxic to normal cells, or the patient as a whole.

The pharmaceutical composition (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical
30 formulation in an appropriate form. Suitable containers are well-known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also
35 include appropriate warnings.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing a compound described herein (e.g., Formulae I, II, III and variations thereof), which matrices are in the form of shaped articles, e.g. films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides, copolymers of L-glutamic acid and gamma-ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid.

In one example, the pharmaceutically effective amount of the compound of the invention administered parenterally per dose will be in the range of about 0.01-100 mg/kg, alternatively about 0.1 to 20 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.3 to 15 mg/kg/day. In another embodiment, oral unit dosage forms, such as tablets and capsules, contain about 5-1000 mg of a compound of the invention.

The compounds of the invention may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal, inhaled and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, aerosols, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. Handbook of Pharmaceutical Excipients. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents,

emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

An example of a suitable oral dosage form is a tablet containing about 25 mg, 50 mg, 100 mg, 250 mg or 500 mg of the compound of the invention compounded with about 90-300 mg anhydrous lactose, about 5-40 mg sodium croscarmellose, about 5-30 mg polyvinylpyrrolidone (PVP) K30, and about 1-10 mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment. An example of an aerosol formulation can be prepared by dissolving the compound, for example 5-400 mg, of the invention in a suitable buffer solution, e.g. a phosphate buffer, adding a tonicifier, e.g. a salt such sodium chloride, if desired. The solution may be filtered, e.g., using a 0.2 micron filter, to remove impurities and contaminants.

In one embodiment, the pharmaceutical composition also includes an additional chemotherapeutic agent. In some embodiments, the additional chemotherapeutic agent is selected from an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders.

An embodiment, therefore, includes a pharmaceutical composition comprising a compound of Formulae I, II, III or variations thereof, or a stereoisomer or pharmaceutically acceptable salt thereof. In a further embodiment includes a pharmaceutical composition comprising a compound of Formulae I, II, III or variations thereof, or a stereoisomer or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or excipient.

Another embodiment includes a pharmaceutical composition comprising a compound of Formulae I, II, III or variations thereof, or a stereoisomer or pharmaceutically acceptable salt thereof, for use in the treatment of an immunological or inflammatory disease. Another embodiment includes a pharmaceutical composition comprising a compound of Formulae I, II, III or variations thereof, or a stereoisomer or pharmaceutically acceptable salt thereof for use in the treatment of psoriasis or inflammatory bowel disease.

Methods of Use

Compounds and compositions of the invention, such as a pharmaceutical composition containing a compound of any formula provided herein or a salt thereof and a pharmaceutically acceptable carrier or excipient, may be used in methods of administration and treatment as provided herein.

The compounds described herein (e.g., Formulae I, II, III and variations thereof) inhibit ITK kinase activity. Accordingly, the compounds of the invention are useful for the treatment of inflammation and immunological diseases. Inflammatory diseases which can be treated according to the methods of this invention include, but are not limited to, asthma, allergic rhinitis, atopic dermatitis, rheumatoid arthritis, psoriasis, contact dermatitis, and delayed hypersensitivity reactions.

In some embodiments, provided is a method of treating a disease responsive to the inhibition of ITK kinase activity in a patient, comprising administering to the patient a therapeutically effective amount of a compound described herein (e.g., or a compound of Formulae I, II, III or variations thereof), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof. In one aspect, provided is a method of treating a disease responsive to the inhibition of ITK kinase activity in a patient, comprising administering to the patient a therapeutically effective amount of a pharmaceutical composition comprising a compound described herein (e.g., or a compound of Formulae I, II, III or variations thereof), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition further comprises a pharmaceutically acceptable carrier, adjuvant or vehicle. In some embodiments, the composition further comprises an additional chemotherapeutic agent. In some embodiments, the treatment methods further comprise administration of an second chemotherapeutic agent which in turn may be an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders.

In some embodiments, provided is a method of treating or lessening the severity of a disease or condition responsive to the inhibition of ITK kinase activity in a patient. The method includes the step of administering to a patient a therapeutically effective amount of a compound of Formula I, II, or III, or any variation thereof described herein, or stereoisomers, tautomers or salts thereof.

In some embodiments, the disease responsive to the inhibition of ITK kinase activity is an inflammatory disease. In some embodiments, the disease responsive to the inhibition of ITK kinase activity is asthma, allergic rhinitis, atopic dermatitis, rheumatoid arthritis, psoriasis, contact dermatitis, and delayed hypersensitivity reactions.

5 An embodiment includes use of a compound of Formula I, II, or III, or any variation thereof described herein, a stereoisomer or pharmaceutically acceptable salt thereof in therapy.

10 Another embodiment includes a compound of Formula I, II, or III, or any variation thereof described herein, a stereoisomer or pharmaceutically acceptable salt thereof for use in therapy.

Another embodiment includes use of a compound of Formula I, II, or III, or any variation thereof described herein, a stereoisomer or pharmaceutically acceptable salt thereof in treating or preventing a disease responsive to the inhibition of ITK kinase.

15 Another embodiment includes use of a compound of Formula I, II, or III, or any variation thereof described herein, a stereoisomer or pharmaceutically acceptable salt thereof in treating or preventing an inflammatory disease.

20 Another embodiment includes use of a compound of Formula I, II, or III, or any variation thereof described herein, a stereoisomer or pharmaceutically acceptable salt thereof in treating asthma, allergic rhinitis, atopic dermatitis, rheumatoid arthritis, psoriasis, contact dermatitis, and delayed hypersensitivity reactions. A further embodiment includes a method of using of a compound described herein in a dose ranging from 25-500 mg for such treatments.

25 Another embodiment includes use of a compound of Formula I, II, or III, or any variation thereof described herein, a stereoisomer or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of an inflammatory disease. A further embodiment includes using of a compound described herein in a dose ranging from 25-500 mg in such uses.

30 Another embodiment includes use of a compound of Formula I, II, or III, or any variation thereof described herein, a stereoisomer or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of asthma, allergic rhinitis, atopic dermatitis, rheumatoid arthritis, psoriasis, contact dermatitis, and delayed hypersensitivity reactions. A further embodiment includes using of a compound described herein in a dose ranging from 25-500 mg for such treatments.

Compounds of the invention are also useful for reducing inflammation in cells that overexpress ITK. Alternatively, compounds of the invention are useful for reducing inflammation in cells that have aberrant or overactive antigen engagement of the T cell receptor. Alternatively, compounds of the invention are useful for reducing inflammation in
5 cells that have over-activation or phosphorylation of PLC γ . Additionally, the compounds can be used for the treatment of inflammation or immunological disorders in cells that overexpress Th2 cytokine. Another embodiment includes a method of treating or preventing cancer in a patient in need of such treatment, wherein the method comprises administering to the patient a therapeutically effective amount of a compound of Formula I, II, or III, or any
10 variation thereof described herein, a stereoisomer or pharmaceutically acceptable salt thereof.

In one embodiment, the disease responsive to the inhibition of ITK kinase is cancer, such as T-cell related cancer, for example, T-cell lymphoproliferative disease: Dierks et al. *Cancer Res* **2010**, 70, 6193-6204.

In one embodiment, the invention includes a compound as described above for use as
15 a therapeutic agent.

In one embodiment, the invention includes the use of a compound as described above in the manufacture of a medicament for the treatment of an inflammatory disease or cancer.

In one embodiment, the invention includes the use of a compound as described above for the treatment of an inflammatory disease or cancer.

In one embodiment, the invention includes a compound as described above for use in
20 the treatment of an inflammatory disease or cancer.

The invention as hereinabove described.

The compounds described herein (e.g., Formulae I, II, III and variations thereof) may be administered by any route appropriate to the disease or condition to be treated. Suitable
25 routes include oral, parenteral (including subcutaneous, intramuscular, intravenous, intraarterial, intradermal, intrathecal and epidural), transdermal, rectal, nasal, topical (including buccal and sublingual), vaginal, intraperitoneal, intrapulmonary, and intranasal. For local immunosuppressive treatment, the compounds may be administered by intralesional administration, including perfusing or otherwise contacting the graft with the inhibitor before
30 transplantation. It will be appreciated that the route may vary with, for example, the condition of the recipient. Where the compound is administered orally, it may be formulated as a pill, capsule, tablet, etc. with a pharmaceutically acceptable carrier or excipient. Where

the compound is administered parenterally, it may be formulated with a pharmaceutically acceptable parenteral vehicle and in a unit dosage injectable form, as detailed below.

A dose to treat human patients may range from about 5 mg to about 1000 mg of a compound described herein (e.g., compound of Formula I, II or III or any variation thereof).

5 A typical dose may be about 5 mg to about 300 mg of a compound described herein (e.g., a compound of Formulae I, II, III and variations thereof). A dose may be administered once a day (QD), twice per day (BID), or more frequently, depending on the pharmacokinetic and pharmacodynamic properties, including absorption, distribution, metabolism, and excretion of the particular compound. In addition, toxicity factors may influence the dosage and
10 administration regimen. When administered orally, the pill, capsule, or tablet may be ingested daily or less frequently for a specified period of time. The regimen may be repeated for a number of cycles of therapy.

Combination Therapy

The compounds described herein (e.g., Formulae I, II, III and variations thereof) may
15 be employed alone or in combination, such as with other chemotherapeutic agents for treatment. The compounds of the present invention can be used in combination with one or more additional drugs, for example an anti- hyperproliferative, anti-cancer, cytostatic, cytotoxic, anti-inflammatory or chemotherapeutic agents. The second compound of the pharmaceutical combination formulation or dosing regimen typically has complementary
20 activities to the compound of this invention such that they do not adversely affect each other. Such agents are suitably present in combination in amounts that are effective for the purpose intended. The compounds may be administered together in a unitary pharmaceutical composition or separately and, when administered separately this may occur simultaneously or sequentially. Such sequential administration may be close or remote in time. In one
25 embodiment, compounds of the present invention are coadministered with a cytostatic compound selected from the group consisting of cisplatin, doxorubicin, taxol, taxotere and mitomycin C. In another embodiment, the cytostatic compound is doxorubicin. In another embodiment, compounds of the present invention are coadministered with an anti-inflammatory agent selected from a NSAID and corticosteroid. In one embodiment,
30 compounds of the present invention are coadministered with an anti-asthmatic agent, including but not limited to beta2-adrenergic agonists, inhaled and oral corticosteroids, leukotriene receptor antagonist, and omalizumab. In another embodiment, compounds of the present invention are coadministered with an anti-asthmatic agent selected from a NSAID, combinations of fluticasone and salmeterol, combinations of budesonide and formoterol,
35 omalizumab, lebrikizumab and corticosteroid selected from fluticasone, budesonide,

mometasone, flunisolide and beclomethasone. In another embodiment, compounds of the present invention are coadministered with an anti-rheumatoid agent, in one example, RITUXAN®. In another embodiment, compounds of the present invention are coadministered with a chemotherapeutic agent selected from etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi), Interleukin 1 (IL-1) blockers such as anakinra (Kineret), monoclonal antibodies against B cells such as rituximab (RITUXAN®), T cell costimulation blockers such as abatacept (Orencia), Interleukin 6 (IL-6) blockers such as tocilizumab (ACTEMERA®); Interleukin 13 (IL-13) blockers such as lebrikizumab; Interferon alpha (IFN) blockers such as Rontalizumab; Beta 7 integrin blockers such as rhuMAb Beta7; IgE pathway blockers such as Anti-Mi prime; Secreted homotrimeric LTa3 and membrane bound heterotrimer LTal/p2 blockers such as Anti-lymphotoxin alpha (LTa).

Another embodiment, therefore, includes a method of treating or lessening the severity of a disease or condition responsive to the inhibition of ITK kinase in a patient, comprising administering to said patient a therapeutically effective amount of a compound of Formula I, II or III or any variation thereof described herein, and further comprising, administering a second therapeutic agent.

The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations. The combined administration includes coadministration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein there is a time period while both (or all) active agents simultaneously exert their biological activities.

Suitable dosages for any of the above coadministered agents are those presently used and may be lowered due to the combined action (synergy) of the newly identified agent and other chemotherapeutic agents or treatments.

In a particular embodiment of therapy, a compound of Formula I, II or III or any variation thereof described herein, or a stereoisomer, geometric isomer, tautomer, solvate, metabolite, or pharmaceutically acceptable salt or prodrug thereof, may be combined with radiation therapy. The phrase "radiation therapy" refers to the use of electromagnetic or particulate radiation in the treatment of neoplasia. Radiation therapy delivers doses of radiation sufficiently high to a target area to cause death of reproducing cells, in both tumor and normal tissues. The radiation dosage regimen is generally defined in terms of radiation absorbed dose (rad), time and fractionation, and must be carefully defined by the oncologist.

The amount of radiation a patient receives will depend on various considerations but two of the most important considerations are the location of the tumor in relation to other critical structures or organs of the body, and the extent to which the tumor has spread. Examples of radiotherapeutic agents are provided in Hellman, Principles of Radiation Therapy, Cancer, in Principles I and Practice of Oncology, 24875 (Devita et al., 4th Ed., Vol 1, 1993). Alternative forms of radiation therapy include three- dimensional conformal external beam radiation, intensity modulated radiation therapy (IMRT), stereotactic radiosurgery and brachytherapy (interstitial radiation therapy), the latter placing the source of radiation directly into the tumor as implanted "seeds". These alternative treatment modalities deliver greater doses of radiation to the tumor, which accounts for their increased effectiveness when compared to standard external beam radiation therapy.

Kits

The invention further provides kits for carrying out the methods of the invention, which comprises one or more compounds described herein (e.g., Formulae I, II, III and variations thereof) or a pharmacological composition comprising a compound described herein. The kits may employ any of the compounds disclosed herein. In one variation, the kit employs a compound described herein (e.g., Formulae I, II, III and variations thereof) or a pharmaceutically acceptable salt thereof. The kits may be used for any one or more of the uses described herein, and, accordingly, may contain instructions for the treatment of diseases, conditions and/or disorders responsive to the inhibition of ITK kinase activity in a patient.

Kits generally comprise suitable packaging. The kits may comprise one or more containers comprising any compound described herein. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit.

The kits may be in unit dosage forms, bulk packages (e.g., multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of a compound as disclosed herein (e.g., Formulae I, II, III and variations thereof) and/or a second pharmaceutically active compound useful for a disease detailed herein to provide effective treatment of an individual for an extended period, such as any of a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (e.g., hospital pharmacies and compounding pharmacies).

The kits may optionally include a set of instructions, generally written instructions, although electronic storage media (*e.g.*, magnetic diskette or optical disk) containing instructions are also acceptable, relating to the use of component(s) of the methods of the present invention. The instructions included with the kit generally include information as to the components and their administration to an individual.

Another embodiment includes a kit for treating a disease or disorder responsive to the inhibition of ITK kinase. The kit includes:

(a) a first pharmaceutical composition comprising a compound of Formula I, II or III or any variation thereof; and

(b) instructions for use.

In another embodiment, the kit further includes:

(c) a second pharmaceutical composition, which includes a chemotherapeutic agent.

In one embodiment, the instructions include instructions for the simultaneous, sequential or separate administration of said first and second pharmaceutical compositions to a patient in need thereof.

In one embodiment, the first and second compositions are contained in separate containers.

In one embodiment, the first and second compositions are contained in the same container.

Containers for use include, for example, bottles, vials, syringes, blister pack, etc. The containers may be formed from a variety of materials such as glass or plastic. The container includes a compound of Formula I or formulation thereof which is effective for treating the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The container includes a composition comprising at least one compound of Formula I. The label or package insert indicates that the composition is used for treating the condition of choice, such as cancer. In one embodiment, the label or package inserts indicates that the composition comprising the compound of Formula I can be used to treat a disorder. In addition, the label or package insert may indicate that the patient to be treated is one having a disorder characterized by overactive or irregular kinase activity. The label or package insert may also indicate that the composition can be used to treat other disorders.

Also provided are articles of manufacture comprising a compound of Formula I, II or III or any variation thereof described herein, or a salt thereof, composition, and unit dosages described herein in suitable packaging for use in the methods described herein. Suitable packaging is known in the art and includes, for example, vials, vessels, ampules, bottles, jars, flexible packaging and the like. An article of manufacture may further be sterilized and/or sealed.

The article of manufacture may comprise (a) a first container with a compound of Formula I, II or III, or any variation thereof described herein, contained therein; and (b) a second container with a second pharmaceutical formulation contained therein, wherein the second pharmaceutical formulation comprises a chemotherapeutic agent. The article of manufacture in this embodiment of the invention may further comprise a package insert indicating that the first and second compounds can be used to treat patients at risk of stroke, thrombus or thrombosis disorder. Alternatively, or additionally, the article of manufacture may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

In order to illustrate the invention, the following examples are included. However, it is to be understood that these examples do not limit the invention and are only meant to suggest a method of practicing the invention. Persons skilled in the art will recognize that the chemical reactions described may be readily adapted to prepare other compounds of Formula I, II or III or any variation thereof described herein, and alternative methods for preparing the compounds are within the scope of this invention. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the invention.

EXAMPLES

The following Examples are provided to illustrate but not to limit the invention.

Compounds detailed herein may be prepared by those of skill in the art by referral to the General Method. Particular examples of the General Method are provided in the Examples below.

General Experimental Conditions

5 Compounds of this invention may be prepared from commercially available starting materials using the general methods illustrated herein. All commercial chemicals, including reagents and solvents, were used as received.

Flash silica chromatography was routinely carried out using a Biotage Isolera 4 flash purification system using a SNAP KP-Sil column.

10 Automated reverse phase HPLC was carried out according to one of two general protocols:

1) Low pH method: Chromatography was carried out using a Waters Sunfire C-18 column as the stationary phase. The mobile phase consisted of a water to acetonitrile gradient, both solvents containing 0.1% formic acid.

15 2) High pH method: Chromatography was carried out using a Waters X-Bridge C-18 column as the stationary phase. The mobile phase consisted of a water to acetonitrile gradient, both solvents containing 0.1% ammonium hydroxide.

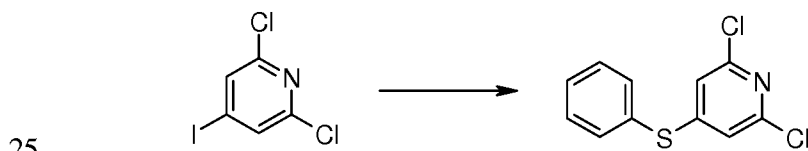
In addition, chiral preparative HPLC was carried out using a Waters Resolution SFC-MS instrument with a Chiralcel OD-H stationary phase.

20 **INTERMEDIATE EXAMPLES**

Examples A through CL are illustrative of the synthetic methods used for the intermediates.

Example A

Synthesis of 2,6-dichloro-4-(phenylsulfanyl)pyridine

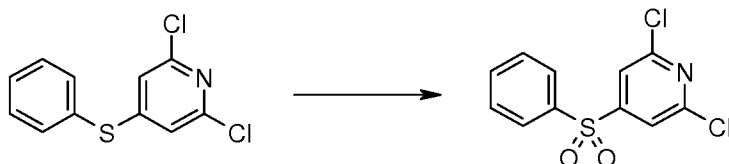


A mixture of 2,6-dichloro-4-iodopyridine (40 g, 146 mmol), benzenethiol (16.4 mL, 160 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (8.45 g, 14.6 mmol), and diisopropylethylamine (48.3 mL, 292 mmol) in dioxane (600 mL) was flushed with N₂ for 5 min before tris(dibenzylideneacetone)dipalladium (0) (6.69 g, 7.30 mmol) was added and the
30 resulting mixture stirred at 110°C for 90 min. The resulting suspension was concentrated in

vacuo and purified by flash chromatography, eluting with DCM (0 – 40 %) in heptane to yield the title compound as a white solid (28.8 g, 77 %). ¹H NMR (500 MHz, DMSO-d₆) δ 8.01- 7.39 (m, 5 H), 7.06 (s, 2 H).

Example B

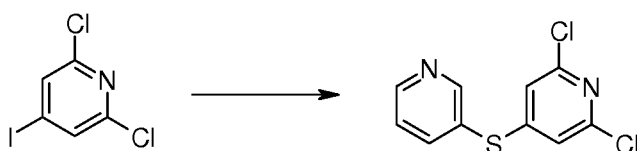
5 Synthesis of 4-(Benzenesulfonyl)-2,6-dichloropyridine



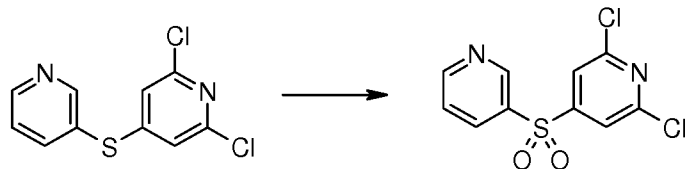
2,6-Dichloro-4-(phenylsulfanyl)pyridine (28.8 g, 112.43 mmol) in DCM (400 mL) was added to a solution of mCPBA (70%, 59.9 g, 304 mmol) in DCM (350 mL) drop wise and the mixture was stirred at room temperature for 4h. The mixture was washed with 0.5M NaOH (2 x 100 mL), brine, then the organic phase was dried (Na₂SO₄), filtered and the filtrate evaporated to dryness. The crude product was purified by flash chromatography, eluting with DCM (0 – 20 %) in heptane to yield the title compound as a white solid (29.3 g, 90 %). ¹H NMR (500 MHz, DMSO-d₆) δ 8.14 (2 H, s), 8.12 (2 H, d, J=7.9 Hz), 7.83 - 7.78 (1 H, m), 7.72 - 7.67 (2 H, m).

15 Example C

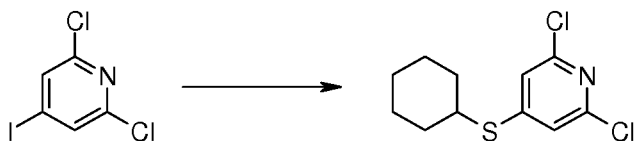
Synthesis of 2,6-Dichloro-4-(pyridine-3-sulfanyl)-pyridine



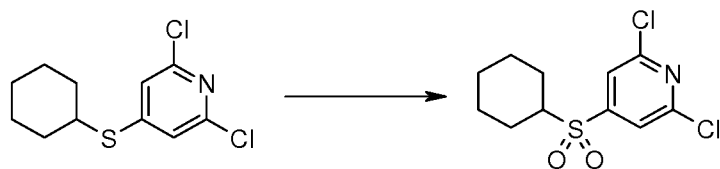
A mixture of 4-iodo-2,6-dichloropyridine (4.40g, 16.4 mmol), Pyridine-3-thiol (1.79g, 16.4 mmol, prepared as described in WO2009/55696), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (929mg, 1.61 mmol), tris(dibenzylideneacetone) dipalladium(0), (735 mg, 0.803 mmol) and DIPEA (4.15g, 32.1 mmol) in 1,4-dioxane (60 mL) was degassed by bubbling a stream of nitrogen gas through the mixture for 3 min and then heated at 110 °C for 3h under a nitrogen atmosphere. The solvent was evaporated and the residue purified by flash chromatography, eluting with EtOAc (25 – 70 %) in heptane to afford the title compound as a yellow solid (2.87 g, 66 %). MS: *m/z* = 256.9 (M+H)⁺.

Example D**Synthesis of 2,6-Dichloro-4-(pyridine-3-sulfonyl)-pyridine**

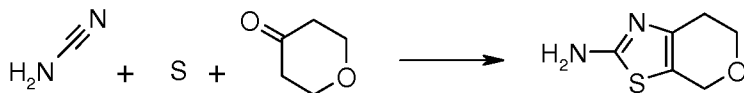
To a solution of 2,6-Dichloro-4-(pyridine-3-sulfanyl)-pyridine (2.87g, 11.2 mmol) in DCM (30 mL) was added 70% mCPBA in one portion (5.14g, 22.3 mmol) and the mixture stirred 3h. Further DCM (100 mL) was added followed by saturated NaHCO₃ (50 mL). The phases were separated and the organic phase was washed with brine (20 mL), dried (Na₂SO₄), the mixture filtered and the filtrate evaporated to dryness to afford the crude product which was dissolved in DCM/MeOH (1:1), pre-adsorbed onto silica and chromatographed, eluting with EtOAc (40 %) in heptane to afford the title compound as a white solid (1.38 g, 43 %). MS: m/z = 288.9 (M+H)⁺.

Example E**Synthesis of 2,6-Dichloro-4-cyclohexylsulfanyl-pyridine**

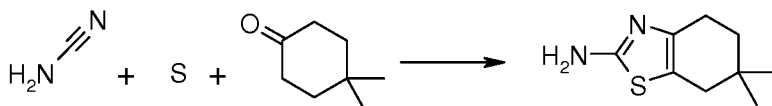
Prepared in an analogous manner to 2,6-Dichloro-4-(pyridine-3-sulfanyl)-pyridine except that pyridine-3-thiol was substituted with cyclohexanethiol. MS: m/z = 261.9 (M+H)⁺.

Example F**Synthesis of 2,6-Dichloro-4-cyclohexanesulfonyl-pyridine**

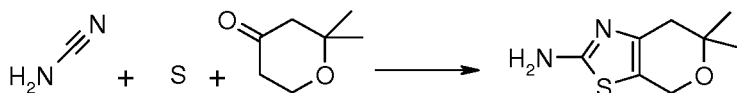
Prepared in an analogous manner to 2,6-Dichloro-4-(pyridine-3-sulfonyl)-pyridine except that 2,6-Dichloro-4-cyclohexylsulfanyl-pyridine was substituted for 2,6-Dichloro-4-(pyridine-3-sulfanyl)-pyridine. MS: m/z = 293.9 (M+H)⁺.

Example G**Synthesis of 6,7-Dihydro-4H-pyrano[4,3-d]thiazol-2-ylamine**

A mixture of tetrahydro-4H-pyran-4-one (500 mg, 4.99 mmol), sulfur (160 mg, 4.99 mmol), cyanamide (210 mg, 4.99 mmol) and pyrrolidine (4 μ L, 0.05 mmol) in isopropanol (3 mL) was stirred at room temperature for 1.5 h. The reaction was partitioned between water and EtOAc and the aqueous phase extracted with further EtOAc. The combined organics were washed with water, brine and dried (MgSO_4). The crude material was purified by flash chromatography, eluting with MeOH (0 - 10%) in DCM to give the title compound as a yellow oil, which crystallized upon standing (500 mg, 64 %). MS: m/z = 156.9 ($\text{M} + \text{H}$)⁺.

Example H**Synthesis of 6,6-Dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-ylamine**

A mixture of 4,4-Dimethyl-cyclohexanone (1.00 g, 7.92 mmol), sulfur (250 mg, 7.92 mmol), cyanamide (330 mg, 7.92 mmol) and pyrrolidine (10 μ L, 0.08 mmol) in isopropanol (5 mL) was stirred at room temperature for 1.5 h. The reaction was partitioned between water and EtOAc and the aqueous extracted with further EtOAc. The combined organics were washed with water, brine and dried over MgSO_4 . The crude material was purified by flash chromatography, eluting with MeOH (0 - 10%) in DCM to give the title compound as a yellow oil, which solidified upon standing (1.62 g, 100 %). MS: m/z = 183.0 ($\text{M} + \text{H}$)⁺.

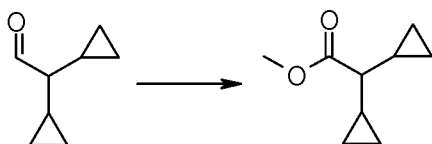
Example I**Synthesis of 6,6-Dimethyl-6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-ylamine**

A mixture of 2,2-dimethyloxan-4-one (2.00 g, 15.6 mmol), sulfur (500 mg, 15.6 mmol), cyanamide (656 mg, 15.6 mmol) and pyrrolidine (13 μ L, 0.156 mmol) was stirred in isopropanol (3 mL) at room temperature for 3 h. The reaction mixture was filtered to remove excess sulfur and chromatographed on silica, eluting with 5% MeOH in DCM to afford the

title compound as a yellow solid (2.87 g, 47 %). ^1H NMR (500 MHz, CDCl_3) δ 4.94 (br. s., 2H), 4.64 (t, $J=1.8$ Hz, 2H), 2.56 (s, 2H), 1.34 - 1.30 (s, 6H).

Example J

Synthesis of Dicyclopropyl-acetic acid methyl ester



5

A solution of Jones reagent was prepared using 6.7g of CrO_3 , 12.5 mL water and 5.8 mL conc. sulfuric acid. This was added drop wise to a stirred solution of dicyclopropyl-acetaldehyde (prepared as described in US2006/264489, 2.99g, 2.14 mmol) in acetone (20 mL) and water (10mL) until the orange color persisted. The mixture was partitioned between diethyl ether (100 mL) and water (30 mL). The phases were separated and the organic phase was washed with brine (20 mL), dried (Na_2SO_4), the mixture filtered and the filtrate evaporated to dryness to afford a green oil. This was dissolved in MeOH (20 mL), 8 drops of c. sulfuric acid added and the solution refluxed for 1h. Most of the solvent was evaporated, DCM added (100 mL) and the solution washed with saturated aq. NaHCO_3 solution (30 mL). The phases were separated and the organic phase was washed with brine (20 mL), dried (Na_2SO_4), the mixture filtered and the filtrate evaporated to dryness to afford the title compound as a green oil (1.99 g, 54 %). ^1H NMR (CDCl_3 , 500MHz): δ 3.48 (s, 3 H), 0.87 - 0.80 (m, 3 H), 0.38 - 0.30 (m, 2 H), 0.26 - 0.19 (m, 2 H), 0.05 - -0.06 (m, 4 H).

Example K

Synthesis of 4,4-Dicyclopropyl-3-oxo-butyronitrile



20

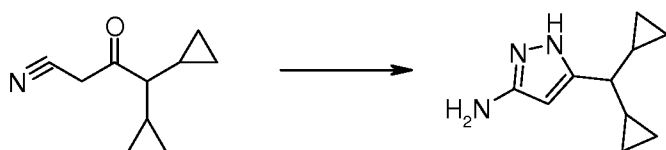
25

To anhydrous THF (20 mL) under a nitrogen atmosphere was added acetonitrile (1.21g, 29.6 mmol) and the solution cooled to -78°C . 2.5M BuLi (in hexanes, 10.8 mL, 27.1 mmol) was added and a white precipitate formed. The mixture was stirred at this temperature for 30 min after which it was treated with a solution of dicyclopropyl-acetic acid methyl ester (1.9g, 12.3 mmol) in THF (10 mL) drop wise. The resulting mixture turned to a clear solution at first and then to a slurry and it was left stirring at -78°C for 1h. It was quenched with acetic acid (circa 0.6 mL, in excess of 40 mmol), the temperature was raised to 25°C and EtOAc

(100 mL) and saturated aq. sodium bicarbonate solution added. The phases were separated and the organic phase was washed with brine (20 mL), dried (Na_2SO_4), the mixture filtered and the filtrate evaporated to dryness to afford the title compound as a yellow oil (1.76 g, 87 %). MS: $m/z = 161.9$ (M-H) $^-$.

5 **Example L**

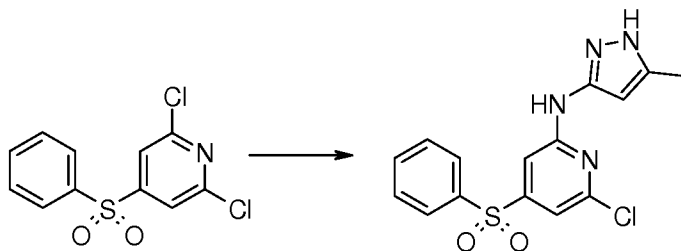
Synthesis of 5-Dicyclopropylmethyl-1H-pyrazol-3-ylamine



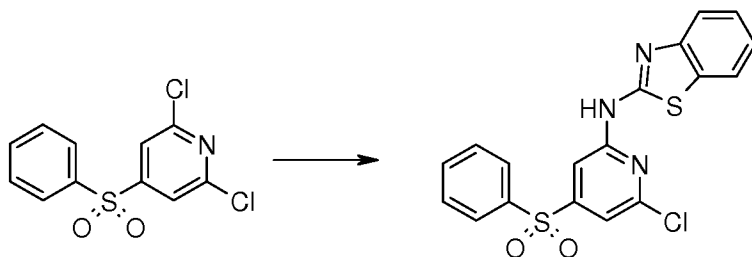
To a solution of 4,4-Dicyclopropyl-3-oxo-butyronitrile (2.30g, 14.1 mmol) in isopropanol (23 mL) was added hydrazine hydrate (775 mg, 15.5 mmol) and the solution heated at 90 °C overnight. The solvent was evaporated, DCM (150 mL) and water added (25 mL). The phases were separated and the organic phase was washed with brine (20mL), dried (Na_2SO_4), the mixture filtered and the filtrate evaporated to dryness to afford the title compound as a yellow oil (1.65 g, 66 %). MS: $m/z = 178.0$ (M+H) $^+$.

Example M

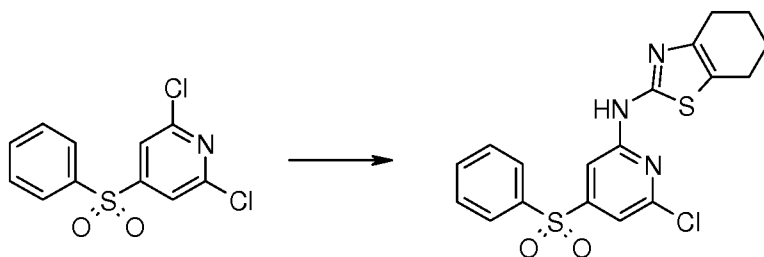
15 **Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine**



To a solution of 4-Benzenesulfonyl-2,6-dichloro-pyridine (5 g, 17.35 mmol) and 3-amino-5-methylpyrazole (1.85 g, 19.09 mmol) in DMSO (15 mL) was added DIPEA (5.7 mL, 34.7 mmol) and the reaction stirred at 100°C for 18 h before more pyrazole 3-amino-5-methylpyrazole (1.00 g, 10.37 mmol) was added and stirring continued for another 6h. The reaction was partitioned between EtOAc and saturated aq. ammonium chloride and the phases were separated. The aqueous was extracted with EtOAc and the combined organics were washed with water and brine and then dried (MgSO_4). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100%) in heptane to give the title compound as a pale yellow solid (3.76 g, 62 %). MS: $m/z = 349.0$ (M + H) $^+$.

Example N**Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-benzothiazol-2-yl-amine**

A mixture of 4-Benzenesulfonyl-2,6-dichloro-pyridine (200 mg, 0.69 mmol), 1,3-benzothiazol-2-amine (125 mg, 0.83 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (40 mg, 0.07 mmol) and Na₂CO₃ (103 mg, 0.97 mmol) in anhydrous 1,4-Dioxane (2 mL) was sonicated under a flow of nitrogen for 5 min before tris(dibenzylideneacetone)dipalladium (0) (32 mg, 0.03 mmol) was added and the reaction heated to 150 °C in a CEM Discover microwave for 45 min. The reaction was filtered through a pad of Celite, washed with EtOAc and concentrated. The crude material was purified by flash chromatography, eluting with EtOAc (0 - 50 %) in heptane to give the title compound as a yellow solid (111 mg, 40 %). MS: *m/z* = 401.9 (M + H)⁺.

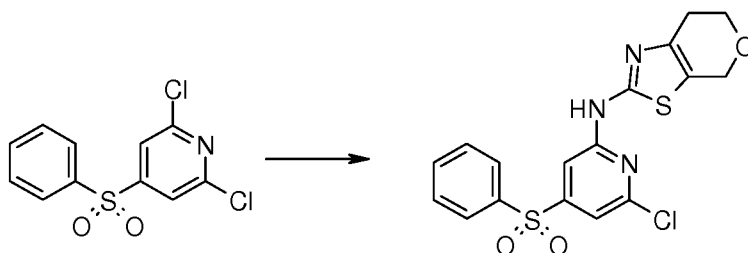
Example O**Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(4,5,6,7-tetrahydro-benzothiazol-2-yl)-amine**

A mixture of 4-Benzenesulfonyl-2,6-dichloro-pyridine (100 mg, 0.35 mmol), 4,5,6,7-tetrahydro-benzothiazol-2-ylamine (64 mg, 0.42 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (20 mg, 0.03 mmol) and Na₂CO₃ (52 mg, 0.49 mmol) in anhydrous 1,4-Dioxane (1.5 mL) was sonicated under a flow of nitrogen for 5 min before tris(dibenzylideneacetone)dipalladium (0) (16 mg, 0.02 mmol) was added and the reaction heated to 100 °C in a sealed tube for 2h. The reaction was filtered through a pad of Celite, washed with EtOAc and concentrated. The crude material was purified by flash

chromatography, eluting with EtOAc (0 - 50 %) in heptane to give the title compound as a pale yellow solid (104 mg, 74 %). MS: $m/z = 406.0$ ($M + H$)⁺.

Example P

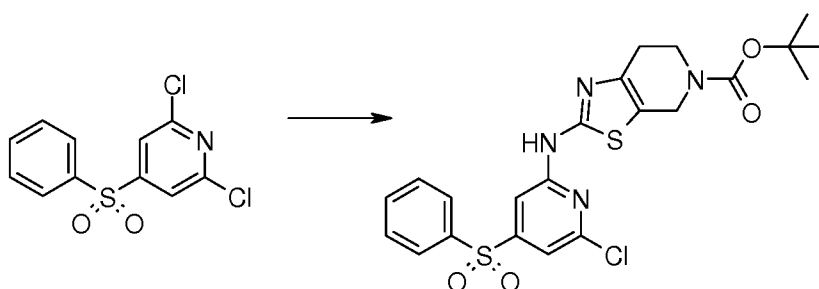
Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-yl)-amine



A mixture of 4-Benzenesulfonyl-2,6-dichloropyridine (375 mg, 1.3 mmol), 6,7-Dihydro-4H-pyrano[4,3-d]thiazol-2-ylamine (244 mg, 1.56 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (75 mg, 0.13 mmol) and Na₂CO₃ (193 mg, 1.82 mmol) in anhydrous 1,4-Dioxane (2 mL) was sonicated under a flow of nitrogen for 5 min before tris(dibenzylideneacetone)dipalladium (0) (60 mg, 0.07 mmol) was added and the reaction heated to 150 °C in the microwave for 45 min. The reaction was filtered through a pad of Celite, washed with EtOAc and concentrated. The crude material was purified by flash chromatography, eluting with EtOAc (0 - 60 %) in heptane to give the title compound as a yellow solid (284 mg, 54 %). MS: $m/z = 407.9$ ($M + H$)⁺.

Example Q

Synthesis of 2-(4-Benzenesulfonyl-6-chloro-pyridin-2-ylamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid *tert*-butyl ester

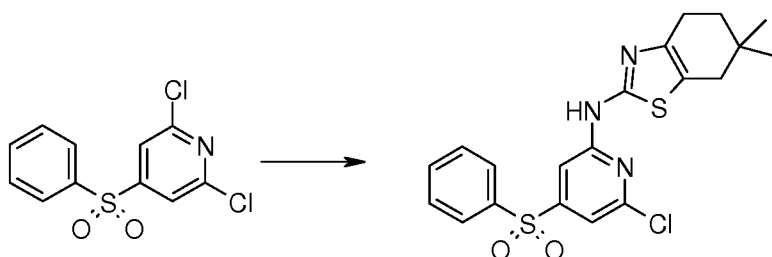


A mixture of 4-Benzenesulfonyl-2,6-dichloropyridine (600 mg, 2.08 mmol), 2-Amino-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid *tert*-butyl ester (638 mg, 2.50 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (120 mg, 0.21 mmol) and Na₂CO₃ (309 mg, 2.92 mmol) in anhydrous 1,4-Dioxane (4 mL) was sonicated under a flow

of nitrogen for 5 min before tris(dibenzylideneacetone)dipalladium (0) (95 mg, 0.1 mmol) was added and the reaction heated to 150 °C in the microwave for 45 min. The reaction was filtered through a pad of Celite, washed with EtOAc and concentrated. The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane to give the title compound as an orange solid (66 mg, 5 %). MS: $m/z = 407.0$ ($M + H$)⁺.

Example R

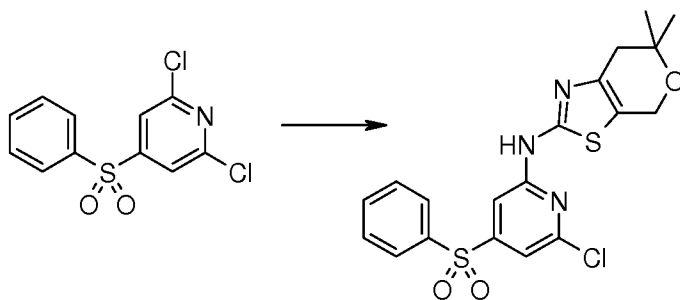
Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-yl)-amine



A mixture of 4-Benzenesulfonyl-2,6-dichloro-pyridine (200 mg, 0.69 mmol), 6,6-Dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-ylamine (90%, 168.7 mg, 0.83 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (40 mg, 0.07 mmol) and Na₂CO₃ (103 mg, 0.97 mmol) in anhydrous 1,4-Dioxane (3 mL) was sonicated under a flow of nitrogen for 5 min before tris(dibenzylideneacetone)dipalladium (0) (32 mg, 0.03 mmol) was added and the reaction heated to 100 °C in a sealed tube for 2 h. The reaction was filtered through a Celite pad, washed with EtOAc and concentrated. The crude material was purified by flash chromatography, eluting with EtOAc (0 - 50 %) in heptane to give the title compound as a yellow solid (119 mg, 38 %). MS: $m/z = 434.0$ ($M + H$)⁺.

Example S

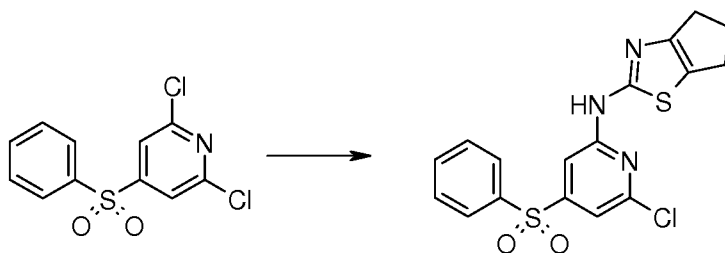
Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(6,6-dimethyl-6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-yl)-amine



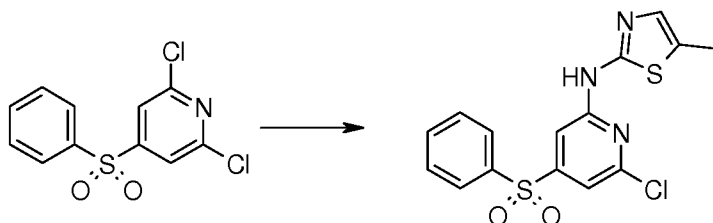
A mixture of 4-(benzenesulfonyl)-2,6-dichloropyridine (400mg, 1.38 mmol), 6,6-Dimethyl-6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-ylamine (307 mg, 1.67 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (80mg, 0.139 mmol), tris(dibenzylideneacetone)dipalladium (0), (63mg, 0.070 mmol) and sodium carbonate (206mg, 1.94 mmol) in 1,4-dioxane (3 mL) was degassed by bubbling a stream of nitrogen gas through the mixture for 3 min and then heated at 100 °C for 2h under a N₂ atmosphere. The mixture was cooled, diluted with EtOAc (20 mL) and filtered to remove inorganics. After evaporation of solvent, the orange oil was chromatographed (heptane: EtOAc 1:2) to afford the title compound as an orange solid (605 mg, 69% purity, 70 % yield). MS: m/z = 435.9 (M+H)⁺.

Example T

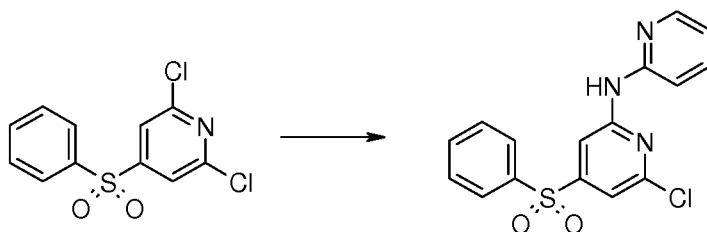
Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5,6-dihydro-4H-cyclopentathiazol-2-yl)-amine



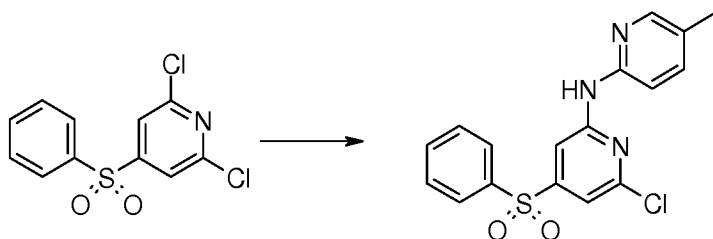
A mixture of 4-Benzenesulfonyl-2,6-dichloro-pyridine (200 mg, 0.69 mmol), 5,6-Dihydro-4H-cyclopentathiazol-2-ylamine (117 mg, 0.83 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (40 mg, 0.07 mmol) and Na₂CO₃ (103 mg, 0.97 mmol) in anhydrous 1,4-Dioxane (2 mL) was sonicated under a flow of nitrogen for 5 min before tris(dibenzylideneacetone)dipalladium (0) (32 mg, 0.03 mmol) was added and the reaction was heated to 100 °C in a sealed tube for 2h. The reaction was filtered through a Celite pad, washed with EtOAc and concentrated. The crude material was purified by flash chromatography, eluting with EtOAc (0 - 50 %) in heptane to give the title compound as a brown solid (101 mg, 37 %). MS: m/z = 391.9 (M + H)⁺.

Example U**Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-thiazol-2-yl)-amine**

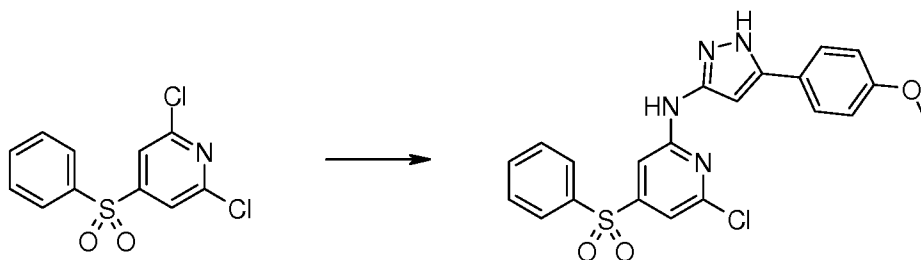
5 A mixture of 4-Benzenesulfonyl-2,6-dichloro-pyridine (100 mg, 0.35 mmol), 5-Methyl-thiazol-2-ylamine (48 mg, 0.42 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (20 mg, 0.03 mmol) and Na₂CO₃ (52 mg, 0.49 mmol) in anhydrous 1,4-Dioxane (3 mL) was sonicated under a flow of nitrogen for 5 min before tris(dibenzylideneacetone)dipalladium (0) (16 mg, 0.02 mmol) was added and the reaction
 10 heated to 100 °C in a sealed tube for 1h. The reaction was cooled, filtered through a pad of Celite, washed with EtOAc and concentrated. The crude material was purified by flash chromatography, eluting with EtOAc (0 - 75 %) in heptane to give the title compound as a yellow/ brown solid (80 mg, 52 %). MS: *m/z* = 365.9 (M + H)⁺.

Example V**Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-pyridin-2-yl-amine**

A mixture of 4-Benzenesulfonyl-2,6-dichloro-pyridine (300 mg, 1.04 mmol), pyridin-2-amine (118 mg, 1.25 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (60 mg, 0.1 mmol) and Na₂CO₃ (154 mg, 1.46 mmol) in anhydrous 1,4-Dioxane (2 mL) was sonicated
 20 under a flow of nitrogen for 5 min before tris(dibenzylideneacetone)dipalladium (0) (48 mg, 0.05 mmol) was added and the reaction was heated to 100 °C in a sealed tube for 45 min. The reaction was cooled, filtered through a pad of Celite, washed with EtOAc and concentrated. The crude material was purified by flash chromatography, eluting with EtOAc (0 – 50 %) in heptane to give the title compound as a yellow solid (550 mg, 73 %). MS: *m/z* = 346.0 (M + H)⁺.
 25

Example W**Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-pyridin-2-yl)-amine**

5 A mixture of 4-Benzenesulfonyl-2,6-dichloropyridine (300 mg, 1.04 mmol), 5-methylpyridin-2-amine (135.11 mg, 1.25 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (60 mg, 0.1 mmol) and Na₂CO₃ (154 mg, 1.46 mmol) in anhydrous 1,4-Dioxane (2 mL) was sonicated under a flow of nitrogen for 5 min before tris(dibenzylideneacetone)dipalladium (0) (47.67 mg, 0.05 mmol) was added and the reaction
 10 was heated to 100 °C in a sealed tube for 45 min. The reaction was cooled, filtered through a pad of Celite, washed with EtOAc and concentrated. The crude material was purified by flash chromatography, eluting with EtOAc (0 - 50%) in heptane to give the title compound as a pale yellow solid (244 mg, 65 %). MS: m/z = 360.0 (M + H)⁺.

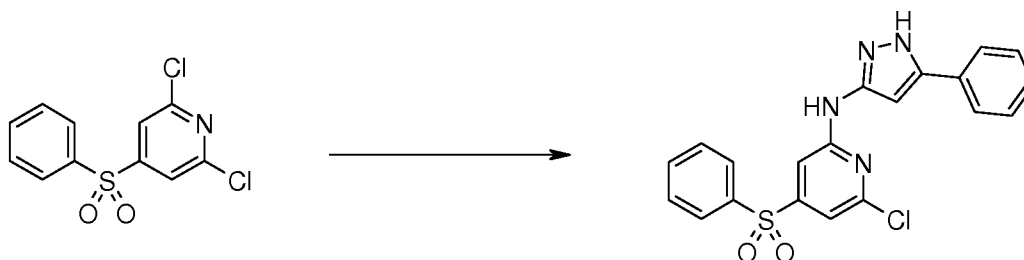
Example X**Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]-amine**

To a solution of 4-(benzenesulfonyl)-2,6-dichloropyridine (300mg, 1.04 mmol) in DMSO (2 mL) was added 5-(4-Methoxy-phenyl)-1H-pyrazol-3-ylamine (256mg, 1.35 mmol) and DIPEA (201mg, 1.56 mmol). The mixture was heated in a CEM Discover microwave for
 20 150 °C for 1h. Two more reactions were carried out on the exact scale and the combined reaction mixture partitioned between water (10 mL) and EtOAc (70 mL). The phases were separated and the organic phase was washed with water (10 mL) brine (20mL), dried (Na₂SO₄), the mixture filtered and the filtrate evaporated to dryness to afford a yellow oil, which

was purified by flash chromatography, eluting with EtOAc (50 – 70 %) to afford the title compound as a yellow foam (1.38 g, 23 %). MS: m/z = 441.0 (M+H)⁺.

Example Y

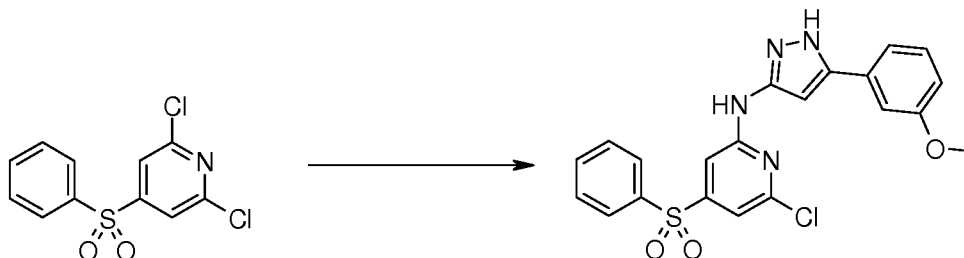
5 Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-phenyl-1H-pyrazol-3-yl]-amine



Prepared in an analogous manner to (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]-amine except that 5-phenyl-1H-pyrazol-3-ylamine was substituted for 5-(4-Methoxy-phenyl)-1H-pyrazol-3-ylamine. MS: m/z = 441.0 (M+H)⁺.

10 Example Z

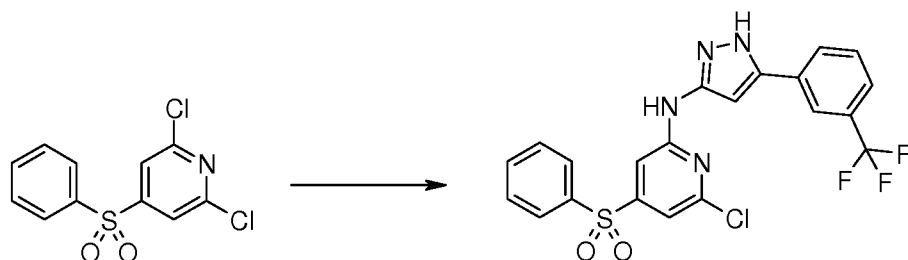
Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-(3-methoxy-phenyl)-1H-pyrazol-3-yl]-amine



15 Prepared in an analogous manner to (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]-amine except that 5-(3-methoxy-phenyl)-1H-pyrazol-3-ylamine was substituted for 5-(4-methoxy-phenyl)-1H-pyrazol-3-ylamine and that microwave heating for a further 1h was carried out at 165 °C. MS: m/z = 441.0 (M+H)⁺.

Example AA

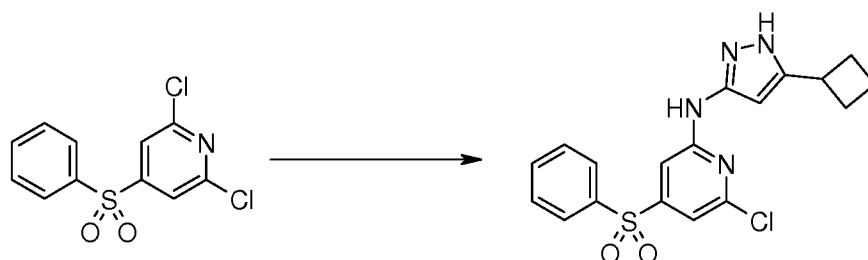
20 Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-(3-trifluoromethyl-phenyl)-1H-pyrazol-3-yl]-amine



Prepared in an analogous manner to (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]-amine except that 5-(3-Trifluoromethyl-phenyl)-1H-pyrazol-3-ylamine was substituted for 5-(4-Methoxy-phenyl)-1H-pyrazol-3-ylamine and that microwave heating for a further 1h was carried out at 165 °C. MS: $m/z = 478.9$ (M+H)⁺.

Example AB

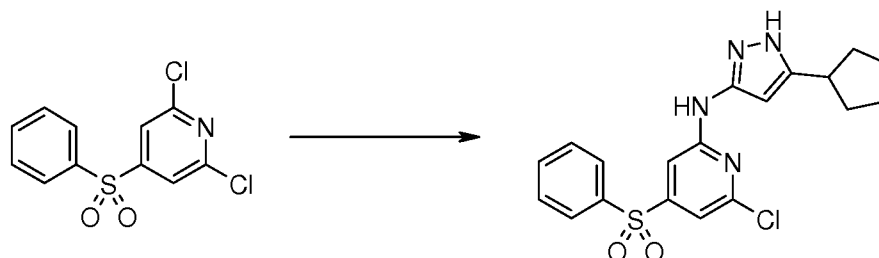
Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-cyclobutyl-1H-pyrazol-3-yl)-amine



Prepared in an analogous manner to (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]-amine except that 5-cyclobutyl-1H-pyrazol-3-ylamine was substituted for 5-(4-Methoxy-phenyl)-1H-pyrazol-3-ylamine. MS: $m/z = 388.9$ (M+H)⁺.

Example AC

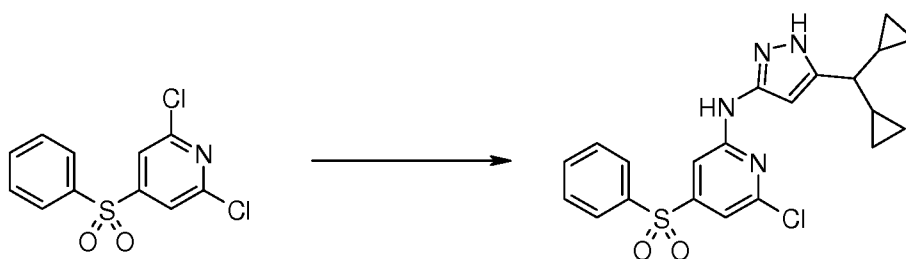
Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-cyclopentyl-1H-pyrazol-3-yl)-amine



Prepared in an analogous manner to (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]-amine except that 5-cyclopentyl-1H-pyrazol-3-ylamine was substituted for 5-(4-Methoxy-phenyl)-1H-pyrazol-3-ylamine. MS: $m/z = 403.0$ (M+H)⁺.

Example AD

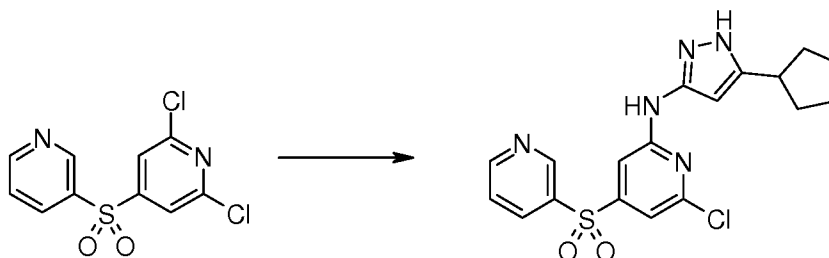
5 Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-dicyclopropylmethyl-1H-pyrazol-3-yl)-amine



To a solution of 4-(benzenesulfonyl)-2,6-dichloropyridine (600 mg, 2.08 mmol) in DMSO (2 mL) was added 5-Dicyclopentylmethyl-1H-pyrazol-3-ylamine (406 mg, 2.29 mmol) and DIPEA (537 mg, 4.16 mmol) and the mixture stirred at 150 °C for 3h. The cooled reaction mixture was treated with EtOAc (50 mL) and water (10mL) and the phases separated. The organic phase was washed with water (2x 5 mL), brine (5 mL), dried (Na₂SO₄), the mixture filtered and the filtrate evaporated to dryness to afford a yellow oil, which was purified by flash chromatography, eluting with EtOAc (20 %) in heptane to give the title compound as a tan solid (290 mg, 90 % purity, 29 % yield). MS: $m/z = 428.9$ (M+H)⁺.

Example AE

Synthesis of [6-Chloro-4-(pyridine-3-sulfonyl)-pyridin-2-yl]-(5-cyclopentyl-1H-pyrazol-3-yl)-amine

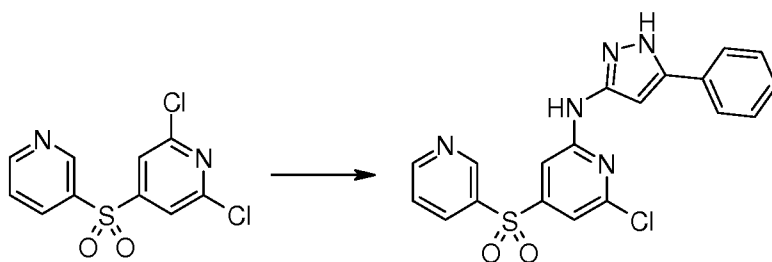


To a solution of 2,6-Dichloro-4-(pyridine-3-sulfonyl)-pyridine (400 mg, 1.38 mmol) in DMSO (2.5 mL) was added 5-cyclopentyl-1H-pyrazol-3-ylamine (249mg, 1.65 mmol) and DIPEA (357mg, 2.77 mmol) and the mixture heated at 150 °C for 3h. The cooled reaction

mixture was treated with EtOAc (80 mL) and water (10mL) and the phases separated. The organic phase was washed with water (2x 5mL), brine (5 mL), dried (Na₂SO₄), the mixture filtered and the filtrate evaporated to dryness to afford a yellow oil, which was purified by flash chromatography, eluting with EtOAc (65 – 100 %) in heptane to afford the title compound as a yellow solid (325 mg, 91 % purity, 53 % yield). MS: m/z = 404.0 (M+H)⁺.

Example AF

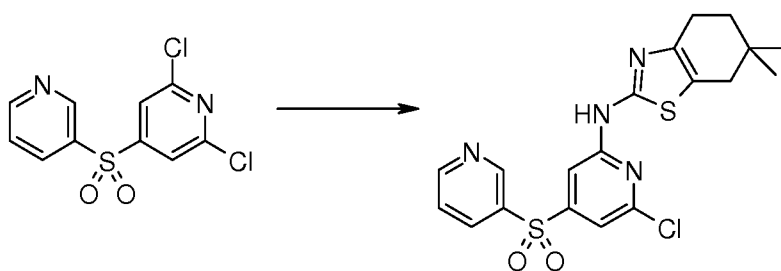
Synthesis of [6-Chloro-4-(pyridine-3-sulfonyl)-pyridin-2-yl]-(5-phenyl-1H-pyrazol-3-yl)-amine



Prepared in an analogous manner to [6-Chloro-4-(pyridine-3-sulfonyl)-pyridin-2-yl]-(5-cyclopentyl-1H-pyrazol-3-yl)-amine except that 5-phenyl-1H-pyrazol-3-ylamine was substituted for (5-cyclopentyl-1H-pyrazol-3-yl)-amine and that the chromatographic elution solvent was 10% MeOH in DCM. MS: m/z = 412.0 (M+H)⁺.

Example AG

Synthesis of [6-Chloro-4-(pyridine-3-sulfonyl)-pyridin-2-yl]-(6,6-dimethyl-4,5,6,7-tetrahydro-benzo thiazol-2-yl)-amine

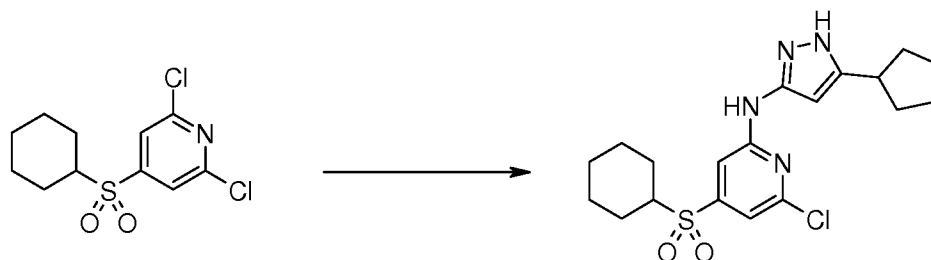


A mixture of 2,6-Dichloro-4-(pyridine-3-sulfonyl)-pyridine (515 mg, 1.78 mmol), 6,6-Dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-ylamine (340 mg, 1.87 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethyl xanthene (103 mg, 0.178 mmol), tris(dibenzylideneacetone)dipalladium (0), (82 mg, 0.089 mmol) and sodium carbonate (378 mg, 3.56 mmol) in 1,4-dioxane (5 mL) was degassed by bubbling a stream of nitrogen gas through the mixture for 3 min and then heated at 100 °C for 4h under a nitrogen atmosphere.

The mixture was cooled and filtered to remove inorganics. After evaporation of solvent, the orange oil was chromatographed, eluting with EtOAc (50 – 100 %) in heptane to afford the title compound as an orange solid (775 mg, 79 %). MS: $m/z = 435.0$ (M+H)⁺.

Example AH

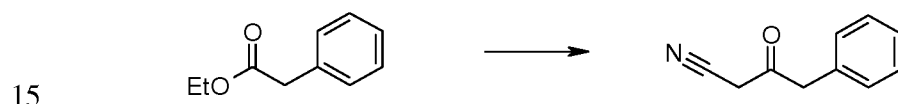
5 Synthesis of (6-Chloro-4-cyclohexanesulfonyl-pyridin-2-yl)-(5-cyclopentyl-1H-pyrazol-3-yl)-amine



10 Prepared in an analogous manner to [6-Chloro-4-(pyridine-3-sulfonyl)-pyridin-2-yl]-(5-cyclopentyl-1H-pyrazol-3-yl)-amine except that 2,6-Dichloro-4-cyclohexanesulfonyl-pyridine was substituted for 2,6-Dichloro-4-(pyridine-3-sulfonyl)-pyridine and that chromatography was carried out via an Isolute SCX-2 column, eluting with MeOH (20 %) in DCM containing 1% NH₄OH. MS: $m/z = 409.0$ (M+H)⁺.

Example AI

Synthesis of 3-Oxo-4-phenyl-butyronitrile`

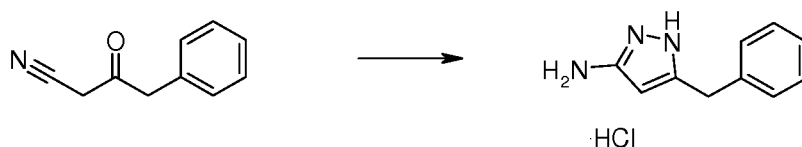


15 To a solution of n-butyl lithium (2.5 M, 16 mL, 40 mmol) in tetrahydrofuran (20 mL) at – 60 °C (IPA/dry ice bath) was added a solution of acetonitrile (2.5 mL, 48 mmol) in tetrahydrofuran (20 mL) at such a rate that the temperature did not rise above - 40 °C. The resulting suspension was stirred for 20 min in the cold before a solution of phenylacetic acid methyl ester (2.9 mL, 20 mmol) in tetrahydrofuran (7.5 mL) was added slowly over a period of 10 min. The mixture was stirred for 1h at -60 °C and then quenched with acetic acid (3 mL), allowed to warm to room temperature and partitioned between EtOAc (300 mL) and water (100 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (100 mL). The combined organic layers were washed with brine (100 mL), dried
20 (MgSO₄), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography, eluting with a gradient of EtOAc (0 – 50%) in heptane to afford the title
25

compound (2.75 g, 87 %). ^1H NMR (500 MHz, CDCl_3) δ ppm 7.43 - 7.31 (3 H, m), 7.24 (2 H, d, $J=7.09$ Hz), 3.88 (2 H, s), 3.47 (2 H, s).

Example AJ

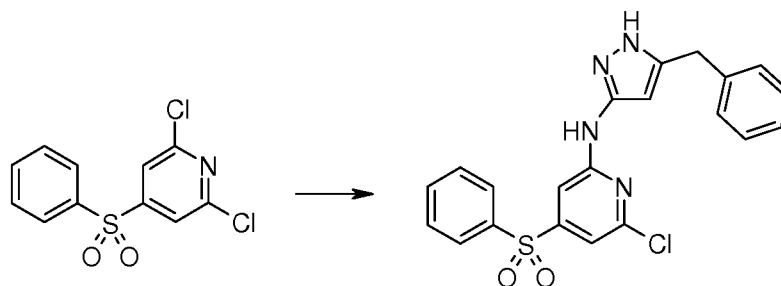
Synthesis of 5-Benzyl-1H-pyrazol-3-ylamine hydrochloride



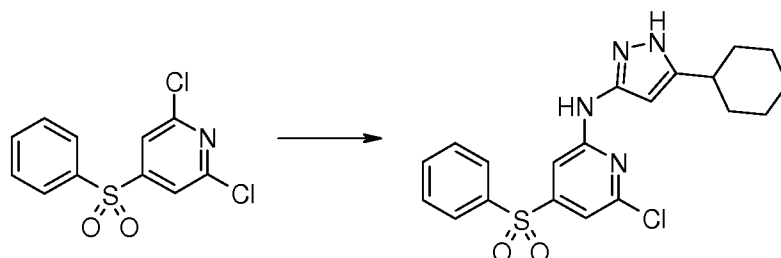
A mixture of 3-oxo-4-phenyl-butyronitrile (2.75 g, 0.017 mol) and hydrazine hydrate (0.9 mL, 0.019 mol) in ethanol (50 mL) was heated under reflux for 12h. The mixture was cooled to room temperature, diluted with methanol (~100 mL) and then made acidic (pH 1) with 1M hydrochloric acid. The solvent was removed and the crystalline solid was washed with EtOAc to give the title compound (2.06 g, 58%). ^1H NMR (500 MHz, MeOD) δ 6.73 - 6.57 (5 H, m), 4.96 (1 H, s), 2.65 (2 H, dt, $J=3.27, 1.60$ Hz).

Example AK

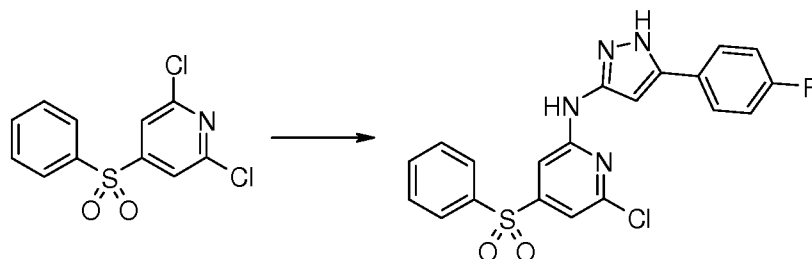
Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-benzyl-1H-pyrazol-3-yl)-amine



A mixture of 4-benzenesulfonyl-2,6-dichloro-pyridine (500 mg, 1.735 mmol), 5-benzyl-1H-pyrazol-3-ylamine hydrochloride (473 mg, 2.26 mmol) and DIPEA (0.72 mL, 4.34 mmol) in DMSO (4 mL) was heated at 100 °C for 1.5h. The mixture was allowed to cool to room temperature, then partitioned between EtOAc (30 mL) and aq. saturated ammonium chloride solution (15 mL). The phases were separated, the aqueous was extracted with EtOAc (2 x 20 mL) and the combined organics were washed with water (20 mL) and brine (20 mL) and then dried (MgSO_4). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100%) in heptane to give the title compound as a pale yellow solid (120 mg, 16 %). MS: $m/z = 425.0$ ($\text{M} + \text{H}$) $^+$.

Example AL**Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-cyclohexyl-1H-pyrazol-3-yl)-amine**

5 A mixture of 4-Benzenesulfonyl-2,6-dichloro-pyridine (500 mg, 1.735 mmol), 3-amino-5-cyclohexylpyrazole hydrochloride (455 mg, 2.256 mmol) and DIPEA (0.7 mL, 4.34 mmol) in DMSO (4 mL) was heated at 100°C for 15 h. The mixture was allowed to cool to room temperature, then partitioned between EtOAc (30 mL) and aq. saturated ammonium chloride solution (15 mL). The phases were separated, the aqueous was extracted with EtOAc
10 (2x20 mL) and the combined organics were washed with water (20 mL), brine (20 mL) and then dried (MgSO₄). The crude material was purified by flash chromatography, eluting with a gradient of EtOAc (0 - 100 %) in heptane to afford the title compound as a pale yellow solid (330 mg, 46 %). MS: $m/z = 417.0$ (M + H)⁺.

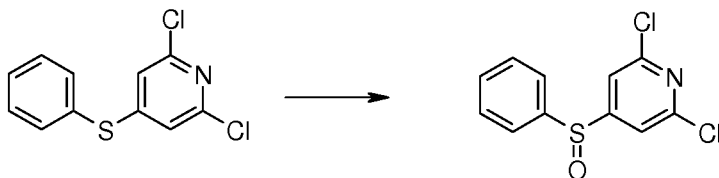
Example AM**15 Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-amine**

20 A mixture of 4-Benzenesulfonyl-2,6-dichloro-pyridine (500 mg, 1.735 mmol), 5-(4-fluorobenzene)-3-aminopyrazole (400 mg, 2.256 mmol) and DIPEA (0.4 mL, 2.603 mmol) in DMSO (4 mL) was heated at 100 °C for 12h, then at 110 °C for a further 24h. The mixture was allowed to cool to room temperature, then partitioned between EtOAc (30 mL) and aq. saturated ammonium chloride solution (15 mL). The phases were separated, the aqueous was extracted with EtOAc (2 x 20 mL) and the combined organics were washed with water (20 mL) and brine (20 mL) and then dried (MgSO₄). The crude material was purified by flash

chromatography, eluting with EtOAc (0 - 100 %) in heptane to afford the title compound as a pale yellow solid (370 mg, 50 %). MS: m/z = 429.0 (M + H)⁺.

Example AN

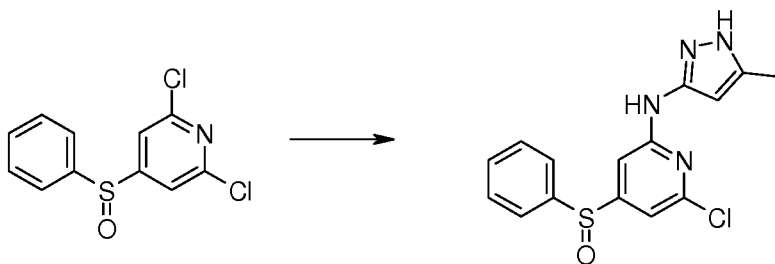
Synthesis of (+/-)-4-Benzenesulfinyl-2,6-dichloro-pyridine



To a solution of 2,6-Dichloro-4-phenylsulfanyl-pyridine (2.38 g, 9.29 mmol) in DCM (25 mL) was added a solution of mCPBA (circa 77%) (2.08g, 9.29 mmol) in DCM (25 mL) dropwise and the mixture was stirred at room temperature for 30 min. The mixture was then washed with 0.2 M NaOH (40 mL), the phases were separated and the aqueous was extracted with DCM (50 mL). The combined organics were washed with 0.2 M NaOH (40 mL), water (30 mL), brine (30 mL) and dried (MgSO₄). The crude material was purified by flash chromatography with a gradient of DCM (0 - 100%) in heptane, followed by a gradient of MeOH (0 - 20%) in DCM to afford the title compound (2.06 g, 81 %). MS: m/z = 271.9 (M + H)⁺.

Example AO

Synthesis of (+/-)-(4-Benzenesulfinyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine

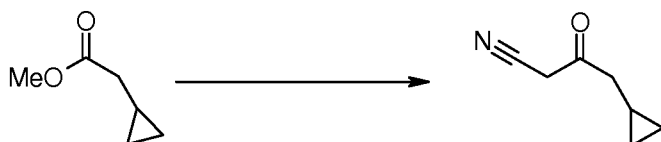


A mixture of (+/-)-4-Benzenesulfinyl-2,6-dichloro-pyridine (300 mg, 1.1 mmol), 5-methyl-1H-pyrazol-3-ylamine (139 mg, 1.433 mmol) and DIPEA (0.3 mL, 1.65 mmol) in DMSO (2 mL) was heated at 100 °C for 15h and at 120 °C for 5h. The temperature was then lowered to 110 °C and the reaction mixture was stirred for a further 15h. The mixture was allowed to cool to room temperature, then partitioned between EtOAc (50 mL) and aq. saturated ammonium chloride solution (30 mL). The phases were separated, the aqueous was extracted with EtOAc (2x20 mL) and the combined organics were washed with water (20

mL) and brine (20 mL) and then dried (MgSO₄). The crude material was purified by flash chromatography with a gradient of EtOAc (0 - 100%) in heptane to afford the title compound as a pale yellow solid (105 mg, 29 %). MS: $m/z = 333.0$ ($M + H$)⁺.

Example AP

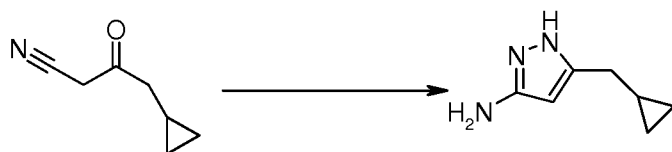
5 Synthesis of 4-Cyclopropyl-3-oxo-butyronitrile



To 31 mL of anhydrous THF under a nitrogen atmosphere in a well dried 3-necked round bottomed flask was added 2.5M BuLi in hexanes (25 mL) and the mixture cooled to -78 °C. To this solution was added a solution of anhydrous MeCN (3.6 mL, 68.12 mmol) in anhydrous THF (45 mL) dropwise over a period of 15 min. The mixture turned into a white/orange slurry after this and was stirred -78 °C for 30 min after which it was treated with a solution of cyclopropyl-acetic acid methyl ester (3.24 g, 28.38 mmol) (prepared according to WO2006/85118) in anhydrous THF (8.6 mL) dropwise for 5 min. The resulting mixture was stirred at -78 °C for 1.5 h after which it was quenched by the addition of acetic acid (circa 0.6 mL). The reaction mixture was then allowed to warm up to room temperature and concentrated *in vacuo* (caution: product is volatile). The crude residue obtained was purified by flash silica chromatography (eluting with 0-10% MeOH in DCM) to give the title compound as a yellow liquid (0.52 g, 15 %). ¹H NMR (500 MHz, CDCl₃) δ 3.54 (s, 2H), 2.49 (d, $J = 7.1$ Hz, 2H), 1.05 - 0.96 (m, 1H), 0.70 - 0.61 (m, 2H), 0.23 - 0.15 (m, 2H).

20 Example AQ

Synthesis of 5-Cyclopropylmethyl-1H-pyrazol-3-ylamine

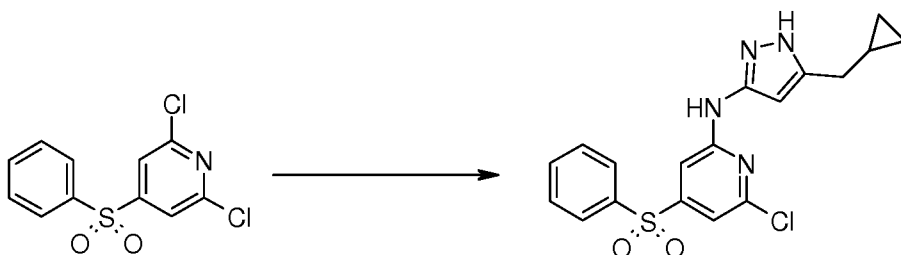


A mixture of 4-cyclopropyl-3-oxo-butyronitrile (0.52 g, 4.25 mmol) and hydrazine hydrate (80%) (0.3 mL, 4.68 mmol) in ethanol (12.9 mL) was heated at 90 °C (external temperature) for 18h in a pressure vial. The mixture was then allowed to cool down to room temperature and concentrated *in vacuo* (caution: product is volatile).. The crude residue obtained was purified by flash silica chromatography (eluting with 1-10% MeOH in DCM) to give the title compound as a light yellow oil (0.07g, 12%). ¹H NMR (500 MHz, CDCl₃): δ

5.53 (s, 1 H), 3.61 (br. s, 2 H), 2.49 (d, $J = 7.1$ Hz, 2 H), 1.02 - 0.94 (m, 1 H), 0.61 - 0.54 (m, 2 H), 0.24 - 0.16 (m, 2 H).

Example AR

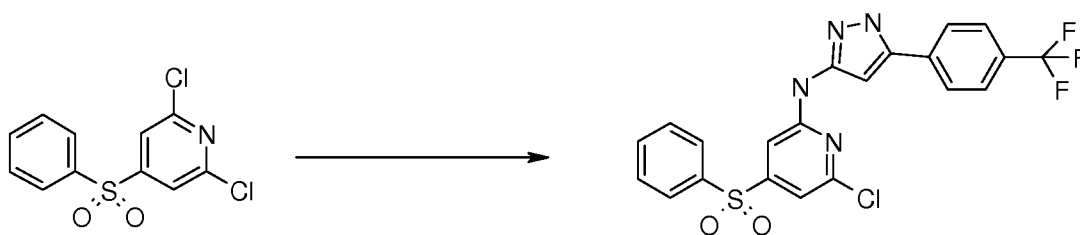
Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-cyclopropylmethyl-1H-pyrazol-3-yl)-amine



A mixture of 4-benzenesulfonyl-2,6-dichloro-pyridine (0.14 g, 0.47 mmol), 5-cyclopropylmethyl-1H-pyrazol-3-ylamine (0.07 g, 0.52 mmol) and DIPEA (0.15 mL, 0.94 mmol) in anhydrous DMSO (1 mL) was heated at 120 °C in a microwave reactor for 1 h. The mixture was then partitioned between EtOAc (10 mL) and saturated aqueous ammonium chloride solution (10 mL). The two phases were separated and the aqueous phase extracted with EtOAc (10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried (MgSO_4), filtered and concentrated *in vacuo*. The crude material was purified by flash silica chromatography (eluting with 1-10% MeOH in DCM) to give the title compound as a yellow solid (0.04 g, 18 %); MS: $m/z = 389.0$ ($\text{M}+\text{H}$)⁺.

Example AS

Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-(4-trifluoromethyl-phenyl)-1H-pyrazol-3-yl]-amine



A mixture of 4-benzenesulfonyl-2,6-dichloro-pyridine (0.30 g, 1.04 mmol), 5-(4-trifluoromethyl-phenyl)-2H-pyrazole-3-ylamine (0.28 g, 1.25 mmol) and DIPEA (0.3 mL, 2.08 mmol) in anhydrous DMSO (4 mL) was flushed with nitrogen and heated at 120 °C in a microwave reactor for 75 min. The reaction mixture was subsequently heated for 2h more at

150 °C in a microwave reactor followed by 3h at 165 °C. The reaction mixture was then partitioned between EtOAc (20 mL) and saturated ammonium chloride solution (10 mL). The aqueous phase was then extracted with EtOAc (2 × 10 mL) and the combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude material was purified by flash silica chromatography, eluting with MeOH (0 - 10%) in DCM to give the title compound (0.29 g, 59 % purity, 34 % yield). MS: *m/z* 479.0 (M+H)⁺.

Example AT

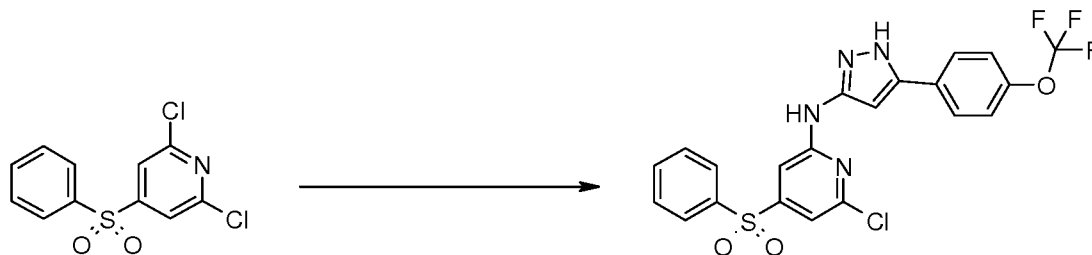
Synthesis of 5-(4-Trifluoromethoxy-phenyl)-1H-pyrazol-3-ylamine



A mixture of 3-oxo-3-[4-(trifluoromethoxy)phenyl]propanenitrile (1.0 g, 4.36 mmol) and hydrazine hydrate (0.3 mL, 5.23 mmol) in ethanol (13.2 mL) was stirred at reflux (90 °C external temperature) for 16 h. The volatiles were then evaporated *in vacuo*. The crude material was purified by flash silica chromatography (eluting with 1-10% MeOH in DCM) to give the title compound as a white solid (0.81g, 76%). MS: *m/z* = 244.0 (M+H)⁺.

Example AU

Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-(4-trifluoromethoxy-phenyl)-1H-pyrazol-3-yl]-amine

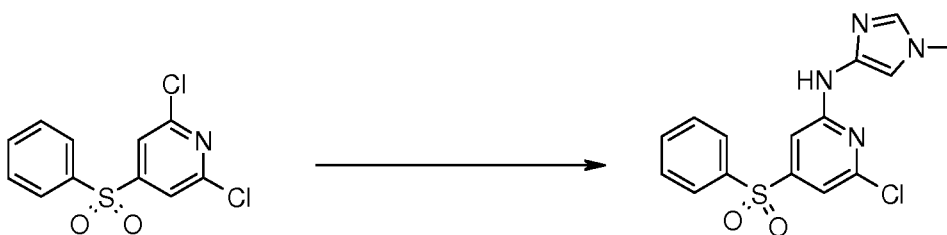


A mixture of 4-benzenesulfonyl-2,6-dichloropyridine (0.40 g, 1.39 mmol), 5-(4-(trifluoromethoxy)phenyl)-1H-pyrazol-3-ylamine (0.41 g, 1.67 mmol) and DIPEA (0.5 mL, 2.78 mmol) in anhydrous DMSO (5.3 mL) was flushed with nitrogen and heated at 150 °C in a microwave reactor for 1 hour 15 min. The mixture was subsequently heated for a further 1 h 15 min at 150 °C in a microwave reactor. The mixture was then partitioned between EtOAc (20 mL) and saturated aq. ammonium chloride solution (10 mL) and the phases separated.

The aqueous phase was extracted with EtOAc (2×10 mL) and the combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude material was purified by flash silica chromatography (eluting with 8-70% EtOAc in heptanes) to give the title compound as a light yellow solid (0.18g, 27%). MS: $m/z = 495.0, 496.7$ ($\text{M}+\text{H}$)⁺.

Example AV

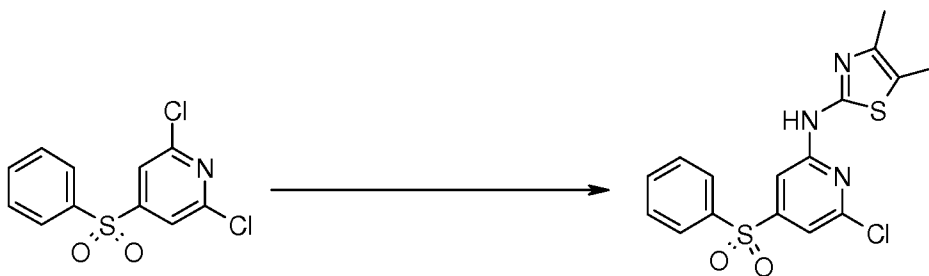
Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(1-methyl-1H-imidazol-4-yl)-amine



A mixture of 4-benzenesulfonyl-2,6-dichloropyridine (0.40 g, 1.39 mmol), 1-methyl-1H-imidazole-4-amine hydrochloride (0.22 g, 1.67 mmol) and DIPEA (0.7 mL, 4.16 mmol) in anhydrous DMSO (4.6 mL) was flushed with nitrogen and heated at 120 °C in a sealed microwave vial (plastic lid) for 2 h. The mixture was then partitioned between EtOAc (20 mL) and saturated aqueous ammonium chloride solution (10 mL) and the phases separated. The aqueous phase was extracted with EtOAc (2×10 mL) and the combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude material was purified by flash silica chromatography (eluting with 1-8% MeOH in DCM) to give the title compound as a yellow solid (0.14g, 82% purity, 24% yield). MS: $m/z = 349.0$ ($\text{M}+\text{H}$)⁺.

Example AW

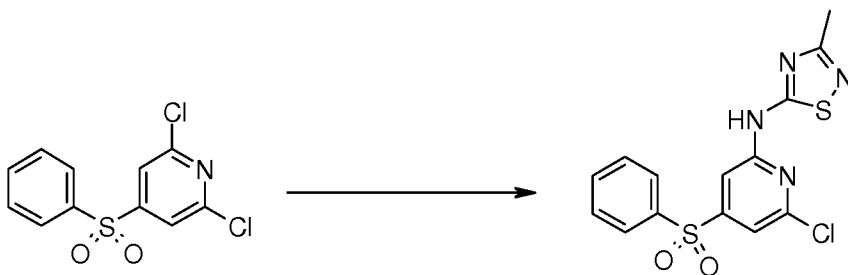
Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(4,5-dimethyl-thiazol-2-yl)-amine



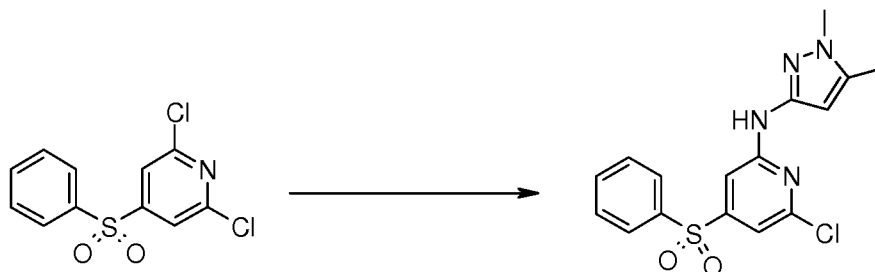
A mixture of 4-benzenesulfonyl-2,6-dichloro-pyridine (0.40 g, 1.39 mmol), 2-amino-4,5-dimethylthiazole hydrobromide (0.35 g, 1.67 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (0.08 g, 0.14 mmol) and Na₂CO₃ (0.44 g, 4.16 mmol) in anhydrous 1,4-dioxane (12 mL) was sonicated under a flow of nitrogen for 5 min before
 5 tris(dibenzylideneacetone)dipalladium (0) (0.06 g, 0.07 mmol) was added and the reaction heated at 100 °C in a sealed tube for 2.5 h. The reaction mixture was then allowed to cool down to room temperature and filtered through a pad of Celite, washed with EtOAc and the filtrate concentrated *in vacuo*. The crude material was purified by flash silica chromatography (eluting with 1-9% MeOH in DCM) to give the title compound as a yellow solid (0.42g, 94%
 10 purity, 75% yield). MS: $m/z = 380.0$ (M+H)⁺.

Example AX

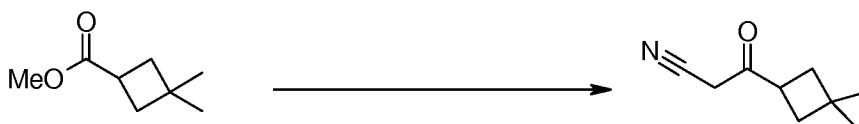
Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(3-methyl-[1,2,4]thiadiazol-5-yl)-amine



15 A mixture of 4-benzenesulfonyl-2,6-dichloro-pyridine (0.40 g, 1.39 mmol), 5-amino-3-methyl-1,2,4-thiadiazole (0.19 g, 1.67 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (0.08 g, 0.14 mmol) and Na₂CO₃ (0.21 g, 1.94 mmol) in anhydrous 1,4-dioxane (12 mL) was sonicated under a flow of nitrogen for 5 min before
 20 tris(dibenzylideneacetone)dipalladium (0) (0.06 g, 0.07 mmol) was added and the reaction heated at 100 °C in a sealed tube for 3h. The reaction mixture was then allowed to cool down to room temperature, filtered through a pad of Celite and washed with EtOAc. The filtrate was then concentrated *in vacuo*. The crude material was purified by flash silica chromatography (eluting with 1-9% MeOH in DCM). The solid obtained after this was taken up in DCM (20 mL) and washed with water (1 × 20 mL), brine (2 × 20 mL) and the
 25 combined aqueous washes extracted with EtOAc (40 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated *in vacuo* to give the title compound as a light yellow solid (0.29g, 57%). MS: $m/z = 366.9$ (M+H)⁺.

Example AY**Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(1,5-dimethyl-1H-pyrazol-3-yl)-amine**

- 5 A mixture of 4-benzenesulfonyl-2,6-dichloropyridine (0.4 g, 1.39 mmol), 1,5-dimethyl-1H-pyrazol-3-amine (0.19 g, 1.67 mmol) and DIPEA (0.5 mL, 2.78 mmol) in anhydrous DMSO (5.0 mL) was heated at 150 °C in a microwave reactor for 1h. The mixture was then partitioned between EtOAc (10 mL) and saturated aq. ammonium chloride solution (10 mL) and the phases separated. The aqueous phase was extracted with EtOAc (10 mL) and the combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude material was purified by flash silica chromatography (eluting with 0-4% MeOH in DCM) to give the title compound as a yellow foam (0.29g, 53%) MS: $m/z = 363.0$ (M+H)⁺.
- 10

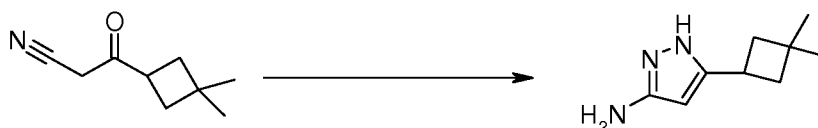
Example AZ**15 Synthesis of 3-(3,3-Dimethyl-cyclobutyl)-3-oxo-propionitrile**

- To 36 mL of anhydrous THF cooled to -78 °C in a well dried 3-necked round bottomed flask under nitrogen was added 2.5M BuLi in hexanes (19.8 mL). To this solution was added a solution of anhydrous acetonitrile (2.82 mL, 53.98 mmol) in anhydrous THF (25 mL) dropwise over a period of 10 min. The mixture turned into a white slurry and it was stirred at the same temperature for 30 min after which it was treated with a solution of 3,3-dimethyl-cyclobutanecarboxylic acid methyl ester (3.51 g, 22.49 mmol) (prepared according to the protocol in WO 2011/018495) in anhydrous THF (6.8 mL) dropwise (for 8 min). The resulting mixture turned to a clear solution at first and then to a slurry and was stirred at -78 °C for 1.5h. The reaction mixture was then quenched with acetic acid (*circa* 0.5 mL) and allowed to warm up to room temperature. The solvent was then evaporated *in vacuo* (caution:
- 20
- 25

product is volatile). The crude material was purified by flash silica chromatography (eluting with 8-70% EtOAc in heptanes) to give the title compound as a yellow oil (1.89g, 51%). ¹H NMR (500 MHz, CDCl₃) δ 3.44 - 3.32 (m, 3 H), 2.12 - 2.06 (m, 2 H), 2.05 - 1.98 (m, 2 H), 1.20 (s, 3 H), 1.08 (s, 3 H).

5 **Example BA**

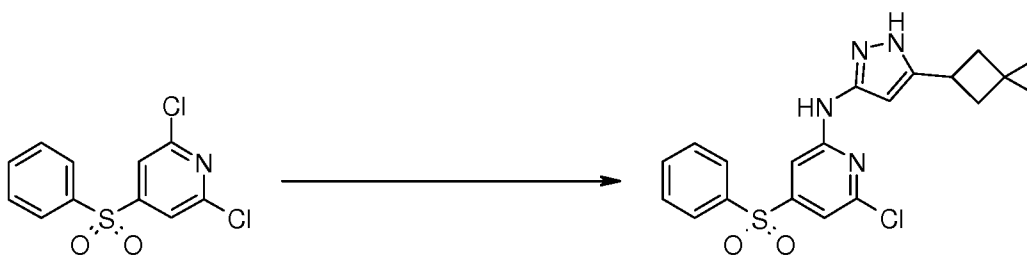
Synthesis of 5-(3,3-Dimethyl-cyclobutyl)-1H-pyrazol-3-ylamine



A mixture of 3-(3,3-dimethyl-cyclobutyl)-3-oxo-propionitrile (1.89 g, 12.49 mmol) and hydrazine hydrate (80%) (0.8 mL, 13.74 mmol) in ethanol (38 mL) was heated at 90 °C (external temperature) in a pressure vial for 18 h. The reaction mixture was then allowed to cool down to room temperature and concentrated *in vacuo*. The crude material was dissolved in DCM (125 mL) and washed with water (30 mL) and brine (50 mL), dried over MgSO₄, filtered and concentrated *in vacuo* (caution: product is volatile) to give to give the title compound as a brown oil (1.92g, 93% purity, 87% yield). MS: *m/z* = 166.0 (M+H)⁺.

15 **Example BB**

Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-(3,3-dimethyl-cyclobutyl)-1H-pyrazol-3-yl]-amine

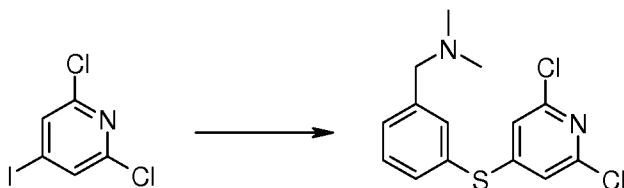


A mixture of 4-benzenesulfonyl-2,6-dichloro-pyridine (0.3 g, 1.04 mmol), 5-(3,3-Dimethyl-cyclobutyl)-1H-pyrazol-3-ylamine (0.21 g, 93% purity, 1.16 mmol) and DIPEA (0.15 mL, 0.94 mmol) in anhydrous DMSO (4.7 mL) was heated at 120 °C in a microwave reactor for 1h. Followed by two further periods of microwave irradiation at this temperature (1h and 0.5h). The reaction mixture was then partitioned between EtOAc (10 mL) and saturated aqueous ammonium chloride solution (10 mL) and the two phases separated. The aqueous phase was extracted with EtOAc (10 mL) and the combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over MgSO₄, filtered and concentrated

in vacuo. The crude material was purified by flash silica chromatography (eluting with 1-9% MeOH in DCM) to give the title compound as a yellow solid (0.27g, 80% purity, 50% yield). MS: m/z 417.0 (M+H)⁺.

Example BC

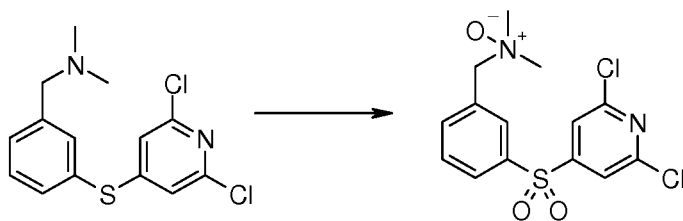
5 Synthesis of [3-(2,6-Dichloro-pyridin-4-ylsulfanyl)-benzyl]-dimethyl-amine



A mixture of 2,6-dichloro-4-iodopyridine (1.35 g, 4.93 mmol), 3-dimethylaminomethyl benzenethiol hydrochloride (1.04 g, 4.93 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (285 mg, 0.493 mmol), and
 10 diisopropylethylamine (2.44 mL, 14.8 mmol) in 1,4-dioxane (25 mL) was flushed with nitrogen for 3 min before tris(dibenzylideneacetone)dipalladium (0) (226 mg, 0.246 mmol) was added and the resulting mixture stirred at 110 °C for 3h. The resulting suspension was concentrated *in vacuo* and purified by flash chromatography, eluting with EtOAc (50 – 100%) in heptane followed by EtOAc:MeOH:Et₃N (90:10:1) to afford the title compound as a
 15 brown oil, which was used without further purification (2.15g). MS: m/z = 312.9 (M+H)⁺.

Example BD

Synthesis of 1-[3-(2,6-dichloropyridine-4-sulfonyl)phenyl]-N,N-dimethylmethanamine oxide

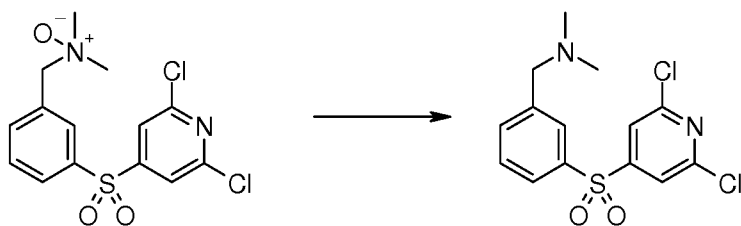


20 To a solution of mCPBA (70 %, 3.4 g, 13.8 mmol) in DCM (30 mL) was added a solution of [3-(2,6-Dichloro-pyridin-4-ylsulfanyl)-benzyl]-dimethyl-amine (1.3 g, 3.94 mmol) in DCM (30 mL) drop wise, and the mixture stirred at room temperature for 1h. More mCPBA (1 g) was added periodically until the reaction had reached completion. The mixture was diluted with DCM (300 mL) and washed with saturated aqueous sodium carbonate (2 x
 25 100 mL), then the organic phase was dried (Na₂SO₄), filtered and the filtrate evaporated to

dryness. The crude product was purified by flash chromatography, eluting with DCM:MeOH:Et₃N (300:50:1) to afford the title compound (303 mg, 21%). MS: m/z = 360.9 (M+H)⁺.

Example BE

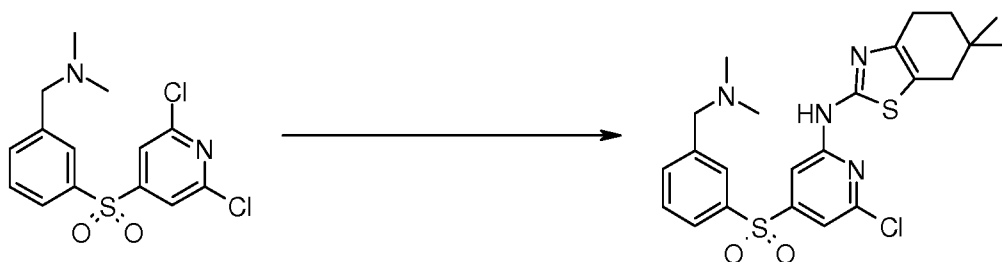
5 Synthesis of [3-(2,6-Dichloro-pyridine-4-sulfonyl)-benzyl]-dimethyl-amine



To a solution of 1-[3-(2,6-dichloropyridine-4-sulfonyl)phenyl]-N,N-dimethylmethanamine oxide (303 mg, 0.839 mmol) in THF (5 mL) was added triethylamine (85 mg, 0.839 mmol) and copper (I) iodide (160 mg, 0.839 mmol) and the mixture heated at 60 °C for 16h. The reaction mixture was then allowed to cool and filtered, washed with THF (15 mL) and the filtrate concentrated *in vacuo* to give the title compound as a brown oil that was used without further purification (375 mg). MS: m/z = 345.0 (M+H)⁺.

Example BF

15 Synthesis of [6-Chloro-4-(3-dimethylaminomethyl-benzenesulfonyl)-pyridin-2-yl]-(6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-yl)-amine

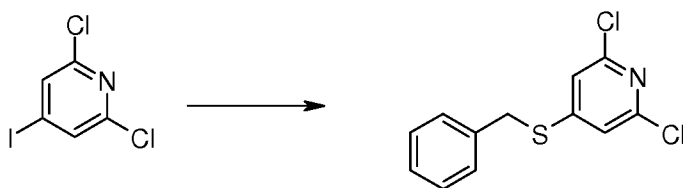


A mixture of [3-(2,6-Dichloro-pyridine-4-sulfonyl)-benzyl]-dimethyl-amine (375 mg, 78% purity, 0.847 mmol), 6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-ylamine (154 mg, 0.847 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (49 mg, 0.085 mmol), tris(dibenzylideneacetone) dipalladium (0), (39 mg, 0.042 mmol) and sodium carbonate (269 mg, 2.45 mmol) in 1,4-dioxane (30 mL) was heated at 110 °C for 2h under a N₂ atmosphere before a further 6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-ylamine (100 mg, 0.549 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (49 mg, 0.085 mmol) and tris(dibenzylideneacetone)dipalladium (0), (30 mg, 0.033 mmol) were added and reflux

continued for 2h . The mixture was cooled, filtered and the solvent evaporated. The crude material was purified by flash chromatography, eluting with EtOAc to EtOAc:MeOH:Et₃N (100:10:1), to afford the title compound as a dark green foam (255 mg, 56 %). MS: m/z = 491.0 (M+H)⁺.

5 **Example BG**

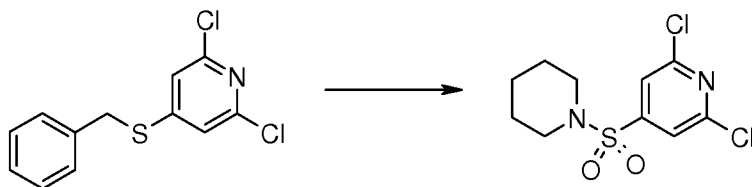
Synthesis of 4-Benzylsulfanyl-2,6-dichloro-pyridine



Prepared in an analogous manner to 2,6-Dichloro-4-(pyridine-3-sulfanyl)-pyridine except that benzenethiol was substituted with phenyl-methanethiol, and toluene was substituted for 1,4-dioxane. The chromatography eluent was EtOAc (10 %) in heptane. MS: m/z = 270.0 (M+H)⁺.

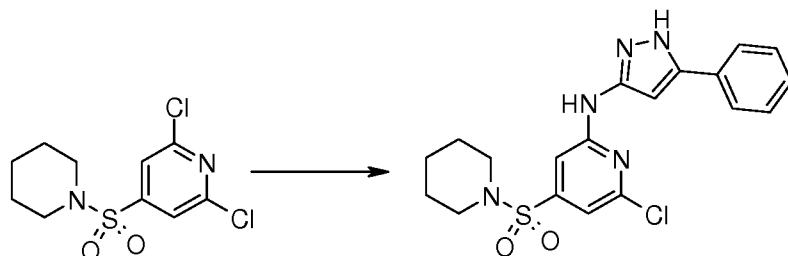
Example BH

Synthesis of 2,6-Dichloro-4-(piperidine-1-sulfonyl)-pyridine

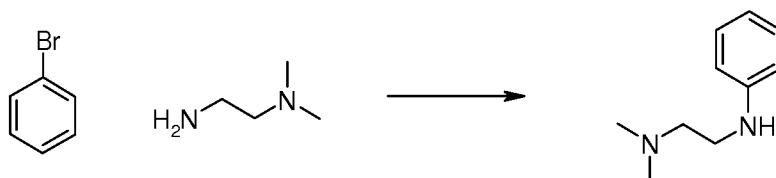


15 A mixture of 4-Benzylsulfanyl-2,6-dichloro-pyridine (520 mg, 1.85 mmol) in acetic acid (18 mL) and water (2 mL) was cooled to below 10 °C and periodically saturated with chlorine gas until the complete disappearance of starting material was observed by LC-MS. The reaction was diluted with DCM (50 mL) and water (20 mL), and the phases separated. The organic phase was washed with brine (2 x 10 mL), dried (Na₂SO₄), filtered, and
20 concentrated *in vacuo* to give colorless oil. This oil was dissolved in DCM (10 mL) and added to a solution of piperidine (440 mg, 3.70 mmol) in DCM (10 mL). The mixture was stirred at room temperature for 5 min, before concentrating *in vacuo* and purifying by flash chromatography, eluting with EtOAc (10 %) in heptane to afford the title compound as an off white solid (525 mg, 96%). MS: m/z = 295.2 (M+H)⁺.

25

Example BI**Synthesis of [6-Chloro-4-(piperidine-1-sulfonyl)-pyridin-2-yl]-(5-phenyl-1H-pyrazol-3-yl)-amine**

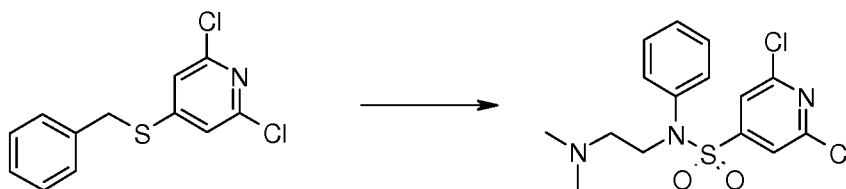
- 5 A mixture of 2,6-Dichloro-4-(piperidine-1-sulfonyl)-pyridine (190 mg, 0.644 mmol), 3-amino-5-phenylpyrazole (113 mg, 0.708 mmol) and DIPEA (249 mg, 1.93 mmol) in anhydrous DMSO (2 mL) was heated at 140 °C for 16h. The mixture was partitioned between EtOAc (50 mL) and water (15 mL) and the phases separated. The organic phase was washed with water (2 x 5 mL), brine (5 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The
- 10 crude material was purified by flash chromatography, eluting with EtOAc (50 %) in heptane to afford the title compound as a brown solid (65 mg, 15%) MS: $m/z = 418.1$ (M+H)⁺.

Example BJ**Synthesis of *N,N*-Dimethyl-*N'*-phenyl-ethane-1,2-diamine**

- 15 A mixture of bromo-benzene (3 g, 19.1 mmol), *N,N*-dimethylethylenediamine (1.85 g, 21.0 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (1.10 g, 1.91 mmol), tris(dibenzylideneacetone) dipalladium (0), (874 mg, 0.955 mmol) and sodium *tert*-butoxide (4.59 g, 47.8 mmol) in 1,4-dioxane (30 mL) was heated at 100 °C for 16h under a nitrogen atmosphere. The mixture was cooled, diluted with EtOAc (50 mL) and filtered. After
- 20 evaporation of solvent, the crude product was purified by flash chromatography, eluting with DCM:MeOH:NH₃ (200:10:1.5), to afford the title compound (2.07 g, 59%). MS: $m/z = 165.0$ (M+H)⁺.

Example BK

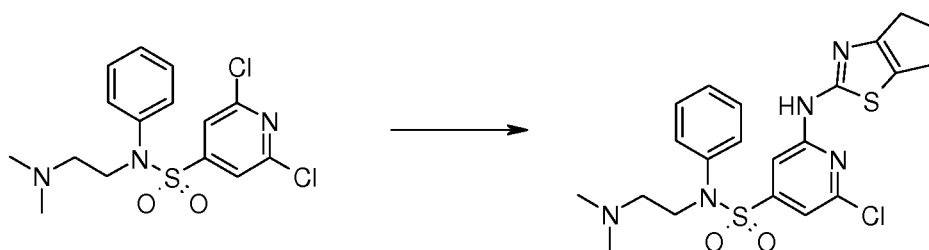
Synthesis of 2,6-Dichloro-pyridine-4-sulfonic acid (2-dimethylamino-ethyl)-phenyl-amide



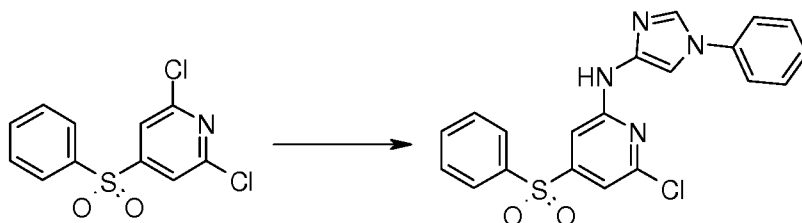
Prepared in an analogous manner to 2,6-Dichloro-4-(piperidine-1-sulfonyl)-pyridine except that piperidine was substituted with N,N-Dimethyl-N'-phenyl-ethane-1,2-diamine, and the chromatographic elution solvent was DCM:MeOH:Et₃N (200:10:1). MS: m/z = 374.0 (M+H)⁺.

Example BL

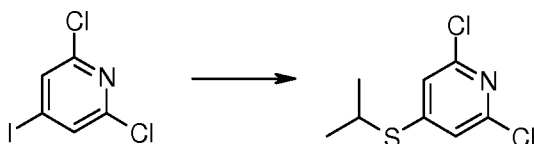
Synthesis of 2-Chloro-6-(5,6-dihydro-4H-cyclopentathiazol-2-ylamino)-pyridine-4-sulfonic acid (2-dimethylamino-ethyl)-phenyl-amide



Prepared in an analogous manner to [6-Chloro-4-(3-dimethylaminomethyl-benzenesulfonyl)-pyridin-2-yl]-(6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-yl)-amine except that [3-(2,6-Dichloro-pyridine-4-sulfonyl)-benzyl]-dimethyl-amine was substituted with 2,6-Dichloro-pyridine-4-sulfonic acid (2-dimethylamino-ethyl)-phenyl-amide, 6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-ylamine was substituted with 5,6-dihydro-4H-cyclopentathiazol-2-ylamine, and the chromatographic elution solvent was a gradient of DCM to DCM:MeOH:Et₃N (200:10:1). MS: m/z = 478.0 (M+H)⁺.

Example BM**Synthesis of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-(1-phenyl-1*H*-imidazol-4-yl)-amine**

5 A mixture of 4-benzenesulfonyl-2,6-dichloro-pyridine (400 mg, 1.39 mmol), 1-Phenyl-1*H*-imidazole-4-amine hydrochloride (0.33 g, 1.67 mmol) and DIPEA (0.69 mL, 4.16 mmol) in anhydrous DMSO (4.6 mL) was flushed with N₂ and heated at 120 °C in a sealed vial for 5.5h. The reaction mixture was subsequently partitioned between EtOAc (20 mL) and saturated aq. ammonium chloride (10 mL) and the two phases separated. The aqueous phase
 10 was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were washed with water (20 mL) and brine (20 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography, eluting with MeOH (0 – 4 %) in DCM to give the title compound as a yellow solid (0.18 g, 80 % purity, 24 %). MS: *m/z* = 411.0 (M+H).

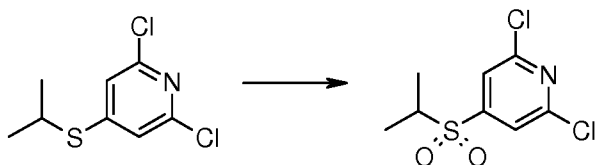
Example BN**Synthesis of 2,6-Dichloro-4-isopropylsulfanyl-pyridine**

A mixture of 2,6-dichloro-4-iodopyridine (3 g, 10.95 mmol), propane-2-thiol (1.12 mL, 12.05 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.63 g, 1.1 mmol) and
 20 DIPEA (3.62 mL, 21.91 mmol) in anhydrous Dioxane (30 mL) was flushed with nitrogen for 5 min before tris(dibenzylideneacetone)dipalladium (0) (0.5 g, 0.55 mmol) was added and the resulting mixture was stirred at 90 °C for 45 min. The reaction was cooled, partitioned between DCM (150 mL) and aq. ammonium chloride solution (150 mL) and the phases separated. The aqueous was extracted with DCM (3 x 100 mL) and the combined organics
 25 were washed with water (100 mL), brine (100 mL) and dried (hydrophobic frit) Concentration afforded crude as a black solid which was purified by flash chromatography,

eluting with EtOAc (0 - 25 %) in heptane to give the title compound as a yellow oil (0.88 g, 35 %). MS: $m/z = 221.8$ (M+H)⁺.

Example BO

Synthesis of 2,6-Dichloro-4-(propane-2-sulfonyl)-pyridine



5

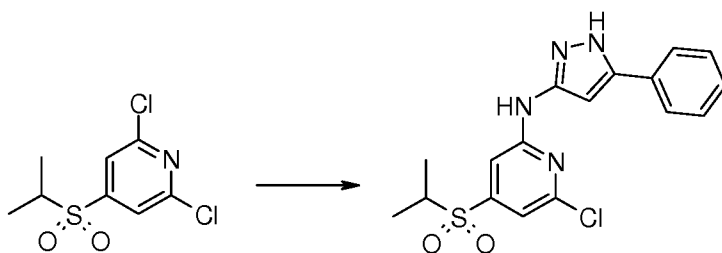
To 2,6-Dichloro-4-isopropylsulfanylpyridine (0.88 g, 3.96 mmol) in DCM (10 mL) was added a solution of mCPBA (70%, 1.95 g, 7.92 mmol) in DCM (10 mL) dropwise and the mixture was stirred at room temperature for 2 h. The reaction was partitioned between 0.25 M NaOH (25 mL) and DCM (20 mL) and the phases were separated. The organic was washed with 0.25 M NaOH (4 x 25 mL), brine (15 mL), dried (hydrophobic frit) and concentrated. The crude material was purified by flash chromatography, eluting with EtOAc (0 - 20 %) in heptane to give the title compound as a white solid (0.8 g, 78 %). MS: $m/z = 253.9$ (M+H)⁺.

10

Example BP

Synthesis of [6-Chloro-4-(propane-2-sulfonyl)pyridin-2-yl]-(5-phenyl-1H-pyrazol-3-yl)-amine

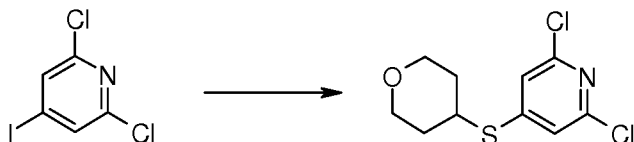
15



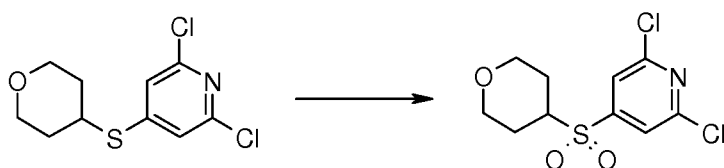
20

25

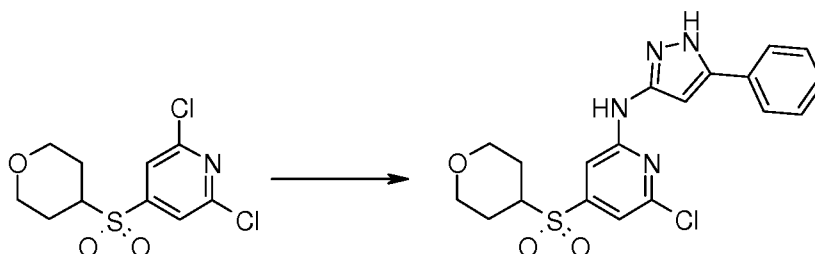
A mixture of 2,6-Dichloro-4-(propane-2-sulfonyl)pyridine (0.4 g, 1.57 mmol), 3-phenyl-1H-pyrazol-5-amine (0.3 g, 1.89 mmol) and DIPEA (0.39 mL, 2.36 mmol) in anhydrous DMSO (3 mL) was stirred at 100 °C for 26 h. The reaction mixture was cooled, partitioned between EtOAc (25 mL) and water (25 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organics washed with water (25 mL), brine (25 mL), dried (MgSO₄) and concentrated. The crude material was purified by flash chromatography, eluting with EtOAc (0 - 60 %) in heptane to give the title compound as a beige solid (237 mg, 39 %). MS: $m/z = 377.0$ (M+H)⁺.

Example BQ**Synthesis of 2,6-dichloro-4-(tetrahydro-pyran-4-ylsulfanyl)-pyridine**

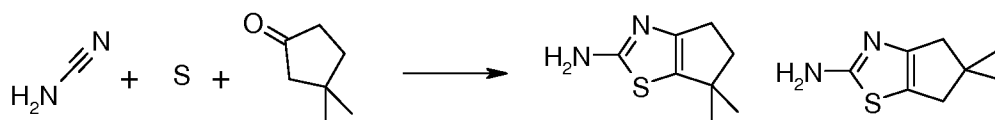
A mixture of 2,6-dichloro-4-iodopyridine (2 g, 7.3 mmol), oxane-4-thiol (0.93 g, 7.86 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (0.42 g, 0.73 mmol) and DIPEA (2.4 mL, 14.6 mmol) in anhydrous 1,4-dioxane (30 mL) was flushed with N₂ for 10 min before tris(dibenzylideneacetone)dipalladium (0) (0.33 g, 0.37 mmol) was added and the resulting mixture was heated to 110 °C for 2h. The volatiles were then evaporated *in vacuo*. The crude material obtained was purified by flash chromatography, eluting with EtOAc (7 – 60 %) in heptane to give the title compound as a dark yellow/orange oil, that solidified to a yellow solid on standing (1.67 g, 84 %). MS: $m/z = 263.9$ (M+H)⁺.

Example BR**Synthesis of 2,6-dichloro-4-(tetrahydro-pyran-4-sulfonyl)-pyridine**

To a solution of 2,6-dichloro-4-(tetrahydro-pyran-4-ylsulfanyl)-pyridine (1.61 g, 6.09 mmol) in anhydrous DCM (15 mL) was added a solution of *m*CPBA (75 %, 2.8 g, 12.19 mmol) in anhydrous DCM (15 mL) dropwise for 10 min (effervescence observed), after which time the mixture turned into a light yellow suspension. The reaction mixture was stirred at room temperature for 2.3h before it was diluted with DCM (20 mL) and washed with saturated aq. Na₂CO₃ (20 mL), water (20 mL) and brine (20 mL). The organic phase was dried (MgSO₄), filtered and concentrated *in vacuo* to give the title compound as a yellow solid (1.7 g, 83% purity, 78 %). MS: $m/z = 295.8$ (M+H)⁺.

Example BS**Synthesis of [6-chloro-4-(tetrahydro-pyran-4-sulfonyl)-pyridin-2-yl]-(5-phenyl-2H-pyrazol-3-yl)-amine, formate salt**

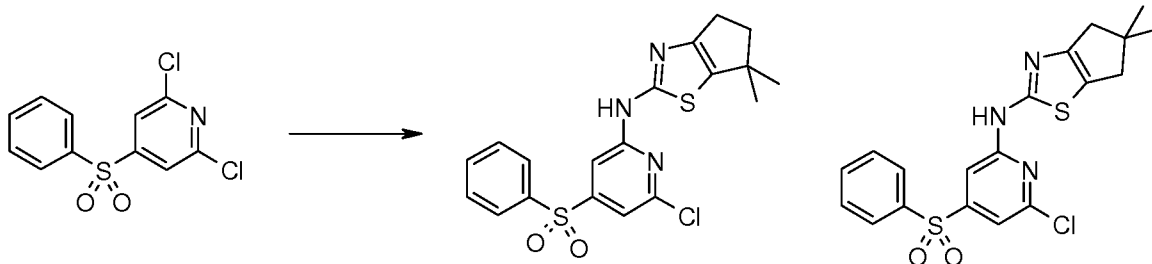
5 To a solution of 2,6-dichloro-4-(tetrahydro-pyran-4-sulfonyl)-pyridine (0.60 g, 2.03 mmol) and 2-amino-5-(phenyl)-pyrazole (0.39 g, 2.43 mmol) in anhydrous DMSO (9 mL) was added DIPEA (0.67 mL, 4.05 mmol). The mixture was flushed with N₂ and then heated to 120 °C in a sealed pressure tube for 2h. The mixture was subsequently heated to 100 °C for 15.5h. The temperature was then raised to 120 °C and heated at this temperature for a further 10 5h. After this the reaction mixture was heated to 150 °C for 2.5h and then at 100 °C for 17h. The mixture was finally heated to 120 °C for a further 5h. The reaction mixture was then allowed to cool down to room temperature and partitioned between EtOAc (55 mL) and saturated aq. ammonium chloride solution (65 mL). The two phases were separated and the aqueous phase extracted with EtOAc (40 mL). The combined organic extracts were washed 15 with water (30 mL) and brine (30 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography eluting with MeOH (1 – 10 %) in DCM. The material obtained was further purified by automated preparative HPLC (low pH method) to give the title compound as a white/light yellow solid (0.1 g, 10.7 %). MS: *m/z* = 418.9 (M+H)⁺.

20 **Example BT****Synthesis of 6,6-Dimethyl-5,6-dihydro-4H-cyclopentathiazol-2-ylamine and 5,5-Dimethyl-5,6-dihydro-4H-cyclopentathiazol-2-ylamine**

Prepared in an analogous manner to 6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-ylamine 25 except that tetrahydro-4H-pyran-4-one was substituted with 3,3-dimethylcyclopentane-1-one. The two isomers were not separated. MS: *m/z* = 169.0 (M + H)⁺.

Example BU

Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(6,6-dimethyl-5,6-dihydro-4H-cyclopenta thiazol-2-yl)-amine and (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5,5-dimethyl-5,6-dihydro-4H-cyclopentathiazol-2-yl)-amine



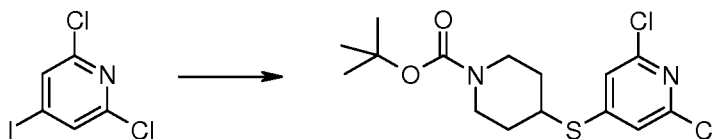
5

A mixture of 4-(benzenesulfonyl)-2,6-dichloropyridine (690 mg, 2.40 mmol), 6,6-Dimethyl-5,6-dihydro-4H-cyclopentathiazol-2-ylamine and 5,5-Dimethyl-5,6-dihydro-4H-cyclopentathiazol-2-ylamine (483 mg, 2.87 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (139 mg, 0.239 mmol), and sodium carbonate (355 mg, 3.35 mmol) in 1,4-dioxane (6 mL) was sonicated under a flow of nitrogen for 5 minutes before tris(dibenzylideneacetone)dipalladium (0) (110 mg, 0.12 mmol) was added and the mixture heated at 100 °C in a sealed tube for 4 h. The mixture was cooled, filtered through Celite and the pad washed with EtOAc. After evaporation of solvent, the orange oil was purified by flash chromatography, eluting with EtOAc (0 - 50%) in heptane to afford a mixture of the title compounds as a yellow solid (500 mg, 75% purity, 37 %). MS: $m/z = 420.0$ (M+H)⁺.

15

Example BV

Synthesis of 4-(2,6-Dichloro-pyridin-4-ylsulfanyl)-piperidine-1-carboxylic acid *tert*-butyl ester



20

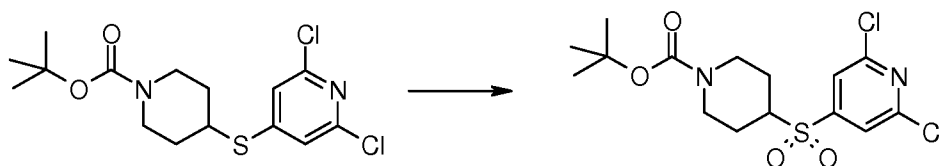
A mixture of 2,6-dichloro-4-iodopyridine (2.06 g, 7.52 mmol), *tert*-butyl 4-sulfanylpiperidine-1-carboxylate (1.8 mL, 8.27 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (0.44 g, 0.75 mmol) and DIPEA (2.5 mL, 15.04 mmol) in anhydrous Dioxane (20 mL) was flushed with nitrogen for 5 minutes before Pd₂(dba)₃ (0.34 g, 0.38 mmol) was added and the resulting mixture was refluxed for 1 h. The reaction was cooled and partitioned between DCM (100 mL) and saturated aq. ammonium chloride solution (100

25

mL). The aqueous was extracted with DCM (80 mL) and the combined organics were washed with water (80 mL), brine (80 mL) and dried (hydrophobic frit). The crude material was purified by flash chromatography, eluting with EtOAc (0 – 30 %) in heptane to give the title compound as a pale yellow oil (2.37 g, 88 %). MS: m/z = 362.95 (M+H)⁺.

5 *Example BW*

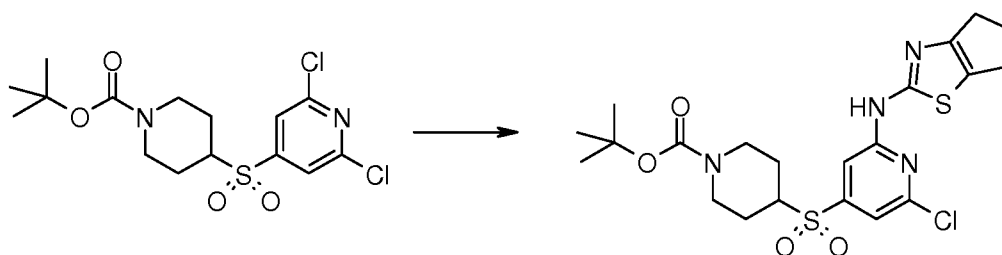
Synthesis of 4-(2,6-Dichloro-pyridine-4-sulfonyl)-piperidine-1-carboxylic acid *tert*-butyl ester



To 4-(2,6-Dichloro-pyridin-4-ylsulfanyl)-piperidine-1-carboxylic acid *tert*-butyl ester (1.94 g, 5.34 mmol) in DCM (20 mL) was added a solution of mCPBA (70%, 2.63 g, 10.68 mmol) in DCM (20 mL) dropwise and the mixture was stirred at room temperature for 1 h. The reaction was partitioned between NaOH solution (0.2 M, 25 mL) and DCM (20 mL) and the phases were separated. The organic was washed with water (15 mL) and brine (15 mL) and then again with NaOH (0.25 M, 6 x 25 mL). This was dried (MgSO₄) and concentrated and the crude material was purified by flash chromatography, eluting with EtOAc (0 - 30 %) in heptane to give the title compound as a white solid (1.75 g, 83 %). MS: m/z = 338.9 (M+H-tBu)⁺.

Example BX

Synthesis of 4-[2-Chloro-6-(5,6-dihydro-4H-cyclopentathiazol-2-ylamino)-pyridine-4-sulfonyl]-piperidine-1-carboxylic acid *tert*-butyl ester

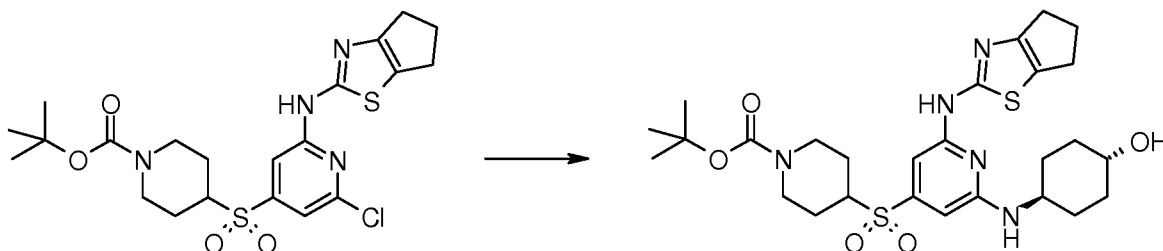


Prepared in an analogous manner to 4-[2-Chloro-6-(6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-ylamino)-pyridine-4-sulfonyl]-4-methyl-piperidine-1-carboxylic acid *tert*-butyl ester except that 6,6-Dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-ylamine was

substituted with 5,6-Dihydro-4*H*-cyclopentathiazol-2-ylamine and the chromatography eluent was EtOAc (0 – 100 %) in heptane. MS: m/z = 499.0 (M + H)⁺.

Example BY

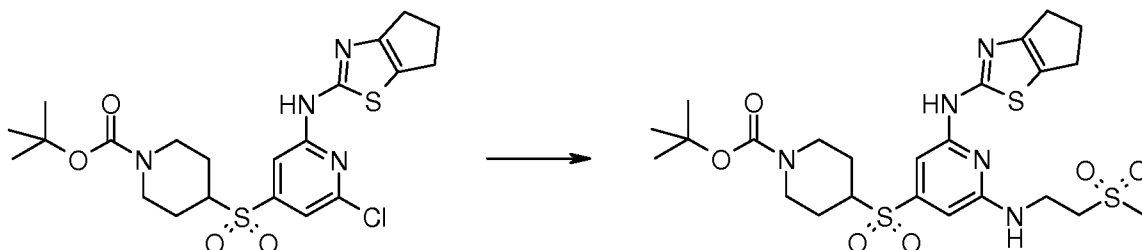
Synthesis of *tert*-butyl 4-[2-({4*H*,5*H*,6*H*-cyclopenta[*d*][1,3]thiazol-2-yl}amino)-6- 5 {[(*trans*)-4-hydroxycyclohexyl]amino}pyridine-4-sulfonyl]piperidine-1-carboxylate



A mixture of 4-[2-Chloro-6-(5,6-dihydro-4*H*-cyclopentathiazol-2-ylamino)-pyridine-4-sulfonyl]-piperidine-1-carboxylic acid *tert*-butyl ester (200 mg, 0.401 mmol), *trans*-4-aminocyclohexanol (138 mg, 1.20 mmol), BINAP (37 mg, 0.06 mmol) and sodium *tert*-butoxide (193 mg, 2.00 mmol) in DME (2.5 mL) was sonicated under a flow of nitrogen for 10 min before tris(dibenzylideneacetone)dipalladium (0) (18 mg, 0.002 mmol) was added and the reaction heated at 85 °C in a pressure tube for 20h. The reaction was cooled, filtered through a pad of Celite and the pad washed with EtOAc. After evaporation of solvent, the crude material was purified by flash chromatography, eluting with EtOAc (40 - 100 %) in heptane to afford the title compound as a yellow solid (100 mg, 43 %). MS: m/z = 578.2 (M+H)⁺.

Example BZ

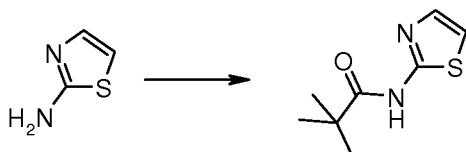
Synthesis of 4-[2-(5,6-Dihydro-4*H*-cyclopentathiazol-2-ylamino)-6-(2-methanesulfonyl-ethylamino)-pyridine-4-sulfonyl]-piperidine-1-carboxylic acid *tert*-butyl ester



Prepared in an analogous manner to 4-[2-(5,6-Dihydro-4*H*-cyclopentathiazol-2-ylamino)-6-(4-hydroxy-cyclohexylamino)-pyridine-4-sulfonyl]-piperidine-1-carboxylic acid *tert*-butyl ester except that *trans*-4-aminocyclohexanol was substituted with 2-Methanesulfonyl-ethylamine hydrochloride and 6 equivalents of sodium *tert*-butoxide were used. MS: $m/z = 586.2$ ($M + H$)⁺.

Example CA

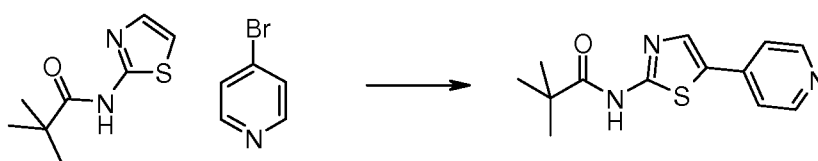
Synthesis of 2,2-Dimethyl-N-thiazol-2-yl-propionamide



To a stirred suspension of 2-aminothiazole (5 g, 49.9 mmol) in DCM (100 mL) at 0 °C was added triethylamine (8.3 mL, 59.9 mmol) followed by 2,2-Dimethyl-propionyl chloride (7.38 mL, 59.9 mmol). The mixture was stirred at room temperature for 30 min and then diluted with DCM (100 mL) and water (100 mL). The phases were separated and the aqueous phase extracted with DCM (2 x 100 mL). The combined organic phases were washed with water (60 mL) and brine (60 mL), and then dried (MgSO₄). Evaporation of the solvent afforded the title compound as a pale yellow solid, which was used without purification (9.2 g). MS: $m/z = 184.9$ ($M + H$)⁺.

Example CB

Synthesis of 2,2-Dimethyl-N-(5-pyridin-4-yl-thiazol-2-yl)-propionamide

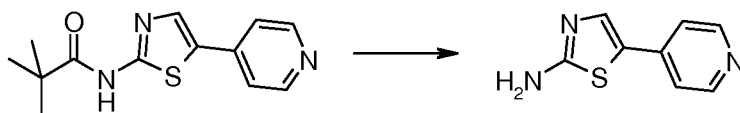


A mixture of 2,2-Dimethyl-N-thiazol-2-yl-propionamide (2.27 g, 12.34 mmol), 4-bromopyridine hydrochloride (2 g, 10.3 mmol), potassium acetate (3 g, 30.9 mmol) and tetrakis (triphenylphosphine)palladium (0) (594 mg, 0.514 mmol) in anhydrous DMA (16 mL) was heated in a sealed tube at 150 °C for 22h. The reaction was cooled and partitioned between EtOAc (100 mL) and water (60 mL). The phases were separated and the aqueous phase extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with water (40 mL) and brine (40 mL), and then dried (MgSO₄). After evaporation of the solvent, the crude was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane

followed by MeOH (0 – 10%) in EtOAc. The material was then passed through an Isololute SCX-2 column, eluting with 7N ammonia in MeOH to afford the title compound (1.25 g, 47 %). MS: $m/z = 262.0$ ($M+H$)⁺.

Example CC

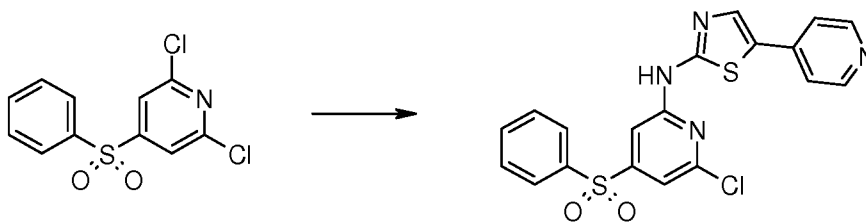
5 Synthesis of 5-Pyridin-4-yl-thiazol-2-ylamine



A solution of 2,2-Dimethyl-N-(5-pyridin-4-yl-thiazol-2-yl)-propionamide (1.25 g, 4.78 mol) in 3M hydrochloric acid (40 mL) was refluxed for 4h, cooled to room temperature, and then the solvent evaporated. The residue was partitioned between DCM (150 mL) and saturated aq. sodium bicarbonate (100 mL), and vigorously stirred for 2 min. The aqueous phase was extracted with a 5:1 mixture of DCM: MeOH (2 x 60 mL), and the combined organic phases washed with water (50 mL), brine (50 mL) and then dried (MgSO₄). Evaporation of the solvent afforded the title compound as a white solid, which was used without purification (594 mg, 70 %). ¹H NMR (500 MHz, DMSO-d₆) δ 8.43 (d, $J = 6.0$, 2H), 7.76 (s, 1H), 7.51 (s, 2H), 7.37 (d, $J = 6.1$, 2H).

Example CD

Synthesis of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-pyridin-4-yl-thiazol-2-yl)-amine

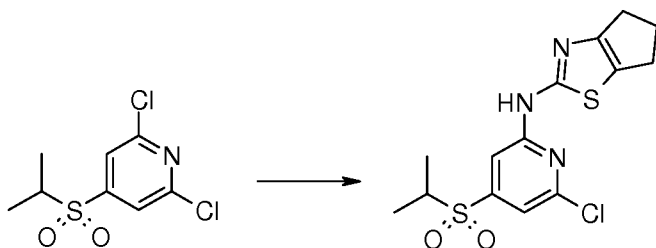


A mixture of 4-Benzenesulfonyl-2,6-dichloro-pyridine (800 mg, 2.776 mmol), 5-Pyridin-4-yl-thiazol-2-ylamine (590 mg, 3.332 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (161 mg, 0.278 mmol) and sodium carbonate (412 mg, 3.887 mmol) in anhydrous 1,4-Dioxane (18 ml) was sonicated under a flow of nitrogen for 5 min. before tris (dibenzylideneacetone) dipalladium (0) (127 mg, 0.139 mmol) was added and the reaction was heated at 100 °C in a sealed tube for 1.5 h. The reaction mixture was filtered through a pad of Celite, washed with DCM: MeOH (4: 1, 500 mL) and concentrated to dryness. The crude material was purified by flash chromatography, eluting with EtOAc (0 – 100 %) in

heptane, followed by MeOH (0 – 20 %) in EtOAc to afford the title compound as a yellow solid (70 mg, 5.6 %). ^1H NMR (500 MHz, DMSO- d_6) δ 12.32 (s, 1H), 8.55 (d, J = 6.0, 2H), 8.22 (s, 1H), 8.06 (d, J = 7.5, 2H), 7.82 (t, J = 7.4, 1H), 7.72 (t, J = 7.8, 2H), 7.61 – 7.55 (m, 3H), 7.51 (s, 1H).

5 **Example CE**

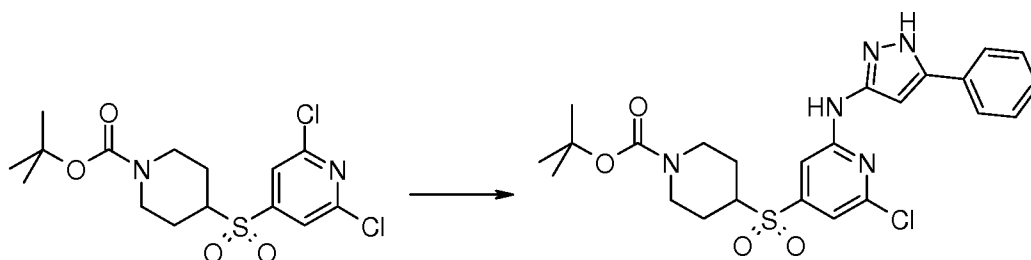
Synthesis of [6-Chloro-4-(propane-2-sulfonyl)-pyridin-2-yl]-(5,6-dihydro-4H-cyclopentathiazol-2-yl)-amine



A mixture of 2,6-Dichloro-4-(propane-2-sulfonyl)-pyridine (0.4 g, 1.57 mmol), 5,6-Dihydro-4H-cyclopentathiazol-2-ylamine (0.26 g, 1.89 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (91 mg, 0.16 mmol) and Na_2CO_3 (0.23 g, 2.2 mmol) in anhydrous 1,4-Dioxane (4 ml) was sonicated under a flow of nitrogen for 5 minutes before tris (dibenzylideneacetone) dipalladium (0) (72 mg, 0.08 mmol) was added and the reaction was heated to 100 °C for 1h. The reaction was cooled, filtered through a pad of Celite and the pad washed with EtOAc (50 mL). The filtrate was concentrated and the crude material purified by flash chromatography, eluting with EtOAc (0 - 50 %) in heptane to give the title compound as a yellow solid (128 mg, 23 %). MS: m/z = 357.95 ($\text{M}+\text{H}$) $^+$.

Example CF

Synthesis of 4-[2-Chloro-6-(5-phenyl-1H-pyrazol-3-ylamino)-pyridine-4-sulfonyl]-4-methyl-piperidine-1-carboxylic acid *tert*-butyl ester

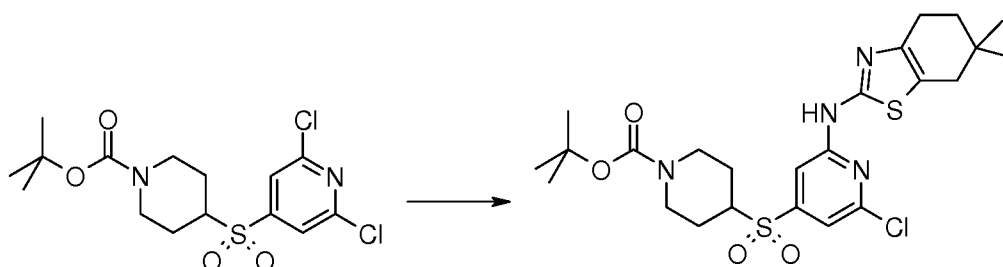


To a solution of 4-(2,6-Dichloro-pyridine-4-sulfonyl)-piperidine-1-carboxylic acid *tert*-butyl ester (600 mg, 1.52 mmol) and 3-phenyl-1H-pyrazol-5-amine (290 mg, 1.82

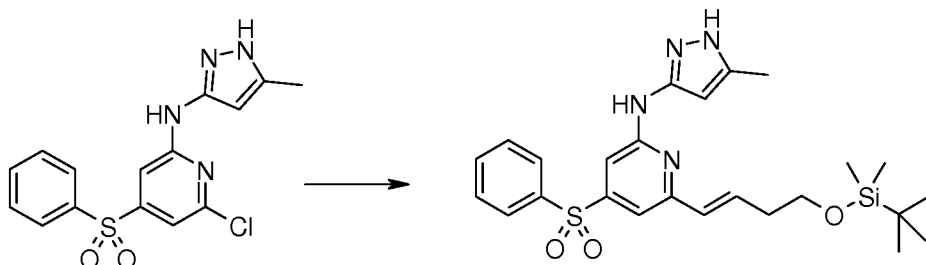
mmol) in DMSO (3 mL) was added DIPEA (0.38 ml, 2.28 mmol) and the reaction stirred at 100 °C for 24 h. The cooled reaction mixture was partitioned between EtOAc (30 mL) and water (30 mL) and the organic phase was washed with water (15 mL), brine (15 mL), dried (MgSO₄) and concentrated. The crude material was purified by flash chromatography, eluting with EtOAc (0 - 60 %) in heptane to give the title compound as a yellow solid (330 mg, 42 %). MS: m/z = 462.0 (M+H)⁺.

Example CG

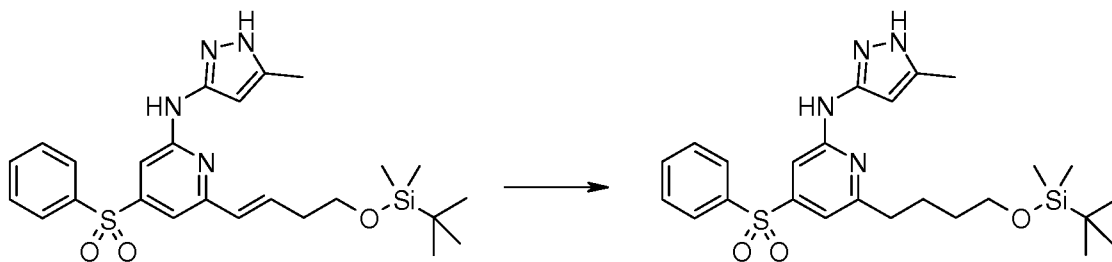
Synthesis of 4-[2-Chloro-6-(6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-ylamino)-pyridine-4-sulfonyl]-4-methyl-piperidine-1-carboxylic acid *tert*-butyl ester



A mixture of 4-(2,6-Dichloro-pyridine-4-sulfonyl)-piperidine-1-carboxylic acid *tert*-butyl ester (350 mg, 0.89 mmol), 6,6-Dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-ylamine (194 mg, 1.06 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (51 mg, 0.09 mmol) and Na₂CO₃ (131 mg, 1.24 mmol) in anhydrous 1,4-Dioxane (4 ml) was sonicated under a flow of nitrogen for 5 minutes before tris(dibenzylideneacetone)dipalladium (0) (41 mg, 0.04 mmol) was added and the reaction was heated at 100 °C for 1 h. The reaction was cooled, filtered through a pad of Celite and the pad washed with EtOAc (50 mL). The filtrate was concentrated and the crude material was purified by flash chromatography, eluting with EtOAc (0 - 50 %) in heptane to give the title compound as a yellow solid (148 mg, 31 %). MS: m/z = 541.1 (M+H)⁺.

Example CH**Synthesis of {4-Benzenesulfonyl-6-[(E)-4-(*tert*-butyl-dimethyl-silanyloxy)-but-1-enyl]-pyridin-2-yl}-(5-methyl-1*H*-pyrazol-3-yl)-amine**

5 A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1*H*-pyrazol-3-yl)-amine (200 mg, 0.573 mmol), 2-[(*E*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-but-1-enyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (197 mg, 0.631 mmol), triphenylphosphine (30 mg, 0.115 mmol), Pd(OAc)₂ and cesium carbonate (374 mg, 1.147 mmol) in acetonitrile: water (4:1) (12.5 mL) was degassed under N₂ and heated at 100 °C for 2 h. Water (5 mL) and EtOAc
 10 were added to the cooled reaction and the phases separated. The organic phase was washed with brine (5 mL), dried (Na₂SO₄), filtered and the filtrate evaporated to afford an orange oil, which was purified by flash chromatography, eluting with EtOAc: heptane (1:2) to afford the title compound as an orange foam (290 mg, 88 %). MS: *m/z* = 499.1 (M+H)⁺.

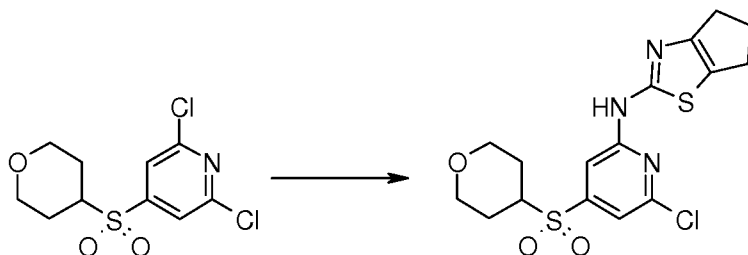
Example CI**Synthesis of {4-Benzenesulfonyl-6-[4-(*tert*-butyl-dimethyl-silanyloxy)-butyl]-pyridin-2-yl}-(5-methyl-1*H*-pyrazol-3-yl)-amine**

20 To a solution of {4-Benzenesulfonyl-6-[(*E*)-4-(*tert*-butyl-dimethyl-silanyloxy)-but-1-enyl]-pyridin-2-yl}-(5-methyl-1*H*-pyrazol-3-yl)-amine (290 mg, 0.506 mmol) in ethanol (15 mL) was added Pd/C (10 %, 30 mg). The system was degassed three times (vacuum/nitrogen) and hydrogenated at 1 atm for 2h before a further Pd/C (10 %, 30 mg) was added and the system degassed and hydrogenated at 1 atm for another 16h. The reaction was filtered

through a pad Celite and the pad washed with ethanol (30 mL). The filtrate was evaporated to afford the title compound as a green oil (238 mg, 94 %). MS: m/z = 501.1 (M+H)⁺.

Example CJ

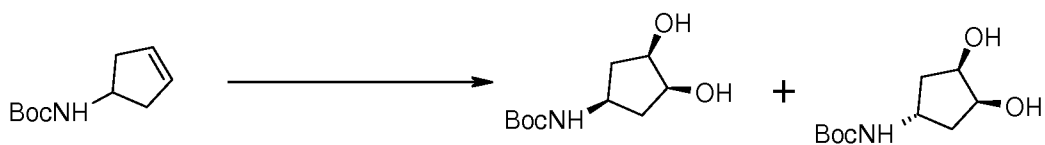
Synthesis of [6-chloro-4-(tetrahydro-pyran-4-sulfonyl)-pyridin-2-yl]-(5,6-dihydro-4H-cyclopentathiazol-2-yl)-amine, formate salt



A mixture of 2,6-dichloro-4-(tetrahydro-pyran-4-sulfonyl)-pyridine (0.44 g, 1.49 mmol), 5,6-dihydro-4H-cyclopentathiazol-2-ylamine (0.25 g, 1.79 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (0.09 g, 0.15 mmol) and Na₂CO₃ (0.22 g, 2.09 mmol) in anhydrous 1,4-dioxane (6 mL) was sonicated under a flow of nitrogen for 5 minutes before tris(dibenzylideneacetone)dipalladium (0) (0.07 g, 0.07 mmol) was added and the reaction was heated to 100 °C for 1.5h. The reaction mixture was cooled down to room temperature and the solvent evaporated *in vacuo*. The crude material was purified by flash chromatography eluting with EtOAc (12 – 100 %) in heptane. The solid obtained was further purified by automated preparative HPLC (low pH method) to give the title compound as a yellow solid (0.01 g, 2 %). MS: m/z = 399.9 (M+H)⁺.

Example CK

Synthesis of *cis* and *trans*-4-Boc-amino-*cis*-1,2-cyclopentanediol

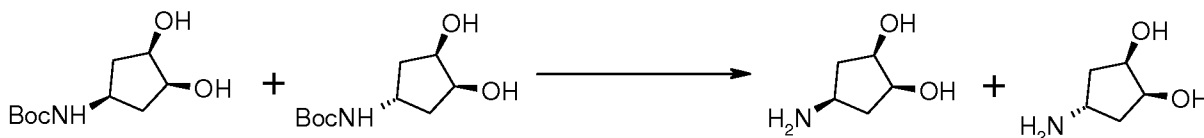


To a solution of *N*-1-Boc-amino-3-cyclopentene (1.94 g, 10.58 mmol) in a mixture of acetone (63 mL)/water (7.8 mL) (8:1) at room temperature was added *N*-methyl morpholine *N*-oxide (2.48 g, 21.16 mmol). After 2 minutes osmium tetroxide (4% in water) (3.37 mL) was added and the resulting mixture stirred at room temperature for 23h. The reaction mixture was then quenched by the addition of aqueous Na₂S₂O₃ (0.2 M, 25 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic extracts were washed with aqueous Na₂S₂O₃ (0.2 M, 10 mL), dried (MgSO₄), filtered and evaporated *in vacuo*. The crude material was purified

by flash chromatography eluting with EtOAc (17 – 100 %) in heptane to give a mixture of the title compounds as a yellow solid (1.31g, 57 %).

Example CL

Synthesis of *cis* and *trans*-4-amino-*cis*-1,2-cyclopentanediol



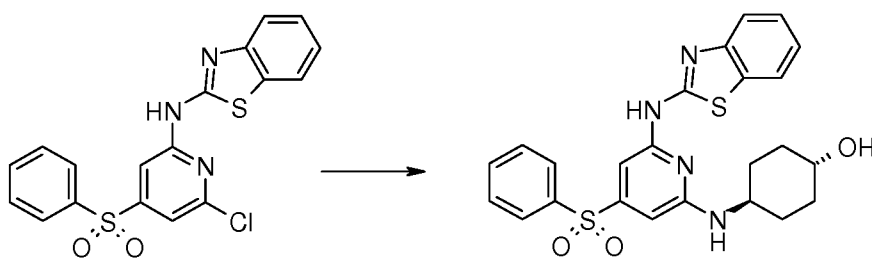
A solution of a mixture of *cis* and *trans*-4-Boc-amino-*cis*-1,2-cyclopentanediol (1.42 g, 6.54 mmol) in MeOH (62 mL) was treated with 4M HCl in dioxane (81.81 mL) and the reaction mixture stirred at room temperature for 1.5h. The volatiles were then concentrated *in vacuo*. The material obtained was then passed through an Isolute SCX-2 column to give a mixture of the title compounds as a yellow oil (0.76 g, 99 %).

PRODUCT EXAMPLES

Examples 1 through 98 are illustrative of the synthetic methods for the products.

Example 1

(*trans*)-4-[4-Benzenesulfonyl-6-(benzothiazol-2-ylamino)-pyridin-2-ylamino]-cyclohexanol

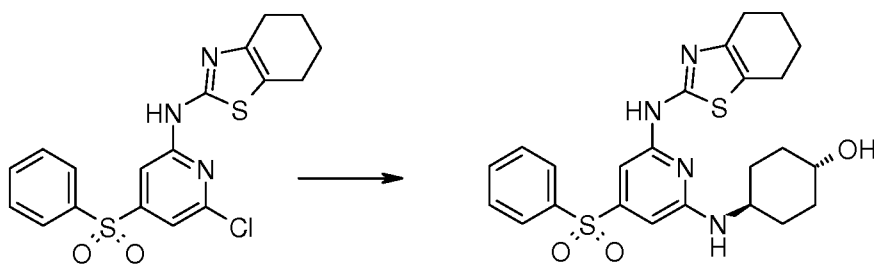


A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-benzothiazol-2-yl-amine (130 mg, 0.32 mmol) and *trans*-4-aminocyclohexanol (110 mg, 0.97 mmol) in DMSO (1.5 mL) was heated at 150 °C in the microwave for 45 min. The reaction mixture was passed through an Isolute SCX-2 column, eluting with 7N ammonia in MeOH. The crude material was purified by flash chromatography, eluting with EtOAc (20 - 60 %) in heptane to give the title compound as a yellow solid (30 mg, 19 %). ¹H NMR (500 MHz, DMSO-d₆) δ 11.51(br.s, 1H), 7.91 (d, J = 7.4 Hz, 2H), 7.78 (dd, J = 14.5, 7.4 Hz, 2H), 7.69 (t, J = 7.7 Hz, 2H), 7.63 (d, J = 7.9 Hz, 1H), 7.38 (t, J = 7.4 Hz, 1H), 7.28 (s, 1H), 7.22 (t, J = 7.5 Hz, 1H),

6.53 (s, 1H), 6.48 (s, 1H), 4.59 (d, J = 5.0 Hz, 1H), 4.02 – 3.89 (m, 1H), 3.51 – 3.41 (m, 1H), 2.06 (d, J = 10.6 Hz, 2H), 1.91 (d, J = 10.0 Hz, 2H), 1.40 (q, J = 10.3 Hz, 2H), 1.31 – 1.23 (m, 2H). MS: m/z = 481.1 (M + H)⁺.

Example 2

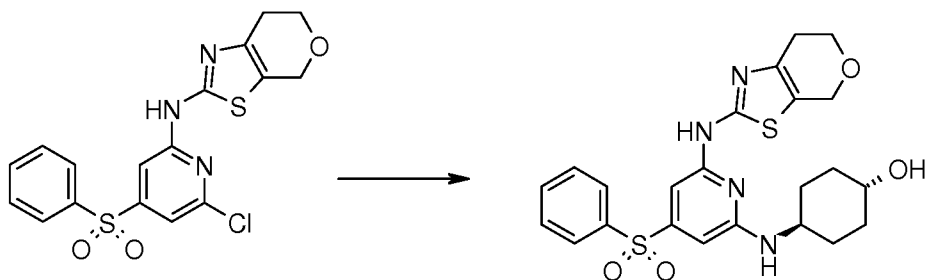
5 (trans)-4-[4-Benzenesulfonyl-6-(4,5,6,7-tetrahydro-benzothiazol-2-ylamino)-pyridin-2-ylamino]-cyclohexanol



A mixture of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-(4,5,6,7-tetrahydro-benzothiazol-2-yl)-amine (77 mg, 0.19 mmol), *trans*-4-aminocyclohexanol (218 mg, 1.9 mmol) and DIPEA (0.31 mL, 1.9 mmol) in DMSO (3 mL) was heated to 120 °C for 7h. The reaction was cooled and partitioned between EtOAc and water and the aqueous extracted twice. The combined organics were washed with water, brine, water, brine and then dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (50 - 100 %) in heptane to give the title compound as a yellow-green solid (31 mg, 32 %). ¹H NMR (500 MHz, CDCl₃) δ 7.96 (d, J = 7.8 Hz, 2H), 7.68 – 7.61 (m, 1H), 7.60 – 7.52 (m, 2H), 6.37 (s, 1H), 6.34 (s, 1H), 4.54 (d, 1H), 3.97 – 3.89 (m, 1H), 3.76 – 3.67 (m, 1H), 3.52 (s, 1H), 2.73 – 2.67 (m, 2H), 2.66 – 2.60 (m, 2H), 2.26 – 2.17 (m, 2H), 2.11 – 2.03 (m, 2H), 1.92 – 1.82 (m, 4H), 1.51 – 1.45 (m, 2H), 1.33 – 1.24 (m, 2H). MS: m/z = 485.1 (M + H)⁺.

Example 3

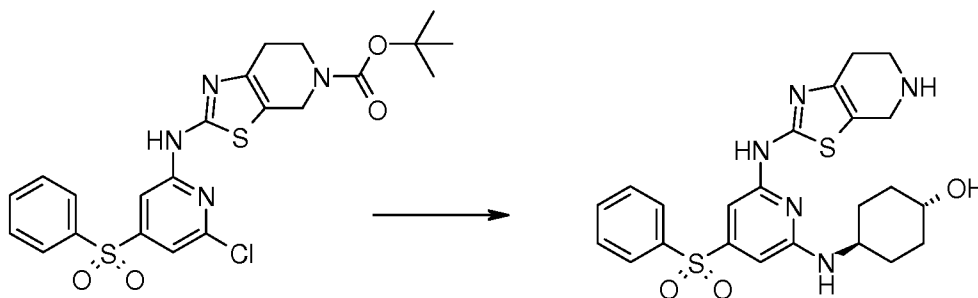
20 (trans)-4-[4-Benzenesulfonyl-6-(6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-ylamino)-pyridin-2-yl amino]-cyclohexanol



A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-yl)-amine (99 mg, 0.24 mmol) and *trans*-4-aminocyclohexanol (84 mg, 0.73 mmol) in DMSO (1 mL) was heated to 150 °C in the microwave for 45 min before more *trans*-4-aminocyclohexanol (56 mg, 0.49 mmol) was added and stirring continued in the microwave at 150 °C for another 30 min. The reaction mixture was passed through an Isolute SCX-2 column, eluting with 7N ammonia in MeOH. The crude material was purified by flash chromatography, eluting with MeOH (0 - 10 %) in DCM to give the title compound as a yellow solid (60 mg, 51%). ¹H NMR (500 MHz, DMSO-d₆) δ 11.13 (s, 1H), 7.89 (d, J = 7.4 Hz, 2H), 7.76 (t, J = 7.4 Hz, 1H), 7.72 – 7.64 (m, 2H), 7.13 (br.s, 1H), 6.43 (s, 1H), 6.36 (s, 1H), 4.67 (s, 2H), 4.55 (d, J = 4.7 Hz, 1H), 3.92 (t, J = 5.5 Hz, 2H), 3.91 – 3.78 (m, 1H), 3.47 – 3.38 (m, 1H), 2.68 – 2.59 (m, 2H), 1.98 (d, J = 11.9 Hz, 2H), 1.84 (d, J = 11.1 Hz, 2H), 1.33 – 1.11 (m, 4H). MS: *m/z* = 487.1 (M + H)⁺.

Example 4

(*trans*)-4-[4-Benzenesulfonyl-6-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-ylamino)-pyridin-2-yl amino]-cyclohexanol

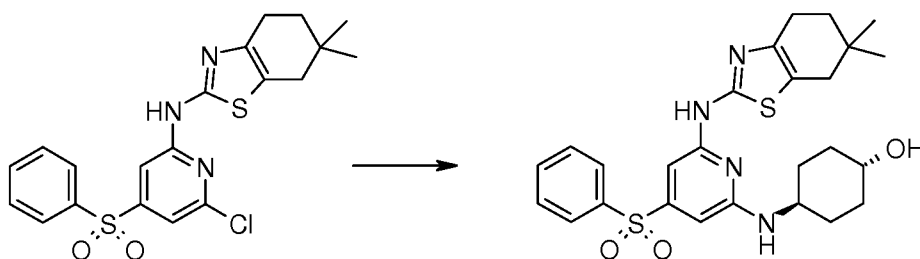


A mixture of 2-(4-Benzenesulfonyl-6-chloro-pyridin-2-ylamino)-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid *tert*-butyl ester (46 mg, 0.09 mmol) and *trans*-4-aminocyclohexanol (31 mg, 0.27 mmol) in DMSO (0.3 mL) was heated to 150 °C in the microwave for 1h before a further *trans*-4-aminocyclohexanol (21 mg, 0.18 mmol) was added and stirring continued in the microwave for 30 min. The reaction was partitioned between EtOAc and water and the aqueous re-extracted twice. The organic was washed with water, brine, water, brine, water and brine before being dried (MgSO₄) to afford 46 mg as yellow oil. This was stirred in 3 mL of HCl (4 M in dioxane) with a drop of MeOH to solubilize, overnight. The solvent was evaporated and the reaction passed through an Isolute SCX-2 column, eluting with 7 N ammonia in MeOH, then purified by flash chromatography, eluting with MeOH (0 - 20 %) in DCM followed by 7 N ammonia in MeOH (20 %) in DCM to give the title compound as a brown solid (10 mg, 23 %). ¹H NMR (500 MHz, MeOD) δ 7.88 –

7.81 (m, 2H), 7.63 – 7.56 (m, 1H), 7.54 – 7.47 (m, 2H), 6.33 (d, $J = 1.3$ Hz, 1H), 6.29 (d, $J = 1.3$ Hz, 1H), 3.95 – 3.87 (m, 1H), 3.80 (s, 2H), 3.53 – 3.45 (m, 1H), 3.01 (t, $J = 5.8$ Hz, 2H), 2.55 (t, $J = 5.7$ Hz, 2H), 2.03 (d, $J = 11.7$ Hz, 2H), 1.90 (d, $J = 11.0$ Hz, 2H), 1.36 – 1.27 (m, 2H), 1.26 – 1.16 (m, 2H). MS: $m/z = 486.4$ ($M + H$)⁺.

5 Example 5

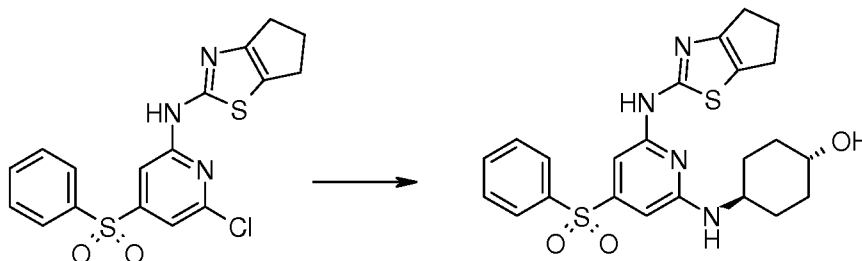
(*trans*)-4-[4-Benzenesulfonyl-6-(6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-ylamino)-pyridin-2-ylamino]-cyclohexanol



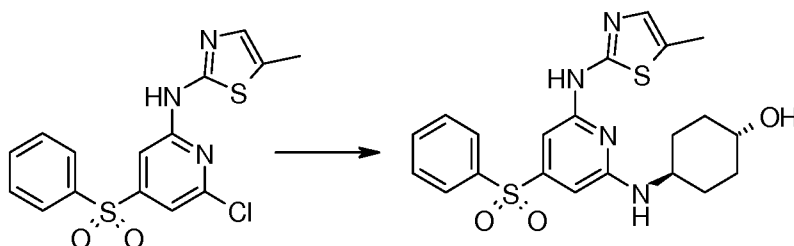
A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-yl)-amine (119 mg, 0.27 mmol), *trans*-4-aminocyclohexanol (90 mg, 0.78 mmol), BINAP (24 mg, 0.04 mmol) and sodium *tert*-butoxide (125 mg, 1.3 mmol) in DME (3mL) was sonicated under a flow of nitrogen for 20 min before tris(dibenzylideneacetone)dipalladium (0) (12 mg, 0.01 mmol) was added and the reaction heated to 85 °C in a pressure tube for 18h. The reaction was cooled and filtered through a pad of Celite, washed with EtOAc and concentrated. The residue was partitioned between EtOAc and water and the aqueous was re-extracted with EtOAc. The organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (40 - 100 %) in heptane to give the title compound as a brown solid (96 mg, 68 %). ¹H NMR (500 MHz, CDCl₃) δ 8.83 (br.s, 1H), 7.90 – 7.81 (m, 2H), 7.59 – 7.50 (m, 1H), 7.49 – 7.42 (m, 2H), 6.30 (d, $J = 0.9$ Hz, 1H), 6.23 (d, $J = 1.0$ Hz, 1H), 3.92 – 3.79 (m, 1H), 4.45 (d, $J = 7.8$ Hz, 1H), 3.69 – 3.58 (m, 1H), 2.62 – 2.54 (m, 2H), 2.39 (s, 2H), 2.14 (d, $J = 11.4$ Hz, 2H), 1.99 (d, $J = 9.9$ Hz, 2H), 1.59 – 1.55 (m, 2H), 1.46 – 1.35 (m, 2H), 1.20 (d, $J = 12.1$ Hz, 2H), 0.98 (s, 6H). MS: $m/z = 513.1$ ($M + H$)⁺.

Example 6

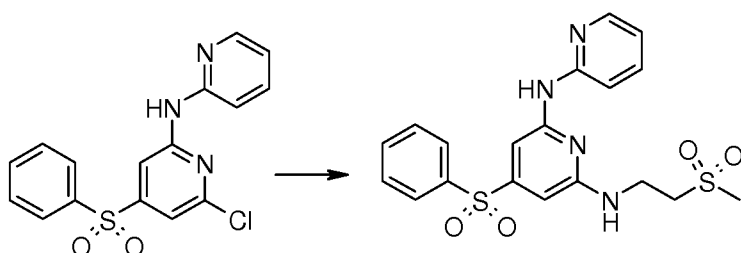
(*trans*)-4-[4-Benzenesulfonyl-6-(5,6-dihydro-4H-cyclopentathiazol-2-ylamino)-pyridin-2-ylamino]-cyclohexanol



5 A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5,6-dihydro-4H-cyclopentathiazol-2-yl)-amine (100 mg, 0.25 mmol), *trans*-4-aminocyclohexanol (87 mg, 0.76 mmol), BINAP (24 mg, 0.04 mmol) and sodium *tert*-butoxide (121 mg, 1.26 mmol) in DME (2mL) was sonicated under a flow of nitrogen for 20 min before tris(dibenzylideneacetone)dipalladium (0) (12 mg, 0.01 mmol) was added and the reaction
 10 heated to 85°C in a sealed tube for 18 h before more *trans*-4-aminocyclohexanol (44 mg, 0.38 mmol), BINAP (12 mg, 0.02 mmol) and sodium *tert*-butoxide (61 mg, 0.63 mmol) was added, followed by sonication under a flow of nitrogen and then tris(dibenzylideneacetone)dipalladium (0) (6 mg, 0.01 mmol) was added. The reaction was
 15 heated to 85 °C in a sealed tube for 2 h. The reaction mixture was cooled and filtered through a pad of Celite, washed with EtOAc and concentrated. The crude material was purified by flash chromatography, eluting with EtOAc (50 - 100 %) in heptane to give 39 mg of the title compound (88 % purity). Further purification was performed by high pH HPLC to give the
 20 title compound as a yellow solid (8 mg, 7 %). ¹H NMR (500 MHz, DMSO-d₆) δ 11.03 (s, 1H), 7.88 (d, J = 7.4 Hz, 2H), 7.76 (t, J = 7.4 Hz, 1H), 7.68 (t, J = 7.7 Hz, 2H), 7.11 (d, J = 6.7 Hz, 1H), 6.44 (s, 1H), 6.34 (s, 1H), 4.60 (d, J = 4.3Hz, 1H), 3.95 – 3.76 (m, 1H), 3.50 – 3.39 (m, 1H), 2.84 – 2.75 (m, 2H), 2.69 – 2.58 (m, 2H), 2.42 – 2.28 (m, 2H), 2.06 – 1.90 (m, 2H), 1.89 – 1.79 (m, 2H), 1.35 – 1.12 (m, 4H). MS: *m/z* = 571.1 (M + H)⁺.

Example 7**(*trans*)-4-[4-Benzenesulfonyl-6-(5-methyl-thiazol-2-ylamino)-pyridin-2-ylamino]cyclohexanol**

- 5 A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-thiazol-2-yl)-amine (75 mg, 0.2 mmol), *trans*-4-aminocyclohexanol (71 mg, 0.61 mmol), BINAP (19 mg, 0.03 mmol) and sodium *tert*-butoxide (99 mg, 1.02 mmol) in DME (2mL) was sonicated under a flow of nitrogen for 20 min before tris(dibenzylideneacetone)dipalladium(0) (9 mg, 0.01 mmol) was added and the resulting mixture was heated to 85°C in a sealed tube for 18h.
- 10 The reaction mixture was cooled and filtered through a pad of Celite, washed with EtOAc and concentrated. The crude material was purified by flash chromatography, eluting with MeOH (0 - 10 %) in DCM to give the title compound as a yellow/brown solid (33 mg, 35 %). ¹H NMR (500 MHz, CDCl₃) δ 10.03 (br.s, 1H), 7.97 (d, J = 7.5 Hz, 2H), 7.64 (t, J = 7.4 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.07 (s, 1H), 6.47 (s, 1H), 6.35 (s, 1H), 4.57 (d, J = 7.7 Hz, 1H), 3.96 (br.s, 1H), 3.81 – 3.66 (m, 1H), 2.43 (s, 3H), 2.24 (d, J = 12.0 Hz, 2H), 2.09 (d, 2H), 1.54 – 1.44 (m, 2H), 1.38 – 1.21 (m, 2H). MS: *m/z* = 445.0 (M + H)⁺.
- 15

Example 8**4-Benzenesulfonyl-N-(2-methanesulfonyl-ethyl)-N'-pyridin-2-yl-pyridine-2,6-diamine**

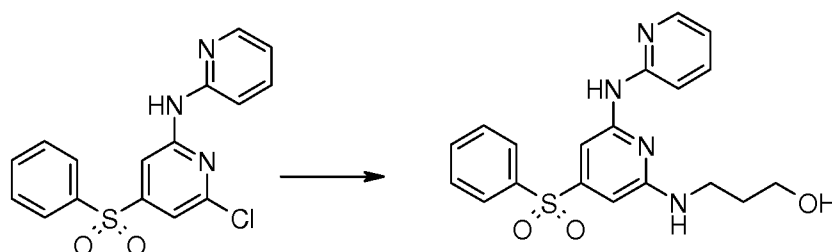
20

A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-pyridin-2-yl-amine (350 mg, 1.01 mmol), 2-methanesulfonylethan-1-amine (623 mg, 5.06 mmol) and DIPEA (0.8 mL, 5.06 mmol) in DMSO (2 mL) was heated to 120°C in a pressure tube for 2h before the temperature was raised to 150°C for 6 h. The reaction was cooled and partitioned between

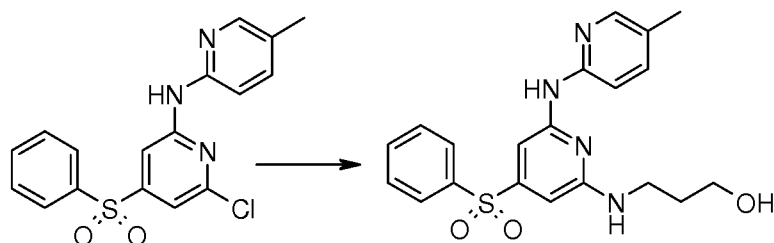
EtOAc and saturated aq. ammonium chloride solution and the aqueous re-extracted with EtOAc. The combined organics were washed with water, then brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane to give the title compound as a yellow solid (81 mg, 18 %). ¹H NMR (500 MHz, CDCl₃) δ 8.20 (d, J=4.9, 1H), 7.91 (d, J=7.4, 2H), 7.60 – 7.52 (m, 2H), 7.52 – 7.45 (m, 2H), 7.45 – 7.37 (m, 1H), 7.16 (s, 1H), 6.86 – 6.80 (m, 1H), 6.39 (s, 1H), 5.14 – 5.04 (m, 1H), 3.89 (q, J=6.1, 2H), 3.33 – 3.24 (m, 2H), 2.87 (s, 3H). MS: *m/z* = 433.0 (M + H)⁺.

Example 9

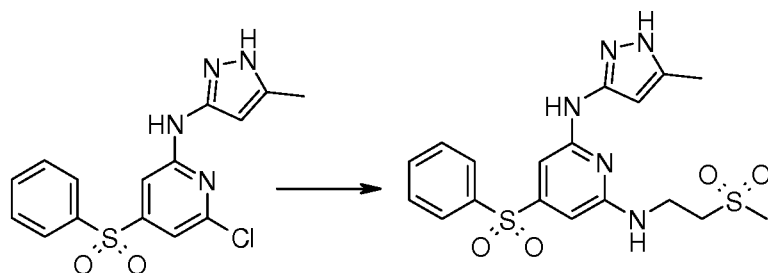
3-[4-Benzenesulfonyl-6-(pyridin-2-ylamino)-pyridin-2-ylamino]-propan-1-ol



A mixture of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-pyridin-2-yl-amine (180 mg, 0.52 mmol), 3-aminopropan-1-ol (195 mg, 2.6 mmol) and DIPEA (0.5 mL, 2.87 mmol) in DMSO (1 mL) was heated to 120°C in a pressure tube for 4h. The reaction was cooled and partitioned between EtOAc and saturated ammonium chloride. The phases were separated and the aqueous re-extracted with EtOAc. The combined organics were washed with water, then brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane to give the title compound as a yellow solid (146 mg, 73 %). ¹H NMR (500 MHz, CDCl₃) δ 8.23 – 8.14 (m, 1H), 7.95 – 7.86 (m, 2H), 7.59 – 7.43 (m, 4H), 7.43 – 7.37 (m, 1H), 7.12 – 7.06 (m, 1H), 6.85 – 6.74 (m, 1H), 6.39 – 6.32 (m, 1H), 4.99 – 4.86 (m, 1H), 3.73 – 3.58 (m, 2H), 3.50 – 3.35 (m, 2H), 2.23 (br.s, 1H), 1.82 – 1.72 (m, 2H). MS: *m/z* = 385.1 (M + H)⁺.

Example 10**3-[4-Benzenesulfonyl-6-(5-methyl-pyridin-2-ylamino)-pyridin-2-ylamino]-propan-1-ol**

- 5 A mixture of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-pyridin-2-yl)-amine (235 mg, 0.65 mmol), 3-aminopropan-1-ol (245 mg, 3.27 mmol) and DIPEA (0.5 mL, 3.27 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube for 7h. The reaction was cooled and partitioned between EtOAc and ammonium chloride and the aqueous re-extracted. The combined organics were washed with water, then brine and dried (MgSO₄)
- 10 The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane to give the title compound as a yellow solid (142 mg, 55 %). ¹H NMR (500 MHz, CDCl₃) δ 8.01 (s, 1H), 7.94 – 7.84 (m, 2H), 7.59 – 7.50 (m, 1H), 7.50 – 7.43 (m, 2H), 7.39 – 7.29 (m, 2H), 7.13 (s, 1H), 7.04 – 6.95 (m, 1H), 6.37 – 6.27 (m, 1H), 4.98 – 4.78 (m, 1H), 3.72 – 3.59 (m, 2H), 3.49 – 3.37 (m, 2H), 2.19 (s, 3H), 1.83 – 1.71 (m, 2H). MS: *m/z* = 399.0
- 15 (M + H)⁺.

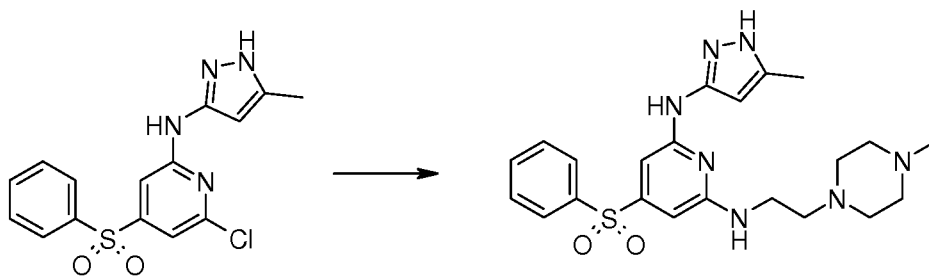
Example 11**4-Benzenesulfonyl-N-(2-methanesulfonyl-ethyl)-N'-(5-methyl-1H-pyrazol-3-yl)-pyridine-2,6-diamine**

- 20 A mixture of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (200 mg, 0.57 mmol), 2-methanesulfonyl-ethan-1-amine hydrochloride (458 mg, 2.87 mmol) and DIPEA (0.5 mL, 2.87 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube for 9h before more 2-methanesulfonyl-ethan-1-amine (302 mg, 1.89 mmol) and DIPEA (0.3 mL, 1.89 mmol) was added and stirring continued for 18h. The reaction was cooled and

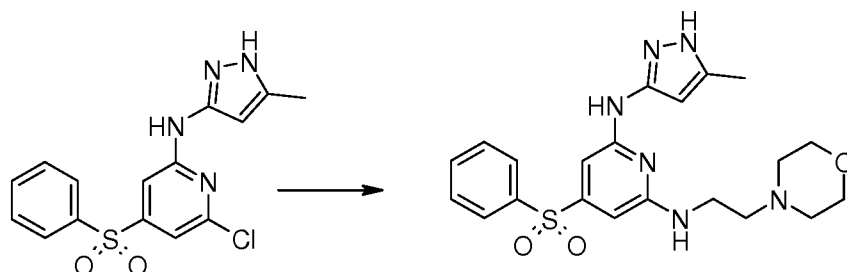
partitioned between EtOAc and saturated aq. ammonium chloride solution. The phases were separated, the aqueous re-extracted with EtOAc and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) followed by MeOH (0 - 10 %) in EtOAc to give the title compound (55 mg, 42 % purity) as a yellow oil, which was further purified by automated reverse phase HPLC (high pH method) to give the title compound as a yellow gummy solid (15 mg, 6%). ¹H NMR (500 MHz, MeOD) δ 7.98 – 7.93 (m, 2H), 7.71 – 7.67 (m, 1H), 7.66 – 7.58 (m, 2H), 6.67 (br.s, 1H), 6.33 (s, 1H), 6.18 (br.s, 1H), 3.84 (t, *J* = 6.8 Hz, 2H), 3.42 (t, *J* = 6.8 Hz, 2H), 2.97 (s, 3H), 2.28 (br.s, 3H). MS: *m/z* = 436.0 (M + H)⁺.

Example 12

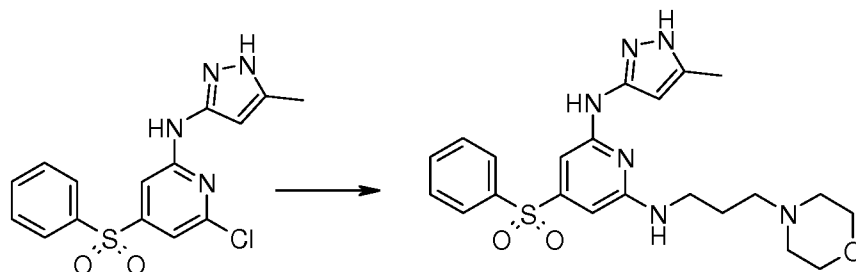
4-Benzenesulfonyl-N-[2-(4-methylpiperazin-1-yl)-ethyl]-N'-(5-methyl-1H-pyrazol-3-yl)-pyridine-2,6-diamine



A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (200 mg, 0.57 mmol), 2-(4-methylpiperazin-1-yl)ethan-1-amine (411 mg, 2.87 mmol) and DIPEA (0.5 mL, 2.87 mmol) in DMSO (1 mL) was heated to 120°C in a pressure tube for 11h before a further 2-(4-methylpiperazin-1-yl)ethan-1-amine (411 mg, 2.87 mmol) and DIPEA (0.5 mL, 2.87 mmol) was added and stirring continued for 2 h. The reaction was cooled and partitioned between EtOAc and saturated ammonium chloride soln. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane, followed by MeOH (0 - 10 %) in EtOAc and finally 7 N ammonia in MeOH (20 %) in DCM affording the title compound as a yellow solid (150 mg, 54 %). ¹H NMR (500 MHz, CDCl₃) δ 7.91 – 7.84 (m, 2H), 7.56 – 7.48 (m, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 6.79 (s, 1H), 6.62 (br.s, 1H), 6.24 (d, *J* = 1.1 Hz, 1H), 5.83 (br.s, 1H), 5.26 (br.s, 1H), 3.33 – 3.24 (m, 2H), 2.59 – 2.49 (m, 2H), 2.42 (br.s, 8H), 2.24 (s, 3H), 2.22 (s, 3H). MS: *m/z* = 456.2 (M + H)⁺.

Example 13**4-Benzenesulfonyl-N-(5-methyl-1H-pyrazol-3-yl)-N'-(2-morpholin-4-yl-ethyl)-pyridine-2,6-diamine**

5 A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (200 mg, 0.57 mmol), 2-(morpholin-4-yl)ethan-1-amine (373 mg, 2.87 mmol) and DIPEA (0.5 mL, 2.87 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube for 11h before further 2-(morpholin-4-yl)ethan-1-amine (373 mg, 2.87 mmol) and DIPEA (0.3 mL, 1.89 mmol) was added and stirring continued for 2h. The reaction was cooled and
 10 partitioned between EtOAc and saturated ammonium chloride soln. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane followed by MeOH (0 - 15 %) in EtOAc to give the title compound as a yellow solid (54 mg, 61 %). ¹H NMR (500 MHz, CDCl₃) δ 7.90 – 7.84 (m, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 6.77 (br.s, 1H), 6.64 (br.s, 1H), 6.25 (d, *J* = 1.1 Hz, 1H), 5.83 (br.s, 1H), 5.21 (br.s, 1H), 3.70 – 3.62 (m, 4H), 3.35 – 3.25 (m, 2H), 2.54 (t, *J* = 5.9 Hz, 2H), 2.45 – 2.35 (m, 4H), 2.22 (s, 3H). MS: *m/z* = 443.1 (M + H)⁺.

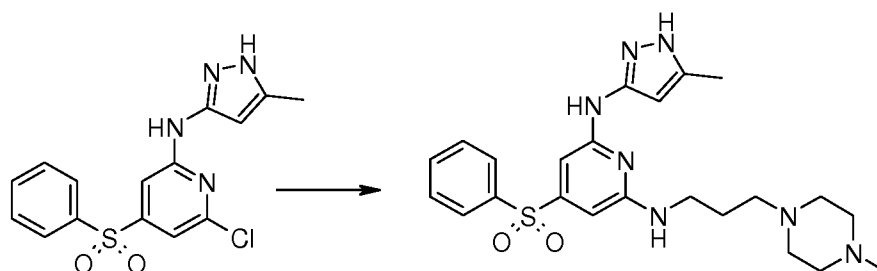
Example 14**4-Benzenesulfonyl-N-(5-methyl-1H-pyrazol-3-yl)-N'-(3-morpholin-4-yl-propyl)-pyridine-2,6-diamine**

A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (200 mg, 0.57 mmol), 3-(morpholin-4-yl)propan-1-amine (410 mg, 2.87 mmol) and

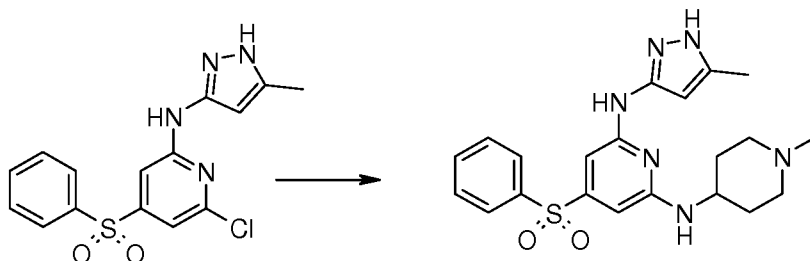
DIPEA (0.5 mL, 2.87 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube for 9h. The reaction was cooled and partitioned between EtOAc and saturated ammonium chloride soln. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with MeOH (0 - 10 %) in DCM, followed by 7 N ammonia in MeOH (20 %) in DCM and then triturated with ether to give the title compound as a yellow solid (150 mg, 54%). ¹H NMR (500 MHz, CDCl₃) δ 7.94 (d, *J* = 7.4 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 6.71 (s, 1H), 6.20 (s, 1H), 5.94 (s, 1H), 3.86 – 3.72 (m, 4H), 3.30 – 3.20 (m, 2H), 2.68 – 2.61 (m, 2H), 2.60 – 2.47 (m, 4H), 2.35 (s, 3H), 1.98 – 1.87 (m, 2H). MS: *m/z* = 457.1 (M + H)⁺.

Example 15

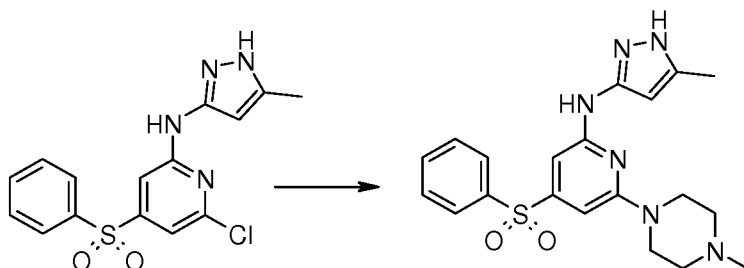
4-Benzenesulfonyl-N-[3-(4-methyl-piperazin-1-yl)-propyl]-N'-(5-methyl-1H-pyrazol-3-yl)-pyridine-2,6-diamine



A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (200 mg, 0.57 mmol), 3-(4-methylpiperazin-1-yl)propan-1-amine (450 mg, 2.87 mmol) and DIPEA (0.5 mL, 2.87 mmol) in DMSO (1 mL) was heated to 120°C in a pressure tube for 9 h. The reaction was cooled and partitioned between EtOAc and saturated aq. ammonium chloride solution. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with MeOH (0 - 10 %) in DCM, followed by 7 N ammonia in MeOH (20 %) in DCM and then triturated with ether to give the title compound as a yellow solid (110 mg, 38 %). ¹H NMR (500 MHz, CDCl₃) δ 7.94 (d, *J* = 7.4 Hz, 2H), 7.64 – 7.56(m, 1H), 7.56 – 7.47 (m, 2H), 6.70 (s, 1H), 6.20 (s, 1H), 5.90 (s, 1H), 3.30 – 3.20 (m, 2H), 2.78 – 2.44 (m, 8H), 2.39 (s, 3H), 2.35 (s, 3H), 2.02 – 1.88 (m, 2H), 1.88 – 1.72 (m, 2H). MS: *m/z* = 470.2 (M + H)⁺.

Example 16**4-Benzenesulfonyl-N-(1-methyl-piperidin-4-yl)-N'-(5-methyl-1H-pyrazol-3-yl)-pyridine-2,6-diamine**

- 5 A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (200 mg, 0.57 mmol), 1-methylpiperidin-4-amine (327 mg, 2.87 mmol) and DIPEA (0.5 mL, 2.87 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube, with a total charge of 1-methylpiperidin-4-amine (655 mg, 5.74 mmol) added periodically over 12h. The reaction was cooled and partitioned between EtOAc and saturated ammonium chloride soln.
- 10 The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with MeOH (0 - 10 %) in DCM, followed by 7N ammonia in MeOH (0 - 15 %) in DCM to give 85 mg of the title compound as a yellow solid (86 % purity), which was further purified by automated reverse phase HPLC (high pH method) to give the title compound as a white solid
- 15 (45 mg, 16 %). ¹H NMR (500 MHz, DMSO-d₆) δ 11.78 (br.s, 1H), 9.18 (br.s, 1H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.74 (t, *J* = 7.4 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 2H), 6.83 (br.s, 1H), 6.65 (br.s, 1H), 6.17 (s, 2H), 3.71 – 3.57 (m, 1H), 2.80 – 2.69 (m, 2H), 2.18 (s, 3H), 2.16 (s, 3H), 2.00 – 1.90 (m, 2H), 1.91 – 1.83 (m, 2H), 1.47 – 1.31 (m, 2H). MS: *m/z* = 427.1 (M + H)⁺.

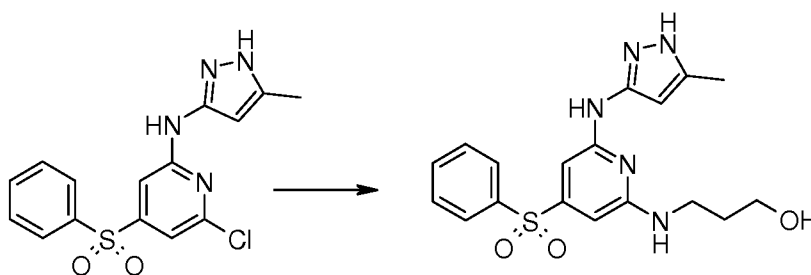
Example 17**[4-Benzenesulfonyl-6-(4-methyl-piperazin-1-yl)-pyridin-2-yl]-(5-methyl-1H-pyrazol-3-yl)-amine**

A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (200 mg, 0.57 mmol), 1-methylpiperazine (287 mg, 2.87 mmol) and DIPEA (0.5 mL, 2.87 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube for 6h. The reaction was cooled and partitioned between EtOAc and saturated aq. ammonium chloride solution.

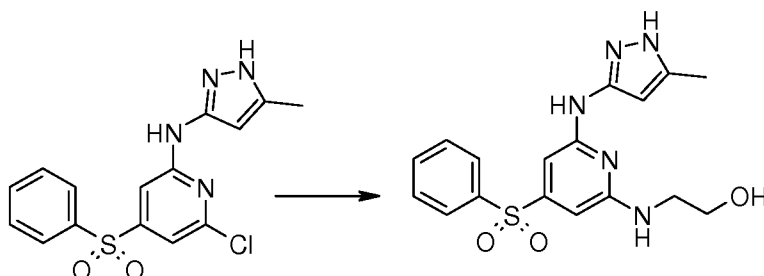
5 The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with MeOH (0 - 15 %) in DCM to give the title compound as a yellow solid (190 mg, 80 %). ¹H NMR (500 MHz, CDCl₃) δ 7.91 – 7.84 (m, 2H), 7.55 – 7.48 (m, 1H), 7.47 – 7.41 (m, 2H), 6.75 (s, 1H), 6.73 (s, 1H), 6.47 (d, *J* = 0.9 Hz, 1H), 5.85 (s, 1H), 3.56 – 3.48 (m, 4H), 2.47 – 2.37 (m, 4H), 2.27 (s, 3H), 2.23 (s, 3H). MS: *m/z* = 413.1 (M + H)⁺.

Example 18

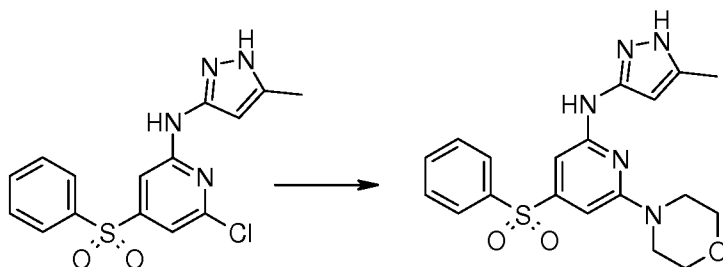
3-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-1-ol



15 A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (150 mg, 0.43 mmol), 3-aminopropan-1-ol (162 mg, 2.15 mmol) and DIPEA (0.4 mL, 2.15 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube for 6h. The reaction was cooled and partitioned between EtOAc and saturated ammonium chloride soln. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane, followed by MeOH (0 - 10 %) in EtOAc to give the title compound as a yellow solid (110 mg, 63 %). ¹H NMR (500 MHz, DMSO-d₆) δ 11.84 (s, 1H), 9.19 (s, 1H), 7.93 (d, *J* = 7.6 Hz, 2H), 7.80 (t, *J* = 7.4 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 2H), 6.87 (d, *J* = 25.0 Hz, 2H), 6.25 (s, 1H), 6.20 (br.s, 1H), 4.53 (br.s, 1H), 3.54 (d, *J* = 5.5 Hz, 2H), 3.38 – 3.29 (m, 2H), 2.24 (s, 3H), 1.77 – 1.69 (m, 2H). MS: *m/z* = 388.1 (M + H)⁺.

Example 19**2-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-ethanol**

5 A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (150 mg, 0.43 mmol), 2-aminoethan-1-ol (131 mg, 2.15 mmol) and DIPEA (0.4 mL, 2.15 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube for 3h before more 2-aminoethan-1-ol (79 mg, 1.29 mmol) was added and stirring continued for 4h. The reaction was cooled and partitioned between EtOAc and saturated ammonium chloride soln. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane, followed by MeOH (0 - 10 %) in EtOAc to give the title compound as a yellow, oily solid (120 mg, 72 %). ¹H NMR (500 MHz, CDCl₃) δ 8.07 (br.s, 1H), 7.80 – 7.74 (m, 2H), 7.48 – 7.41 (m, 1H), 7.40 – 7.31 (m, 2H), 6.58 (s, 1H), 6.15 (s, 1H), 5.73 (s, 1H), 5.11 (br.s, 1H), 3.72 – 3.63 (m, 2H), 3.37 – 3.28 (m, 2H), 2.13 (s, 3H). MS: *m/z* = 374.1 (M + H)⁺.

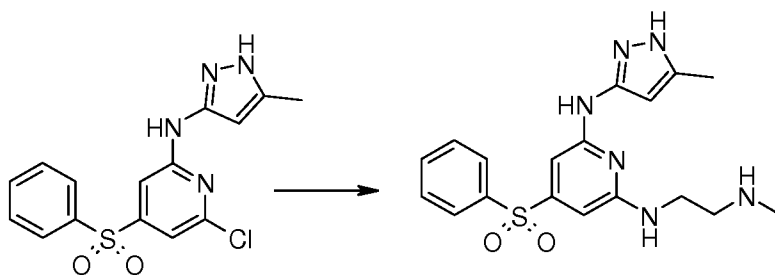
Example 20**(4-Benzenesulfonyl-6-morpholin-4-yl-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine**

20 A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (150 mg, 0.43 mmol), morpholine (187 mg, 2.15 mmol) and DIPEA (0.4 mL, 2.15 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube for 4h. The reaction was

cooled and partitioned between EtOAc and saturated aq. ammonium chloride solution. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane, followed by MeOH (0 - 10 %) in EtOAc to give the title compound as a yellow solid (90 mg, 52 %). ¹H NMR (500 MHz, CDCl₃) δ 8.00 – 7.92 (m, 2H), 7.64 – 7.58 (m, 1H), 7.57 – 7.50 (m, 2H), 6.91 (s, 1H), 6.89 (s, 1H), 6.53 (d, J = 0.9 Hz, 1H), 5.96 (s, 1H), 3.84 – 3.78 (m, 4H), 3.58 – 3.50 (m, 4H), 2.33 (s, 3H). MS: *m/z* = 400.0 (M + H)⁺.

Example 21

4-Benzenesulfonyl-N-(2-methylamino-ethyl)-N'-(5-methyl-1H-pyrazol-3-yl)-pyridine-2,6-diamine

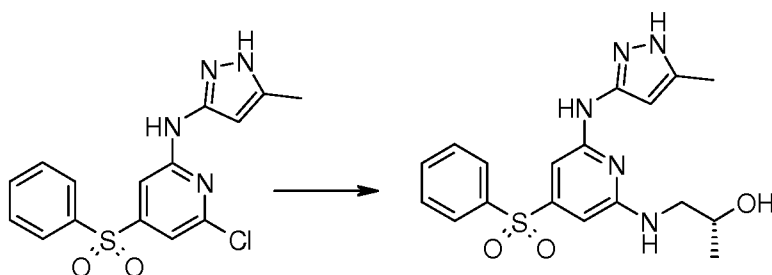


A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (200 mg, 0.57 mmol), *tert*-butyl N-(2-aminoethyl)-N-methylcarbamate (500 mg, 2.87 mmol) and DIPEA (0.5 mL, 2.87 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube, with a further total of *tert*-butyl N-(2-aminoethyl)-N-methylcarbamate (500 mg, 2.87 mmol) added periodically over 12h. The reaction was cooled and partitioned between EtOAc and saturated ammonium chloride soln. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) followed by MeOH (0 - 10 %) in EtOAc to give 125 mg of {2-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-ethyl}-methyl-carbamic acid *tert*-butyl ester as a yellow oil, which was dissolved in dioxane (1 mL) and to it added 4M HCl in dioxane (2 mL) and a drop of methanol. The solution was stirred for 2 h before the solvent was evaporated and the residue passed through an Isolute SCX-2 column, eluting with 7N ammonia in MeOH to produce crude material as a free base, which was purified by flash chromatography, eluting with MeOH (0 - 20 %) in DCM, followed by 7 N ammonia in MeOH (0 - 10 %) in DCM to give the title compound as a yellow solid (48 mg, 21 % over 2 steps). ¹H NMR (500 MHz, CDCl₃) δ 7.89 – 7.82 (m, 2H), 7.56 – 7.49 (m, 1H), 7.48 – 7.41 (m, 2H), 6.59 (br.s, 1H), 6.21 (d, J =

0.9 Hz, 1H), 5.81 (br.s, 1H), 5.31 (br.s, 1H), 3.40 – 3.33 (m, 2H), 2.82 – 2.74 (m, 2H), 2.38 (s, 3H), 2.21 (s, 3H). MS: m/z = 387.1 (M + H)⁺.

Example 22

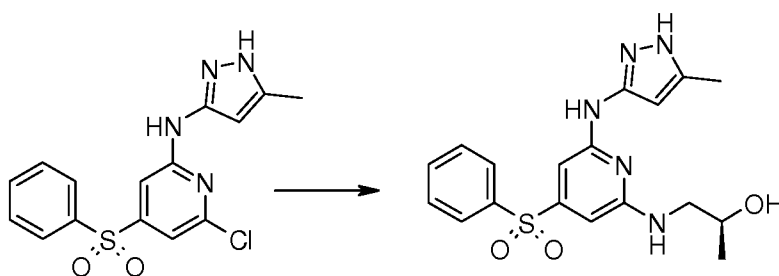
5 (R)-1-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-2-ol



A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (150 mg, 0.43 mmol), (2R)-1-aminopropan-2-ol (162 mg, 2.15 mmol) and DIPEA (0.4 mL, 2.15 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube, with a further total charge of (2R)-1-aminopropan-2-ol (355 mg, 4.73 mmol) added periodically over 13h. The reaction was cooled and partitioned between EtOAc and saturated ammonium chloride soln. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane, followed by MeOH (0 - 10 %) in EtOAc to give the title compound as a yellow oil (95 mg, 56 %). ¹H NMR (500 MHz, CDCl₃) δ 8.76 (br.s, 1H), 7.98 – 7.92 (m, 2H), 7.66 – 7.58 (m, 1H), 7.58 – 7.50 (m, 2H), 6.79 (s, 1H), 6.32 (d, J = 1.1 Hz, 1H), 5.91 (s, 1H), 5.10 (s, 1H), 4.15 – 3.96 (m, 1H), 3.44 – 3.35 (m, 2H), 2.31 (s, 3H), 1.28 (d, J = 6.3 Hz, 3H). MS: m/z = 388.1 (M + H)⁺.

20 Example 23

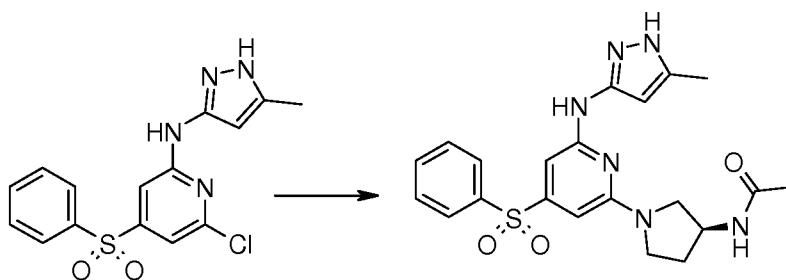
(S)-1-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-2-ol



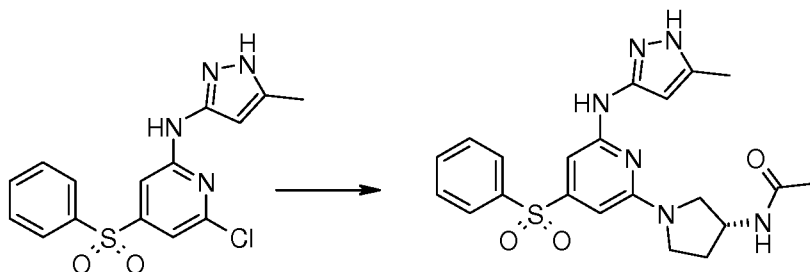
A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (150 mg, 0.43 mmol), (2*S*)-1-aminopropan-2-ol (162 mg, 2.15 mmol) and DIPEA (0.4 mL, 2.15 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube, with more (2*S*)-1-aminopropan-2-ol (258 mg, 3.44 mmol) added periodically over 13h. The reaction was cooled and partitioned between EtOAc and saturated aq. ammonium chloride solution. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane, followed by MeOH (0 - 10 %) in EtOAc to give the title compound as a yellow solid (91 mg, 54 %). ¹H NMR (500 MHz, CDCl₃) δ 8.52 (br.s, 1H), 7.80 – 7.70 (m, 2H), 7.47 – 7.39 (m, 1H), 7.39 – 7.30 (m, 2H), 6.59 (s, 1H), 6.13 (d, *J* = 1.1 Hz, 1H), 5.72 (s, 1H), 4.96 – 4.86 (m, 1H), 3.91 – 3.80 (m, 1H), 3.23 – 3.11 (m, 2H), 2.12 (s, 3H), 1.09 (d, 3H). MS: *m/z* = 388.1 (M + H)⁺.

Example 24

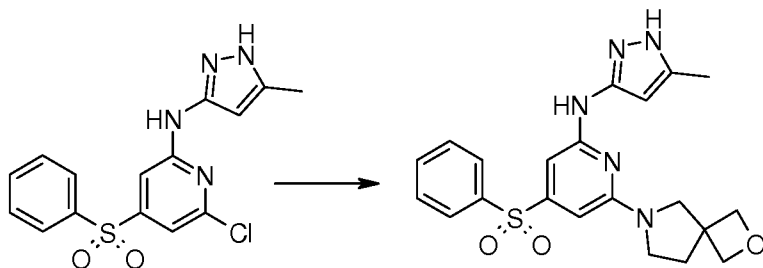
N-[(*S*)-1-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-yl]-pyrrolidin-3-yl]-acetamide



A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (180 mg, 0.52 mmol), N-[(3*S*)-pyrrolidin-3-yl]acetamide (331 mg, 2.58 mmol) and DIPEA (0.4 mL, 2.58 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube for 4h. The reaction was cooled and partitioned between EtOAc and saturated ammonium chloride soln. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was triturated with diethyl ether to give the title compound as a yellow solid (205 mg, 86 %). ¹H NMR 500 MHz, CDCl₃) δ 7.87 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.06 (br.s, 1H), 6.50 (br.s, 1H), 6.11 (s, 1H), 6.08 (br.s, 1H), 5.82 (br.s, 1H), 4.60 – 4.40 (m, 1H), 3.60 (dd, *J* = 10.8, 5.9 Hz, 1H), 3.43 (d, *J* = 7.5 Hz, 2H), 3.29 (d, *J* = 10.3 Hz, 1H), 2.21 (s, 3H), 2.20 – 2.13 (m, 1H), 1.98 – 1.86 (m, 4H). MS: *m/z* = 441.1 (M + H)⁺.

Example 25**N-[(R)-1-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-yl]-pyrrolidin-3-yl]-acetamide**

5 A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (120 mg, 0.34 mmol), N-[(3R)-pyrrolidin-3-yl]acetamide (220 mg, 1.72 mmol) and DIPEA (0.3 mL, 1.72 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube for 6h. The reaction was cooled and partitioned between EtOAc and saturated aq. ammonium chloride solution. The aqueous was re-extracted and the combined organics were washed with
 10 water, brine and dried (MgSO₄). Purification was attempted by triturating with diethyl ether but both precipitate and filtrate needed to be recombined and purified by flash chromatography, eluting with EtOAc (40 - 100 %) in heptane, followed by MeOH (0 - 10 %) in EtOAc to give the title compound as a yellow solid (62 mg, 41 %). ¹H NMR (500 MHz, CDCl₃) δ 7.88 (d, J = 7.7 Hz, 2H), 7.57 – 7.50 (m, 1H), 7.49 – 7.41 (m, 2H), 6.86 (s, 1H),
 15 6.53 (s, 1H), 6.15 (s, 1H), 5.90 – 5.74 (m, 2H), 4.53 (br.s, 1H), 3.69 – 3.57 (m, 1H), 3.53 – 3.40 (m, 2H), 3.30 (d, J = 7.7 Hz, 1H), 2.27 – 2.12 (m, 4H), 1.99 – 1.86 (m, 4H). MS: *m/z* = 441.0 (M + H)⁺.

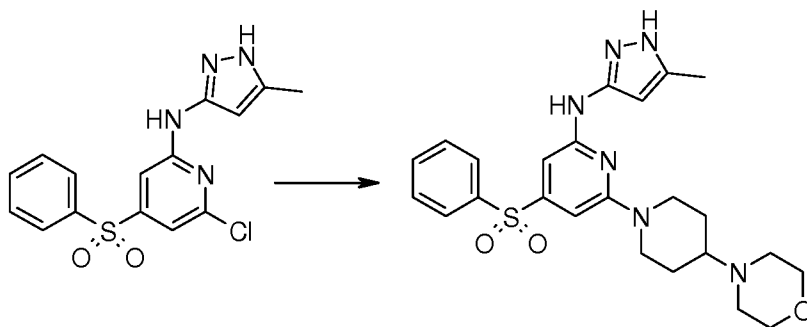
Example 26**[4-Benzenesulfonyl-6-(2-oxa-6-aza-spiro[3.4]oct-6-yl)-pyridin-2-yl]-(5-methyl-1H-pyrazol-3-yl)-amine**

A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (62 mg, 0.18 mmol), 2-oxa-6-azaspiro[3.4]octane (101 mg, 0.89 mmol) and DIPEA

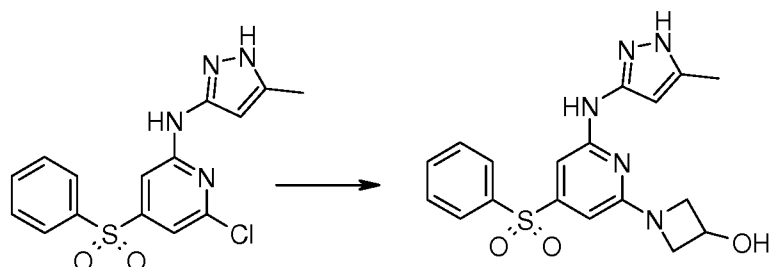
(0.1 mL, 0.82 mmol) in DMSO (0.5 mL) was heated to 120 °C in a pressure tube for 6h. The reaction was cooled and partitioned between EtOAc and saturated ammonium chloride soln. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane, followed by MeOH (0 - 10 %) in EtOAc to give the title compound as a yellow solid (40 mg, 53 %). ¹H NMR (500 MHz, CDCl₃) δ 8.01 – 7.92 (m, 2H), 7.65 – 7.58 (m, 1H), 7.57 – 7.50 (m, 2H), 6.91 (s, 1H), 6.64 (s, 1H), 6.27 (s, 1H), 5.97 (br.s, 1H), 4.73 (d, J = 6.2 Hz, 2H), 4.66 (d, J = 6.2 Hz, 2H), 3.75 (s, 2H), 3.52 (t, J = 6.7 Hz, 2H), 2.38 – 2.26 (m, 5H). MS: *m/z* = 426.1 (M + H)⁺.

Example 27

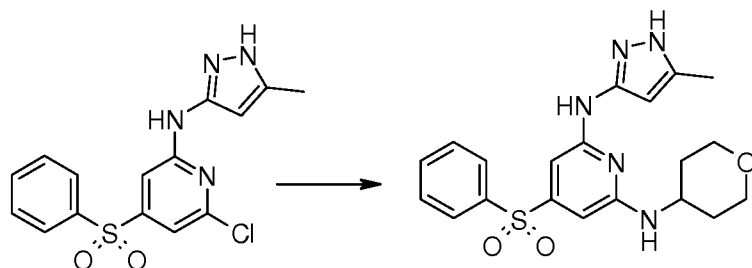
(4'-Benzenesulfonyl-4-morpholin-4-yl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl)-(5-methyl-1H-pyrazol-3-yl)-amine



A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (180 mg, 0.52 mmol), 4-(piperidin-4-yl)morpholine (439 mg, 2.58 mmol) and DIPEA (0.4 mL, 2.58 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube for 4h. The reaction was cooled and partitioned between EtOAc and saturated aq. ammonium chloride solution. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄) to give the title compound as a yellow solid (150 mg, 58 %). ¹H NMR (500 MHz, MeOD) δ 7.89 – 7.82 (m, 2H), 7.60 – 7.53 (m, 1H), 7.53 – 7.45 (m, 2H), 6.61 (br.s, 1H), 6.39 (s, 1H), 5.98 (br.s, 1H), 4.29 (d, J = 11.1 Hz, 2H), 3.63 – 3.53 (m, 4H), 2.82 – 2.69 (m, 2H), 2.52 – 2.42 (m, 4H), 2.34 (t, J = 11.3 Hz, 1H), 2.15 (s, 3H), 1.87 (d, J = 11.2 Hz, 2H), 1.41 – 1.27 (m, 2H). MS: *m/z* = 483.4 (M + H)⁺.

Example 28**1-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-yl]-azetidin-3-ol**

5 A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (200 mg, 0.57 mmol), azetidin-3-ol hydrochloride (314 mg, 2.87 mmol) and DIPEA (0.5 mL, 2.87 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube for 4h. The reaction was cooled and partitioned between EtOAc and saturated ammonium chloride soln. The aqueous was re-extracted and the combined organics were washed with water, brine and
 10 dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane, followed by MeOH (0 - 10 %) in EtOAc to give the title compound as a yellow solid (35 mg, 16%). ¹H NMR (500 MHz, CDCl₃) δ 7.92 – 7.84 (m, 2H), 7.59 – 7.51 (m, 1H), 7.51 – 7.42 (m, 2H), 6.79 (s, 1H), 6.55 (s, 1H), 6.08 (s, 1H), 5.82 (br.s, 1H), 4.76 – 4.65 (m, 1H), 4.29 – 4.16 (m, 2H), 3.84 – 3.73 (m, 2H), 2.22 (s, 3H). MS:
 15 *m/z* = 386.1 (M + H)⁺.

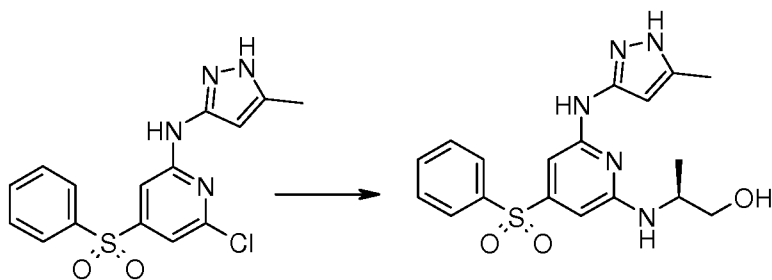
Example 29**4-Benzenesulfonyl-N-(5-methyl-1H-pyrazol-3-yl)-N'-(tetrahydro-pyran-4-yl)-pyridine-2,6-diamine**

20 A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (150 mg, 0.43 mmol), oxan-4-amine hydrochloride (296 mg, 2.15 mmol) and DIPEA (0.4 mL, 2.15 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube, with a further total of oxan-4-amine hydrochloride (533 mg, 3.87 mmol) and DIPEA (0.1 mL, 0.86 mmol)

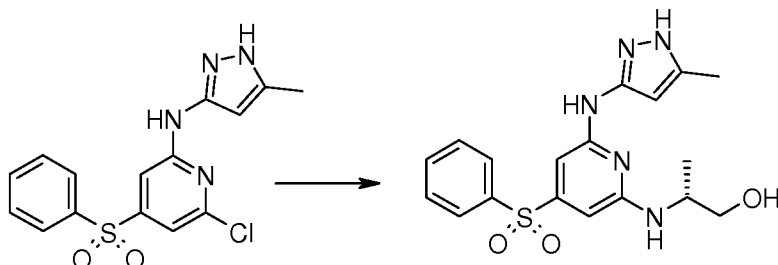
added periodically over 27h (no heating or addition overnight). The reaction was cooled and partitioned between EtOAc and saturated ammonium chloride soln. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane followed by MeOH (0 - 10 %) in EtOAc to give the title compound as a brown solid (19 mg, 11%). ¹H NMR (500 MHz, CDCl₃) δ 7.91 – 7.83 (m, 2H), 7.58 – 7.50 (m, 1H), 7.50 – 7.42 (m, 2H), 6.78 (s, 1H), 6.63 (s, 1H), 6.21 (d, J = 1.1 Hz, 1H), 5.90 (s, 1H), 4.53 (d, J = 6.9 Hz, 1H), 3.98 – 3.89 (m, 2H), 3.84 – 3.71 (m, 1H), 3.53 – 3.39 (m, 2H), 2.23 (s, 3H), 1.99 – 1.90 (m, 2H), 1.50 – 1.38 (m, 2H). MS: *m/z* = 414.1 (M + H)⁺.

Example 30

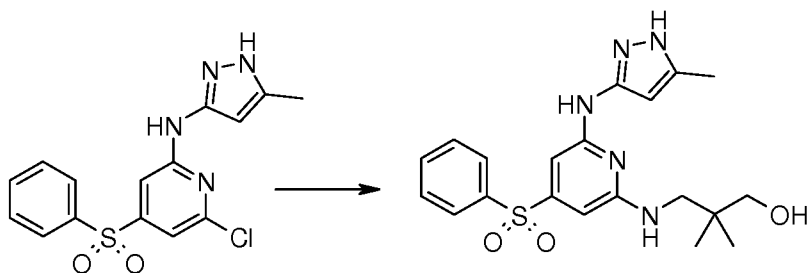
(S)-2-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-1-ol



A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (150 mg, 0.43 mmol), (2S)-2-aminopropan-1-ol (162 mg, 2.15 mmol) and DIPEA (0.4 mL, 2.15 mmol) in DMSO (1 mL) was heated to 120°C in a pressure tube, with a further total of (2S)-2-aminopropan-1-ol (194 mg, 2.58 mmol) added periodically over 10h. The reaction was cooled and partitioned between EtOAc and saturated ammonium chloride soln. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane, followed by MeOH (0 - 10 %) in EtOAc to give the title compound as a yellow solid (58 mg, 33%). ¹H NMR (500 MHz, CDCl₃) δ 8.09 (br.s, 1H), 7.89 – 7.82 (m, 2H), 7.57- 7.50 (m, 1H), 7.48 – 7.42 (m, 2H), 6.69 (s, 1H), 6.23 (d, J = 1.0 Hz, 1H), 5.82 (s, 1H), 4.57 (d, J = 5.8 Hz, 1H), 4.03- 3.91 (m, 1H), 3.75 – 3.63 (m, 1H), 3.58 – 3.47 (m, 1H), 2.23 (s, 3H), 1.15 (d, J = 6.7 Hz, 3H). MS: *m/z* = 388.1 (M + H)⁺.

Example 31**(R)-2-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-1-ol**

5 A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (150 mg, 0.43 mmol), (2R)-2-aminopropan-1-ol (162 mg, 2.15 mmol) and DIPEA (0.4 mL, 2.15 mmol) in DMSO (1 mL) was heated to 120°C in a pressure tube, with a further total of (2R)-2-aminopropan-1-ol (226 mg, 3.01 mmol) added periodically over 15 h. The reaction was cooled and partitioned between EtOAc and saturated ammonium chloride soln. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane, followed by MeOH (0 - 6 %) in EtOAc to give the title compound as a yellow solid (36 mg, 21%). ¹H NMR (500 MHz, CDCl₃) δ 8.31 (br.s, 1H), 8.13 – 8.01 (m, 2H), 7.79 – 7.72 (m, 1H), 7.72 – 7.63 (m, 2H), 6.91 (s, 1H), 6.46 (d, J = 0.9 Hz, 1H), 6.04 (s, 1H), 4.80 (d, J = 5.8 Hz, 1H), 4.27 – 4.13 (m, 1H), 3.96 – 3.88 (m, 1H), 3.81 – 3.71 (m, 1H), 2.45 (s, 3H), 1.38 (d, J = 6.7 Hz, 3H). MS: *m/z* = 388.1 (M + H)⁺.

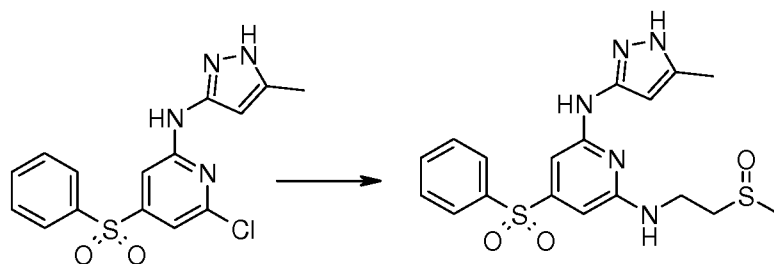
Example 32**3-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-2,2-di methyl-propan-1-ol**

20 A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (150 mg, 0.43 mmol), 3-amino-2,2-dimethylpropan-1-ol (222 mg, 2.15 mmol) and DIPEA (0.4 mL, 2.15 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube, with

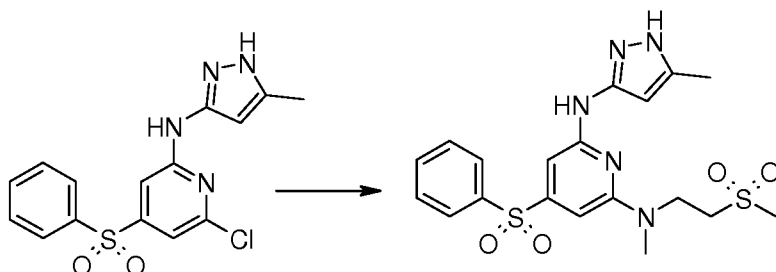
a total of 3-amino-2,2-dimethylpropan-1-ol (222 mg, 2.15 mmol) added periodically over 11h. The reaction was cooled and partitioned between EtOAc and saturated ammonium chloride soln. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane, followed by MeOH (0 - 5 %) in EtOAc to give the title compound as a white solid (84 mg, 47%). ¹H NMR (500 MHz, CDCl₃) δ 8.83 (br.s, 1H), 7.92 – 7.81 (m, 2H), 7.59 – 7.49 (m, 1H), 7.48 – 7.41 (m, 2H), 6.72 (s, 1H), 6.19 (d, J = 1.2 Hz, 1H), 5.80 (s, 1H), 4.73 – 4.61 (m, 1H), 3.19 (s, 2H), 3.16 (d, J = 6.9 Hz, 2H), 2.23 (s, 3H), 0.86 (s, 6H). MS: *m/z* = 416.1 (M + H)⁺.

Example 33

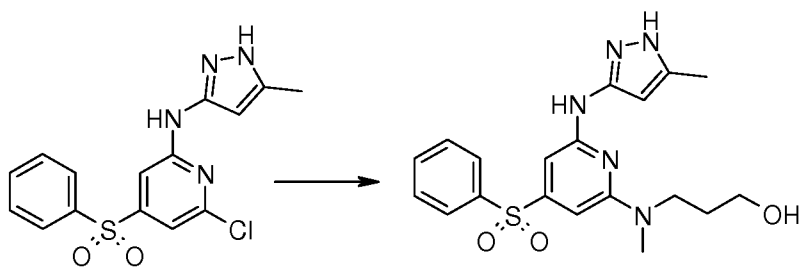
(+/-)-4-Benzenesulfonyl-N-(2-methanesulfinylethyl)-N'-(5-methyl-1H-pyrazol-3-yl)-pyridine-2,6-diamine



A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (200 mg, 0.57 mmol), (+/-)-2-methanesulfinylethan-1-amine (230 mg, 2.15 mmol) and DIPEA (0.5 mL, 2.87 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube for 6h. The reaction was cooled and partitioned between EtOAc and saturated ammonium chloride soln. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with MeOH (0 - 20%) in DCM, followed by 7 N ammonia soln. in MeOH (0 - 20 %) in DCM to give the title compound as a yellow solid (50 mg, 27%). ¹H NMR (500 MHz, CDCl₃) δ 8.79 (br.s, 1H), 7.97 – 7.89 (m, 2H), 7.64 – 7.58 (m, 1H), 7.57 – 7.49 (m, 2H), 6.76 (s, 1H), 6.26 (s, 1H), 5.92 (s, 1H), 3.92 – 3.81 (m, 1H), 3.80 – 3.71 (m, 1H), 3.18 – 3.05 (m, 1H), 2.97 – 2.83 (m, 1H), 2.68 (s, 3H), 2.32 (s, 3H). MS: *m/z* = 420.0 (M + H)⁺.

Example 34**4-Benzenesulfonyl-N-(2-methanesulfonyl-ethyl)-N-methyl-N'-(5-methyl-1H-pyrazol-3-yl)-pyridine-2,6-diamine**

5 A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (100 mg, 0.29 mmol), (2-methanesulfonyl-ethyl)-methyl-amine (197 mg, 1.43 mmol) and DIPEA (0.2 mL, 0.95 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube for 19h. The reaction was cooled and partitioned between EtOAc and saturated ammonium chloride soln. The aqueous was re-extracted and the combined organics were washed with
 10 water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane, followed by MeOH (0 - 10 %) in EtOAc to give the title compound as a brown solid (32 mg, 25%). ¹H NMR (500 MHz, CDCl₃) δ 7.93 – 7.85 (m, 2H), 7.57 – 7.50 (m, 1H), 7.49 – 7.42 (m, 2H), 6.90 (s, 1H), 6.76 (s, 1H), 6.33 (d, J = 0.9 Hz, 1H), 5.95 (s, 1H), 4.03 – 3.95 (m, 2H), 3.33 – 3.25 (m, 2H), 3.02 (s, 3H), 2.82 (s, 3H),
 15 2.25 (s, 3H). MS: m/z = 450.1 (M + H)⁺.

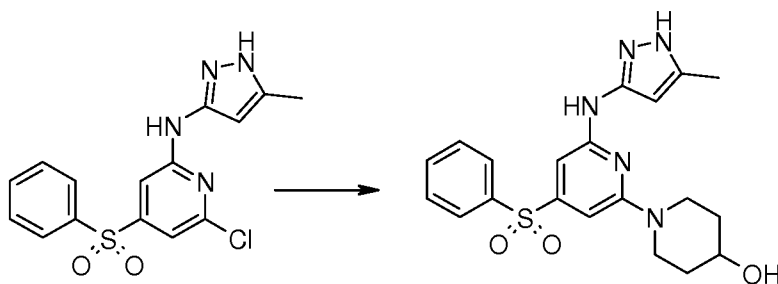
Example 35**3-[[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-yl]-methyl-amino}-propan-1-ol**

20 A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (150 mg, 0.43 mmol), 3-(methylamino)propan-1-ol (192 mg, 2.15 mmol) and DIPEA (0.4 mL, 2.15 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube for 2h before a further 3-(methylamino)propan-1-ol (115 mg, 1.29 mmol) was added and stirring continued

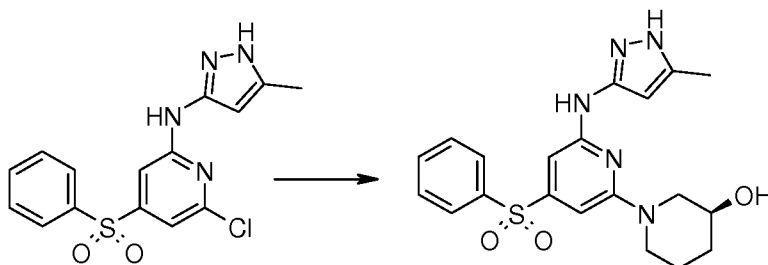
for another 2h. The reaction was cooled and partitioned between EtOAc and saturated ammonium chloride soln. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane followed by MeOH (0 - 10 %) in EtOAc to give the title compound as a yellow solid (131 mg, 76 %). ¹H NMR(500 MHz, CDCl₃) δ 7.92 – 7.85 (m, 2H), 7.58 – 7.50 (m, 1H), 7.49 – 7.42 (m, 2H), 6.66 (s, 1H), 6.33 (s, 1H), 5.77 (s, 1H), 3.66 (t, J = 6.2 Hz, 2H), 3.50 (t, J = 5.4 Hz, 2H), 2.92 (s, 3H), 2.22 (s, 3H), 1.78 – 1.68 (m, 2H). MS: *m/z* = 402.1 (M + H)⁺.

Example 36

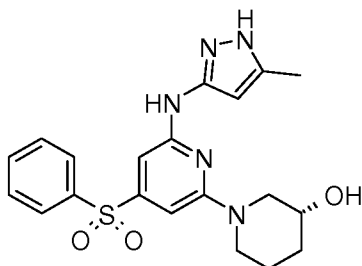
1-[4-(benzenesulfonyl)-6-[(5-methyl-1H-pyrazol-3-yl)amino]pyridin-2-yl]piperidin-4-ol



A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (180 mg, 0.52 mmol), piperidin-4-ol (261 mg, 2.58 mmol) and DIPEA (0.4 mL, 2.58 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube for 2h. The reaction was cooled and partitioned between EtOAc and saturated ammonium chloride soln. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by triturating with diethyl ether to give the title compound as a yellow solid (149 mg, 68%). ¹H NMR (500 MHz, CDCl₃) δ 7.88 (m, 2H), 7.52 (m, 1H), 7.44 (m, 2H), 6.75 (s, 1H), 6.69 (s, 1H), 6.50 (s, 1H), 5.86 (s, 1H), 4.01 – 3.92 (m, 2H), 3.91 – 3.83 (m, 1H), 3.14 (ddd, J = 13.1, 9.7, 3.2 Hz, 2H), 2.23 (s, 3H), 1.94 – 1.85 (m, 2H), 1.53 – 1.45 (m, 2H). MS: *m/z* = 414.1 (M + H)⁺.

Example 37**(3S)-1-[4-(benzenesulfonyl)-6-[(5-methyl-1H-pyrazol-3-yl)amino]pyridin-2-yl]piperidin-3-ol**

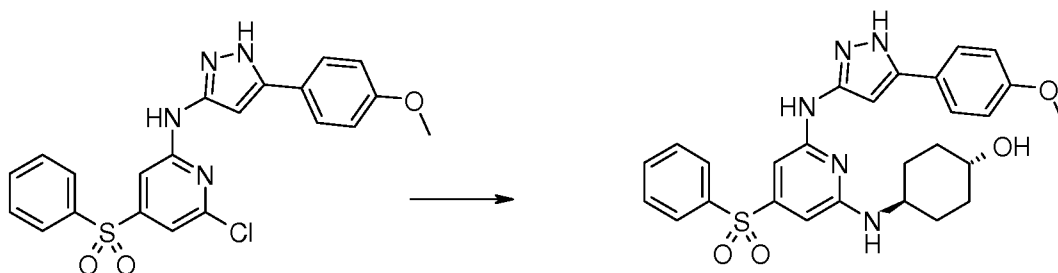
5 A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (180 mg, 0.52 mmol), (3*S*)-piperidin-3-ol hydrochloride (355 mg, 2.58 mmol) and DIPEA (0.4 mL, 2.58 mmol) in DMSO (1 mL) was heated to 120 °C in a pressure tube for 7h before a further (3*S*)-piperidin-3-ol hydrochloride (142 mg, 1.03 mmol) was added and stirring continued for another 4h. The reaction was cooled and partitioned between EtOAc and saturated aq. ammonium chloride solution. The aqueous was re-extracted and the combined organics were washed with water, brine and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane, followed by MeOH (0 - 5 %) in EtOAc to give the title compound as a yellow solid (98 mg, 46%). ¹H NMR (500 MHz, CDCl₃) δ 7.92 – 7.83 (m, 2H), 7.56 – 7.49 (m, 1H), 7.49 – 7.42 (m, 2H), 6.83 (s, 1H), 6.68 (s, 1H), 6.50 (s, 1H), 5.83 (s, 1H), 3.84 – 3.77 (m, 1H), 3.77 – 3.71 (m, 1H), 3.61 – 3.50 (m, 1H), 3.46 – 3.37 (m, 1H), 3.36 – 3.26 (m, 1H), 2.23 (s, 3H), 1.92 – 1.83 (m, 1H), 1.83 – 1.73 (m, 1H), 1.62 – 1.53 (m, 1H), 1.55 – 1.46 (m, 1H). MS: *m/z* = 414.1 (M + H)⁺.

Example 38**(3R)-1-[4-(benzenesulfonyl)-6-[(5-methyl-1H-pyrazol-3-yl)amino]pyridin-2-yl]piperidin-3-ol**

The title compound was synthesized according to Example 37 by substituting (3*S*)-piperidin-3-ol hydrochloride with (3*R*)-piperidin-3-ol hydrochloride. ¹H NMR (500 MHz, CDCl₃) δ 7.92 – 7.81 (m, 2H), 7.56 – 7.49 (m, 1H), 7.49 – 7.41 (m, 2H), 6.81 (s, 1H), 6.69 (s, 1H), 6.50 (s, 1H), 5.83 (s, 1H), 3.83 – 3.77 (m, 1H), 3.78 – 3.71 (m, 1H), 3.60 – 3.50 (m, 1H), 3.44 – 3.36 (m, 1H), 3.36 – 3.25 (m, 1H), 2.23 (s, 3H), 1.91 – 1.83 (m, 1H), 1.82 – 1.73 (m, 1H), 1.62 – 1.53 (m, 1H), 1.53 – 1.47 (m, 1H). MS: *m/z* = 414.1 (M + H)⁺.

Example 39

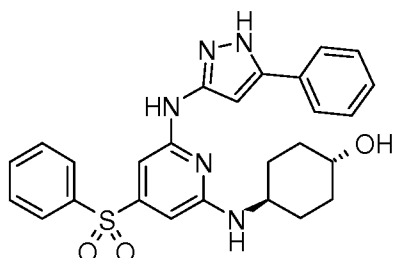
(*trans*)-4-{4-Benzenesulfonyl-6-[5-(4-methoxy-phenyl)-1H-pyrazol-3-ylamino]-pyridin-2-yl amino}-cyclohexanol



A mixture of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]-amine (185 mg, 0.386 mmol) and *trans*-4-aminocyclohexanol (170 mg, 1.48 mmol) in DMSO (2 mL) was heated at 170 °C in a CEM Discover microwave for 60 min. The cooled mixture was partitioned between saturated ammonium chloride solution (15 mL) and EtOAc (45 mL). The phases were separated and the organic phase was washed with water (3 x 10 mL), brine (5 mL), dried (Na₂SO₄), the mixture filtered and the filtrate evaporated to dryness to afford an orange oil which was subjected to automated reverse-phase HPLC (low pH method), affording the title compound as an orange oil (34 mg, 17%). ¹H NMR (500MHz, MeOD): δ 8.00-7.95 (m, 2 H), 7.73 - 7.68 (m, 1 H), 7.66 - 7.60 (m, 4 H), 7.01 (d, *J*=8.8 Hz, 2 H), 6.49 (br. s, 2 H), 6.28 (d, *J*=1.1 Hz, 1H), 3.78 - 3.69 (m, 1 H), 3.65 - 3.57 (m, 1 H), 2.12 (d, *J*=11.3 Hz, 2 H), 2.00 (d, *J*=10.9 Hz, 2 H), 1.41 - 1.51 (m, 2 H), 1.38 - 1.29 (m, 2 H). MS: *m/z* = 520.0 (M + H)⁺.

Example 40

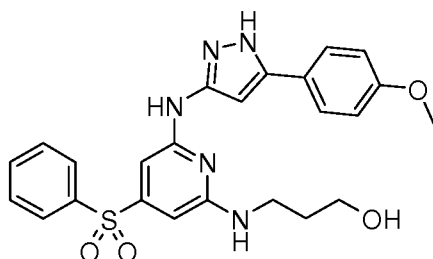
(*trans*)-4-[4-Benzenesulfonyl-6-(5-phenyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-cyclohexanol



5 The title compound was synthesized according to Example 39 by substituting (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-(4-methoxy-phenyl)-1H-pyrazol-3-yl]-amine with (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-phenyl-1H-pyrazol-3-yl]-amine. In this case microwave heating was carried out at 160 °C for 1h followed by 170 °C for a further 40 min. ¹H NMR (500 MHz, MeOD): δ 8.00 – 7.96 (m, 2 H), 7.75 – 7.66 (m, 3 H), 7.65 – 7.61 (m, 2 H), 7.44 (t, J=7.6 Hz, 2 H), 7.37 – 7.32 (m, 1 H), 6.57 (br. s., 1H), 6.49 (s, 1 H), 6.28 (d, J=1.1 Hz, 1 H), 3.72 (br. s., 1 H), 3.65 – 3.57 (m, 1 H), 2.12 (d, J=12.3 Hz, 2 H), 2.01 (d, J=9.9 Hz, 2 H), 1.51 – 1.42 (m, 2 H), 1.39 – 1.30 (m, 2 H). MS: *m/z* = 490.1 (M + H)⁺.

Example 41

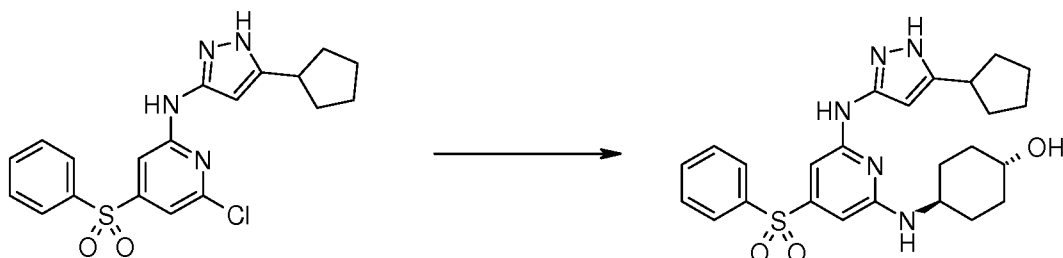
15 **3-{4-Benzenesulfonyl-6-[5-(4-methoxy-phenyl)-1H-pyrazol-3-ylamino]-pyridin-2-ylamino}-propan-1-ol**



20 The title compound was synthesized according to Example 39 by substituting *trans*-4-aminocyclohexanol with 3-aminopropanol. ¹H NMR (MeOD, 500 MHz): δ 7.96 – 8.00 (m, 2 H), 7.68 – 7.73 (m, 1 H), 7.61 – 7.67 (m, 4 H), 6.99 (d, J=8.8 Hz, 2 H), 6.52 (s, 1 H), 6.44 (br. s., 1 H), 6.32 (d, J=1.1 Hz, 1 H), 3.84 (s, 3 H), 3.68 (t, J=6.2 Hz, 2 H), 3.47 (t, J=6.9 Hz, 2 H), 1.87 (quin, J=6.5 Hz, 2 H). MS: *m/z* = 480.0 (M + H)⁺.

Example 42

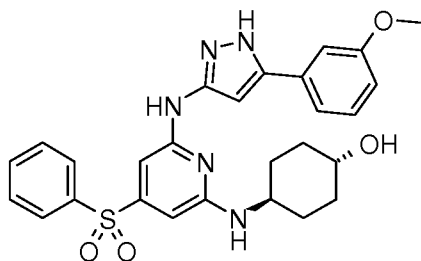
(*trans*)-4-[4-Benzenesulfonyl-6-(5-cyclopentyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-cyclohexanol, formate salt



5 To a solution of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-cyclopentyl-1H-pyrazol-3-yl)-amine (290mg, 0.72 mmol) in DMSO (3 mL) was added *trans* 4-aminocyclohexanol (600 mg, 5.21 mmol) and DIPEA (600 mg, 4.65 mmol) and the mixture heated at 120°C for 3h. The cooled mixture was then partitioned between saturated ammonium chloride solution (10 mL) and EtOAc (45 mL). The phases were separated and the organic phase was washed with water (2 x 5 mL), brine (5 mL), dried (Na₂SO₄), the mixture filtered and the filtrate evaporated to dryness to afford an orange oil. This was dissolved in MeOH and submitted to low pH prep. HPLC to afford the product as a yellow solid (63 mg, 18%). ¹H NMR (500MHz, MeOD): δ 8.14 (0.4H,s), 7.96 (d, J=7.7 Hz, 2 H), 7.71 - 7.67 (m, 1 H), 7.64 - 7.58 (m, 2 H), 6.46 (s, 1 H), 6.25 (s, 1 H), 6.12 (s, 1 H), 3.71 (br. s., 1H), 3.64 - 3.56 (m, 1 H), 3.07 (quin, J=8.1 Hz, 1 H), 2.15 - 2.04 (m, 4 H), 1.99 (d, J=10.9 Hz, 2 H), 1.88 - 1.79 (m, 2 H), 1.76 - 1.64 (m, 4 H), 1.49 - 1.39 (m, 2 H), 1.36 - 1.26 ppm (m, 2 H). MS: *m/z* = 482.1 (M + H)⁺.

Example 43

(*trans*)-4-[4-Benzenesulfonyl-6-[5-(3-methoxy-phenyl)-1H-pyrazol-3-ylamino]-pyridin-2-ylamino]cyclohexanol

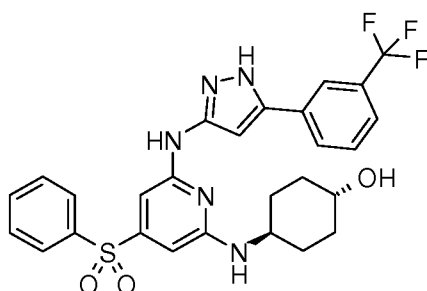


The title compound was synthesized according to Example 42 by substituting 6-Chloro-4-(pyridine-3-sulfonyl)-pyridin-2-yl]-5-cyclopentyl-1H-pyrazol-3-yl)-amine with 4-Benzenesulfonyl-6-chloro-pyridin-2-yl]-[5-(3-methoxy-phenyl)-1H-pyrazol-3-yl]-amine. ¹H

NMR (500MHz, MeOD): δ 8.00 – 7.96 (m, 2 H), 7.73 - 7.68 (m, 1 H), 7.65 - 7.60 (m, 2 H), 7.39 - 7.33 (m, 1 H), 7.30 (d, $J=5.4$ Hz, 1 H), 6.92 (dd, $J=8.1, 1.5$ Hz, 1 H), 6.49 (br. s., 1 H), 6.28 (d, $J=1.1$ Hz, 1 H), 3.87 (s, 3 H), 3.77 - 3.66 (m, 1 H), 3.64 - 3.57 (m, 1 H), 2.12 (d, $J=11.3$ Hz, 2 H), 2.00 (d, $J=10.9$ Hz, 2 H), 1.43 (br. s., 2 H), 1.39 - 1.29 (m, 2 H). MS: m/z = 520.1 (M + H)⁺.

Example 44

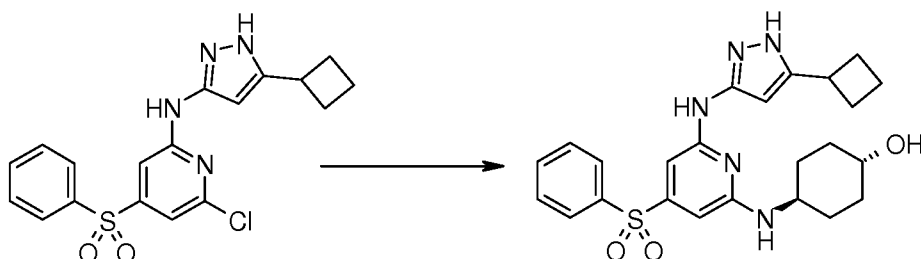
(*trans*)-4-[4-Benzenesulfonyl-6-[5-(3-trifluoromethyl-phenyl)-1H-pyrazol-3-ylamino]-pyridin-2-ylamino]-cyclohexanol



The title compound was synthesized according to Example 42 by substituting (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-cyclopentyl-1H-pyrazol-3-yl)-amine with (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-(3-trifluoromethyl-phenyl)-1H-pyrazol-3-yl]-amine. ¹H NMR (500MHz, MeOD): δ 8.05 (1 H, s), 7.97 (3 H, d, $J=7.88$ Hz), 7.72 - 7.59 (5 H, m), 6.44 (2 H, br. s.), 6.28 (1 H, s), 3.68 - 3.56 (2H, m), 2.11 (2 H, d, $J=11.51$ Hz), 1.99 (2 H, d, $J=10.56$ Hz), 1.50 - 1.41 (2 H, m), 1.38 - 1.27 (2 H, m). MS: m/z = 558.0 (M + H)⁺.

Example 45

(*trans*)-4-[4-Benzenesulfonyl-6-(5-cyclobutyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-cyclohexanol

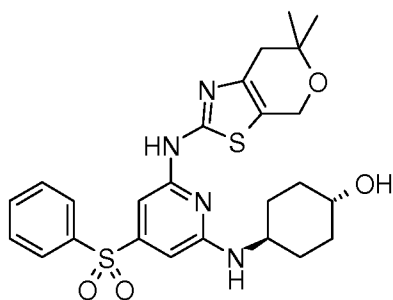


To a solution of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-cyclobutyl-1H-pyrazol-3-yl)-amine (260 mg, 0.669 mmol) in DMSO was added *trans*-4-aminocyclohexanol (231 mg, 2.01 mmol) and the mixture irradiated at 170 °C for 1h in a CEM Discover microwave. The cooled mixture was partitioned between saturated ammonium chloride solution (15 mL)

and EtOAc (45 mL). The phases were separated and the organic phase was washed with water (3 x 10 mL), brine (5 mL), dried (Na₂SO₄), the mixture filtered and the filtrate evaporated to dryness to afford an orange oil which was subjected to low pH preparative HPLC. Product containing fractions were evaporated and then partitioned between saturated NaHCO₃ (15 mL) and DCM (45 mL). The phases were separated and the organic phase was dried (Na₂SO₄), the mixture filtered and the filtrate evaporated to dryness to afford the product as an orange oil. ¹H NMR (500MHz, MeOD): δ 7.90 - 7.77 (m, 2 H), 7.60 - 7.55 (m, 1 H), 7.49 (t, J=7.7 Hz, 2 H), 6.38 - 5.96 (m, 3 H, partially exchanged), 3.67 - 3.55 (m, 1 H), 3.52 - 3.38 (m, 2 H), 2.30 - 2.02 (m, 4 H), 2.01 - 1.79 (m, 6 H), 1.37 - 1.11 (m, 4 H). MS: *m/z* = 468.1 (M + H)⁺.

Example 46

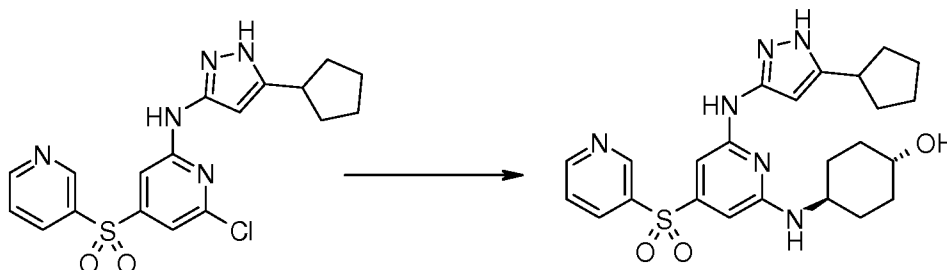
(*trans*)-4-[4-Benzenesulfonyl-6-(6,6-dimethyl-6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-ylamino)-pyridin-2-ylamino]-cyclohexanol, formate salt



The title compound was synthesized according to Example 42 by substituting (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-cyclopentyl-1H-pyrazol-3-yl)-amine with (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(6,6-dimethyl-6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-yl)-amine. ¹H NMR (MeOD, 500MHz): δ 8.17 (s, 0.4 H), 7.96 (d, J=7.6 Hz, 2 H), 7.74 - 7.68 (m, 1 H), 7.66 - 7.60 (m, 2 H), 6.46 (s, 1 H), 6.42 (d, J=0.9 Hz, 1 H), 4.74 (s, 2 H), 4.02 (t, J=10.8 Hz, 1 H), 3.66 - 3.58 (m, 1 H), 2.59 (s, 2 H), 2.15 (d, J=11.8 Hz, 2 H), 2.01 (d, J=10.6 Hz, 2 H), 1.50 - 1.39 (m, 2H), 1.37 - 1.28 (m, 8 H). MS: *m/z* = 515.0 (M+H)⁺.

Example 47

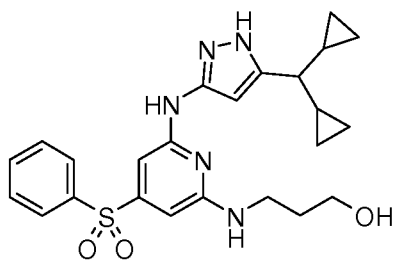
(*trans*)-4-[6-(5-Cyclopentyl-1H-pyrazol-3-ylamino)-4-(pyridine-3-sulfonyl)-pyridin-2-ylamino]-cyclohexanol



5 To a solution of [6-Chloro-4-(pyridine-3-sulfonyl)-pyridin-2-yl]-(5-cyclopentyl-1H-pyrazol-3-yl)-amine (200 mg, 0.495 mmol) in DMSO (3 mL) was added *trans* 4-aminocyclohexanol (600 mg, 5.21 mmol), and DIPEA (639 mg, 4.95 mmol) and the mixture heated at 140 °C for 2h. More *trans*-4-aminocyclohexanol was added each hour (100 mg) with continued heating until the reaction had reached about 70 % completion, as judged by
 10 LC-MS. The cooled mixture was then partitioned between saturated ammonium chloride solution (50 mL) and EtOAc (45 mL). The phases were separated and the organic phase was washed with water (2 x 5 mL), brine (5 mL), dried (Na₂SO₄), the mixture filtered and the filtrate evaporated to dryness to afford an orange oil. This was dissolved in MeOH and submitted to automated reverse-phase HPLC (low pH method) to afford the product as a
 15 yellow solid. (75 mg, 32 %). ¹H NMR (500MHz, MeOD): δ 9.09 (d, J=1.9 Hz, 1 H), 8.83 (dd, J=4.9, 1.3 Hz, 1 H), 8.35 (dt, J=8.2, 1.8 Hz, 1 H), 7.66 (dd, J=8.0, 4.9 Hz, 1 H), 6.52 (s, 1H), 6.28 (d, J=1.1 Hz, 1 H), 6.15 (br. s., 1 H), 3.75 (br. s., 1 H), 3.64 - 3.56 (m, 1 H), 3.12 - 3.03 (m, 1 H), 2.15 - 2.06 (m, 4 H), 1.99 (d, J=11.0 Hz, 2 H), 1.88- 1.79 (m, 2 H), 1.76 - 1.63 (m, 4 H), 1.49 - 1.39 (m, 2 H), 1.35 - 1.26 (m, 2 H). MS: m/z= 483.1 (M + H)⁺.

20 **Example 48**

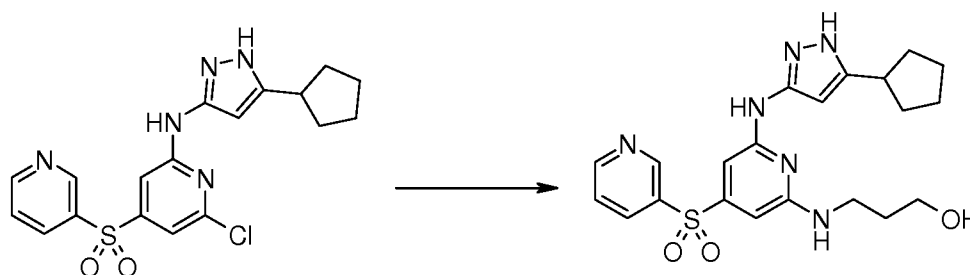
3-[4-Benzenesulfonyl-6-(5-dicyclopropylmethyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-1-ol, formate salt



The title compound was synthesized according to Example 47 by substituting [6-Chloro-4-(pyridine-3-sulfonyl)-pyridin-2-yl]-(5-cyclopentyl-1H-pyrazol-3-yl)-amine with (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-dicyclopropylmethyl-1H-pyrazol-3-yl)-amine and *trans*-4-aminocyclohexanol with 3-aminopropanol. ¹H NMR (500MHz, MeOD): δ 7.96 (br. s., 0.7 H), 7.79 - 7.73 (m, 2 H), 7.51 - 7.46 (m, 1 H), 7.43 - 7.38 (m, 2 H), 6.31 (d, J=0.9 Hz, 1 H), 6.09 (d, J=1.3 Hz, 1 H), 5.94 (s, 1 H), 3.44 (t, J=6.3 Hz, 2 H), 3.24 (t, J=6.8 Hz, 2 H), 1.62 (quin, J=6.5 Hz, 2 H), 1.37 (t, J=8.7 Hz, 1 H), 0.93 - 0.85 (m, 2 H), 0.42 - 0.33 (m, 2H), 0.28 - 0.21 (m, 2 H), 0.11 (dq, J=9.5, 4.9 Hz, 2 H), -0.01 (dq, J=9.6, 4.9 Hz, 2 H). MS: m/z= 468.1 (M + H)⁺.

Example 49

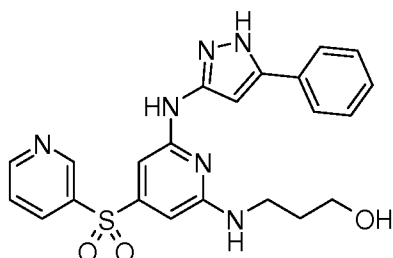
3-[6-(5-Cyclopentyl-1H-pyrazol-3-ylamino)-4-(pyridine-3-sulfonyl)-pyridin-2-ylamino]-propan-1-ol, formate salt



To a solution of [6-Chloro-4-(pyridine-3-sulfonyl)-pyridin-2-yl]-(5-cyclopentyl-1H-pyrazol-3-yl)-amine (125mg, 0.309 mmol) in DMSO (3 mL) was added 3-aminopropanol (232 mg, 3.10 mmol) and the solution heated at 140 °C for 3h. The cooled mixture was then partitioned between saturated aq. ammonium chloride solution (10 mL) and EtOAc (45 mL). The phases were separated and the organic phase was washed with water (2x 5 mL), brine (5 mL), dried (Na₂SO₄), the mixture filtered and the filtrate evaporated to dryness to afford an orange oil. This was dissolved in MeOH and submitted to automated reverse phase HPLC (low pH method) to afford the product as a yellow solid (64 mg, 46 %). ¹H NMR (500MHz, MeOD): δ 9.10 (d, J=1.7 Hz, 1 H), 8.83 (dd, J=4.9, 1.6 Hz, 1 H), 8.38 - 8.34 (m, 1 H), 8.15 (s, 0.3H), 7.66 (dd, J=8.1, 5.0 Hz, 1 H), 6.57 (d, J=0.9 Hz, 1 H), 6.33 (d, J=1.3 Hz, 1 H), 6.08 (s, 1 H), 3.66 (t, J=6.2 Hz, 2 H), 3.45 (t, J=6.8 Hz, 2 H), 3.07 (quin, J=8.0 Hz, 1 H), 2.12 - 2.05 (m, 2 H), 1.87 - 1.80 (m, 4H), 1.74 - 1.64 (m, 4 H). MS: m/z= 443.1 (M + H)⁺.

Example 50

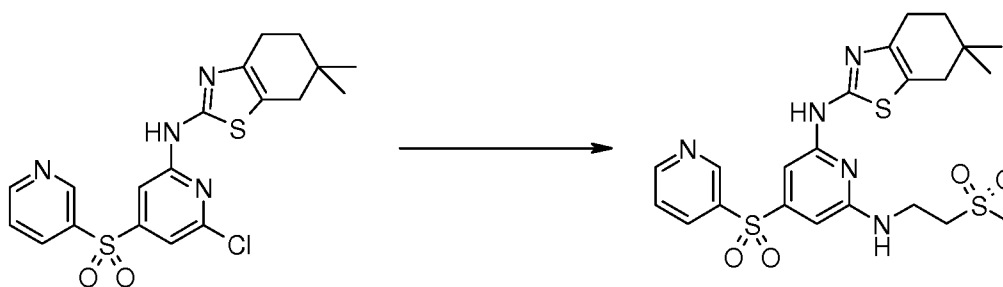
3-[6-(5-Phenyl-1H-pyrazol-3-ylamino)-4-(pyridine-3-sulfonyl)-pyridin-2-ylamino]-propan-1-ol], formate salt



5 The title compound was synthesized according to Example 49 by substituting [6-Chloro-4-(pyridine-3-sulfonyl)-pyridin-2-yl]-(5-cyclopentyl-1H-pyrazol-3-yl)-amine with 6-Chloro-4-(pyridine-3-sulfonyl)-pyridin-2-yl]-(5-phenyl-1H-pyrazol-3-yl)-amine. The reaction mixture was heated at 150 °C for 4h. ¹H NMR (500MHz, MeOD): δ 9.12 (d, J=1.7 Hz, 1 H), 8.84 (dd, J=4.9, 1.6 Hz, 1 H), 8.40 - 8.35 (m, 1 H), 8.17 (br. s., 0.4 H), 7.75 - 7.71 (m, 2 H), 7.67 (ddd, J=8.1, 4.9, 0.7 Hz, 1 H), 7.43 (t, J=7.6 Hz, 2 H), 7.38 - 7.33 (m, 1 H), 6.58 (s, 1 H), 6.54 (br. s., 1 H), 6.37 (d, J=1.3 Hz, 1 H), 3.69 (t, J=6.2 Hz, 2 H), 3.49 (t, J=6.8 Hz, 2 H), 1.88 (quin, J=6.5 Hz, 2 H). MS: m/z= 451.0 (M + H)⁺.

Example 51

15 **N-(6,6-Dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-yl)-N'-(2-methanesulfonyl-ethyl)-4-(pyridine-3-sulfonyl)-pyridine-2,6-diamine, formate salt**

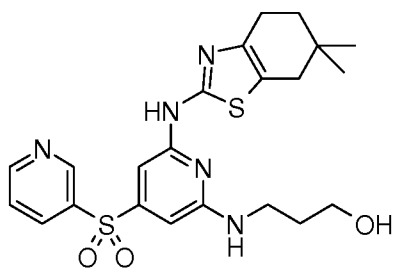


20 To a solution of [6-Chloro-4-(pyridine-3-sulfonyl)-pyridin-2-yl]-(6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-yl)-amine (150 mg, 0.324 mmol) was added DIPEA (209 mg, 6.02 mmol) and 2-methylsulphonyl ethanamine (199 mg, 1.62 mmol) and the mixture heated at 150 °C for 5h. The mixture was cooled and the solution partitioned between EtOAc (60 mL) and saturated ammonium chloride solution (30 mL). The phases were separated and the organic phase was washed with water (5 mL), brine (5 mL), dried (Na₂SO₄), the mixture filtered and the filtrate evaporated to dryness to afford an orange solid. The crude sulfone was

dissolved in MeOH, a few drops of 1M HCl added to help solubilize it and the solution was submitted to automated reverse phase HPLC (low pH method), affording the product as an orange solid (11 mg, 7%). ¹H NMR (500MHz, MeOD): δ 8.99 (d, J=1.7 Hz, 1 H), 8.73 (dd, J=4.9, 1.4 Hz, 1 H), 8.27 - 8.23 (m, 1 H), 8.10 (br. s., 1 H), 7.58 - 7.53 (m, 1 H), 6.49 (d, J=1.3 Hz, 1 H), 6.41 (d, J=1.3 Hz, 1 H), 3.93 (t, J=7.0 Hz, 2 H), 3.38 (t, J=6.9 Hz, 2 H), 2.89 (s, 3 H), 2.48 (m, 2 H), 2.35 (s, 2 H), 1.50 (t, J=6.4 Hz, 2 H), 0.92ppm (s, 6 H). MS: m/z= 522.0 (M + H)⁺.

Example 52

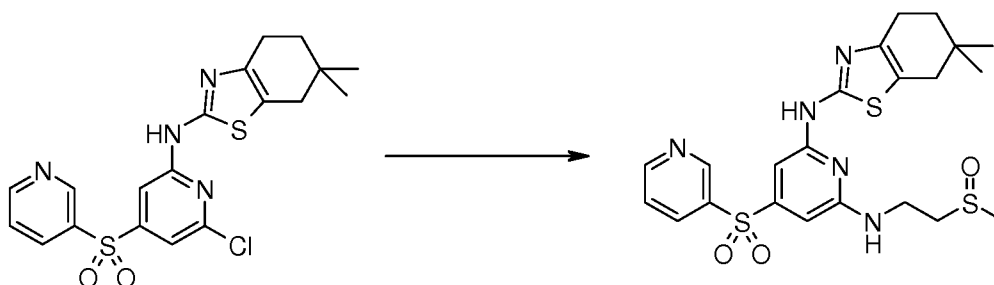
3-[6-(6,6-Dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-ylamino)-4-(pyridine-3-sulfonyl)-pyridin-2-ylamino]-propan-1-ol



The title compound was synthesized according to Example 51 by substituting of 2-methylsulfonyl-ethanamine with 3-aminopropanol (10 equivalents, no DIPEA added). The reaction was heated at 120 °C for 5h. After the aqueous workup, the crude isolated product was triturated with MeOH, filtered, the solid washed with MeOH and water then dried in air. ¹H NMR (500MHz, MeOD): δ 9.01 (d, J=1.7 Hz, 1 H), 8.72 (dd, J=5.0, 1.5 Hz, 1 H), 8.22 (dt, J=8.2, 1.9 Hz, 1 H), 7.52 (dd, J=8.0, 4.9 Hz, 1 H), 6.40 - 6.42(bs, 1 H), 6.34 (d, J=1.3 Hz, 1 H), 3.62 (t, J=6.2 Hz, 2 H), 3.52 (t, J=6.7 Hz, 2 H), 2.50 (t, J=6.4 Hz, 2H), 2.35 (s, 2 H), 1.80 (t, J=6.5 Hz, 2 H), 1.52 (t, J=6.4Hz, 2 H), 0.90 - 0.97(m, 6 H). MS: m/z= 474.0 (M+H)⁺.

Example 53

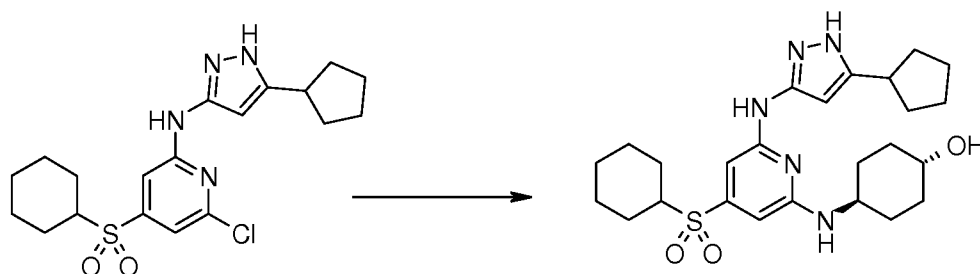
(+/-)-N-(6,6-Dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-yl)-N'-(2-methanesulfinyl-ethyl)-4-(pyridine-3-sulfonyl)-pyridine-2,6-diamine, formate salt



To a solution of 6-Chloro-4-(pyridine-3-sulfonyl)-pyridin-2-yl]-(6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-yl)-amine (200 mg, 0.46 mmol) in DMSO (2.5 mL) was added 2-methylthioethanamine (210 mg, 2.30 mmol) and the mixture heated at 150 °C for 4 h. The cooled solution was partitioned between EtOAc (50mL) and saturated ammonium chloride solution (15 mL). The phases were separated and the organic phase was washed with brine (20mL), dried (Na₂SO₄), the mixture filtered and the filtrate evaporated to dryness. The residue was dissolved in DCM (5 mL), and solid *meta*-chloroperoxybenzoic acid was added (70%, 142mg, 0.575mmol). The mixture was stirred for 1 h, then further DCM was added (50 mL), followed by saturated sodium bicarbonate (10 mL). The phases were separated and the organic phase was washed with brine (5 mL), dried (Na₂SO₄), the mixture filtered and the filtrate evaporated to dryness. The residue was subjected to low pH preparative HPLC to afford the title compound as an orange oil (46 mg, 20%). ¹H NMR (500MHz, MeOD): δ 9.11 (d, J=1.9 Hz, 1 H), 8.85 (dd, J=4.8, 1.2 Hz, 1 H), 8.36 (dt, J=8.1, 1.8 Hz, 1 H), 8.13 (s, 1 H), 7.67 (dd, J=8.0, 4.9 Hz, 1H), 6.61 (d, J=1.1 Hz, 1 H), 6.53 (d, J=1.3 Hz, 1 H), 4.09 - 4.02 (m, 1 H), 4.00 - 3.92 (m, 1 H), 3.29 - 3.23 (m, 1 H), 3.12 - 3.06 (m, 1 H), 2.69 (s, 3H), 2.61 (t, J=6.2 Hz, 2H), 2.47 (s, 2 H), 1.63 (t, J=6.4 Hz, 2 H), 1.05 (s, 6 H). MS: *m/z* = 506.0 (M + H)⁺.

Example 54

(*trans*)-4-[4-Cyclohexanesulfonyl-6-(5-cyclopentyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-cyclohexanol

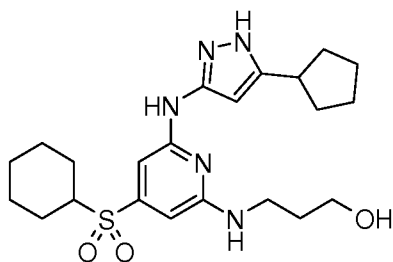


To a solution of (6-Chloro-4-cyclohexanesulfonyl-pyridin-2-yl)-(5-cyclopentyl-1H-pyrazol-3-yl)-amine (170mg, 0.416 mmol) in DMSO (3 mL) was added *trans*-4-aminocyclohexanol (479 mg, 4.16 mmol), DIPEA (536 mg, 4.16 mmol) and the mixture heated at 140 °C for 3h. The cooled mixture was partitioned between saturated aq. ammonium chloride solution (20 mL) and EtOAc (45 mL). The phases were separated and the organic phase was washed with water (2x 5 mL), brine (5 mL), dried (Na₂SO₄), the mixture filtered and the filtrate evaporated to dryness to afford an orange oil. This was dissolved in MeOH and submitted to automated reversed-phase HPLC (low pH method) to afford the title compound as a tan solid (30 mg, 15 %). ¹H NMR (500MHz, MeOD): δ 6.42

(s, 1 H), 6.19 (d, $J=1.1$ Hz, 1 H), 6.16 (br. s., 1 H), 3.76 (br. s., 1 H), 3.65 - 3.59 (m, 1 H), 3.12 - 3.05 (m, 2 H), 2.16 - 1.98 (m, 9 H), 1.92 - 1.83 (m, 4 H), 1.76 - 1.67 (m, 5 H), 1.51 - 1.39 (m, 4 H), 1.39 - 1.30 (m, 4 H). MS: $m/z = 488.2$ ($M+H$)⁺.

Example 55

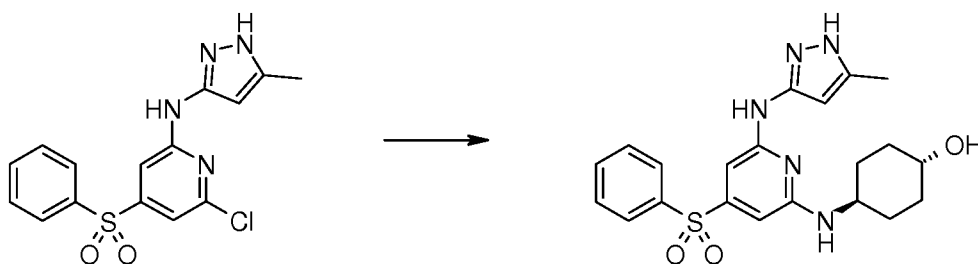
5 3-[4-Cyclohexanesulfonyl-6-(5-cyclopentyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-1-ol



The title compound was synthesized according to Example 49 by substituting of 6-Chloro-4-(pyridine-3-sulfonyl)-pyridin-2-yl]-(5-cyclopentyl-1H-pyrazol-3-yl)-amine with (6-Chloro-4-cyclohexanesulfonyl-pyridin-2-yl)-(5-cyclopentyl-1H-pyrazol-3-yl)-amine. Further purification was carried out by automated reverse phase HPLC (high pH method). ¹H NMR (500MHz, MeOD): δ 6.54 (br. s., 1 H), 6.31 - 6.19 (m, 2 H), 3.69 (br. s., 2 H), 3.52 - 3.44 (m, 2 H), 3.12 - 3.02 (m, 2 H), 2.12 - 2.01 (m, 4 H), 1.95 - 1.80 (m, 6 H), 1.70 (br. s., 5 H), 1.49 - 1.18 (m, 5 H). MS: $m/z = 448.2$ ($M + H$)⁺.

15 Example 56

(*trans*)-4-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-cyclohexanol, formate salt



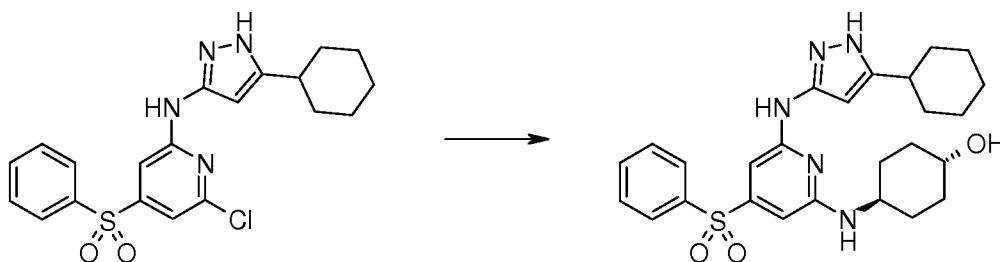
To a solution of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (220 mg, 0.631 mmol) in anhydrous DMSO (4 mL) was added *trans*-4-aminocyclohexanol (730 mg, 6.31 mmol) and DIPEA (1 mL, 6.31 mmol) and the mixture was stirred at 120 °C. More *trans*-4-aminocyclohexanol (500 mg, 4.34 mmol) was added periodically over 7h. The mixture was allowed to cool to room temperature and it was

partitioned between EtOAc (20 mL) and saturated aq. ammonium chloride solution (10 mL) and the phases were separated. The aqueous was extracted with EtOAc (2x10 mL) and the combined organics were washed with water (40 mL) and brine (40 mL) and then dried over MgSO₄. The crude material was purified by flash chromatography, eluting with a gradient of

5 EtOAc (0 - 100 %) in heptane, followed by a gradient of MeOH (0-10%) in EtOAc. The material isolated was further purified by automated reverse phase HPLC (low pH method) to afford the title compound (60 mg, 22 %). ¹H NMR (500 MHz, MeOD) δ 8.41 (s, 0.2H), 7.96 (d, J=7.5, 2H), 7.69 (t, J=7.4, 1H), 7.62 (t, J=7.7, 2H), 6.45 (s, 1H), 6.23 (s, 1H), 6.09 (s, 1H), 3.73 – 3.64 (m, 1H), 3.64 – 3.55 (m, 1H), 2.27 (s, 3H), 2.10 (d, J=12.5, 2H), 2.00 (d, J=11.0, 2H), 1.51 – 1.37 (m, 2H), 1.37 – 1.25 (m, 2H). MS: *m/z* = 428.1 (M + H)⁺.

Example 57

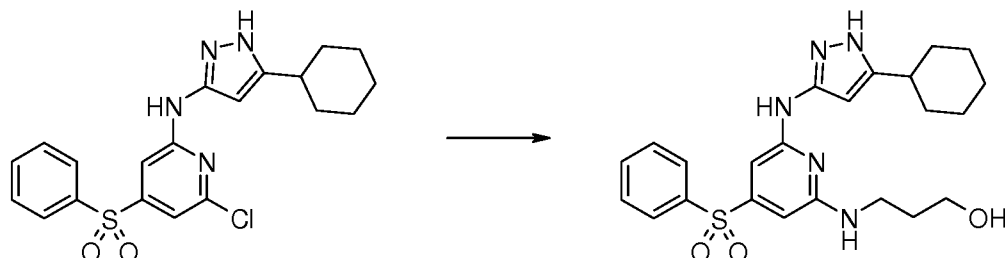
(*trans*)-4-[4-Benzenesulfonyl-6-(5-cyclohexyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-cyclohexanol



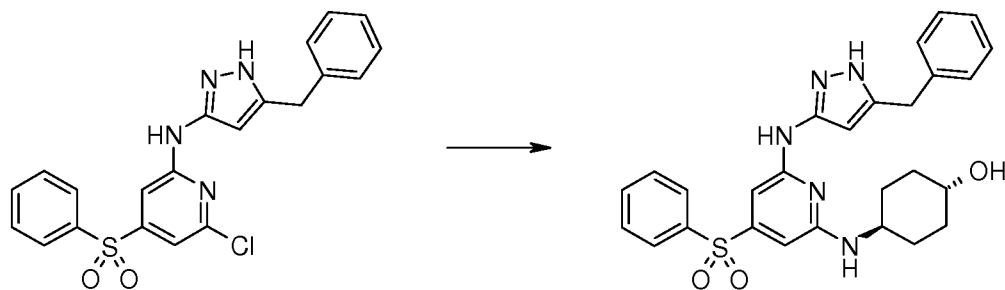
15 To a solution of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-cyclohexyl-1H-pyrazol-3-yl)-amine (200 mg, 0.48 mmol) in anhydrous DMSO (2 mL) was added *trans*-4-aminocyclohexanol (276 mg, 2.4 mmol) and DIPEA (0.4 mL, 2.4 mmol) and the mixture was stirred at 120°C. More *trans*-4-aminocyclohexanol (276 mg, 2.4 mmol) was added periodically over 20 h. The mixture was allowed to cool to room temperature and it was

20 partitioned between EtOAc (20 mL) and saturated aq. ammonium chloride solution (10 mL) and the phases were separated. The aqueous was extracted with EtOAc (2x10 mL) and the combined organics were washed with water (40 mL) and brine (40 mL) and then dried (MgSO₄). The crude material was purified by flash chromatography, eluting with a gradient of EtOAc (0 – 100 %) in heptane, followed by a gradient of MeOH (0 – 10 %) in EtOAc to

25 give the title compound as a pale yellow solid (128 mg, 54%). ¹H NMR (500 MHz, DMSO-d₆) δ 11.80 (s, 1H), 9.16 (s, 1H), 7.86 (d, J=7.6, 2H), 7.74 (t, J=7.4, 1H), 7.66 (t, J=7.7, 2H), 6.72 (d, J=6.5, 1H), 6.64 (s, 1H), 6.20 (s, 1H), 6.15 (s, 1H), 4.57 (d, J=3.7, 1H), 3.68 (s, 1H), 3.42 (d, J=3.9, 1H), 2.59 – 2.54 (m, 1H), 1.88 (dd, J=34.4, 11.4, 6H), 1.74 (d, J=12.1, 2H), 1.65 (d, J=12.2, 1H), 1.49 – 1.08 (m, 9H). MS: *m/z* = 496.1 (M + H)⁺.

Example 58**3-[4-Benzenesulfonyl-6-(5-cyclohexyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-1-ol**

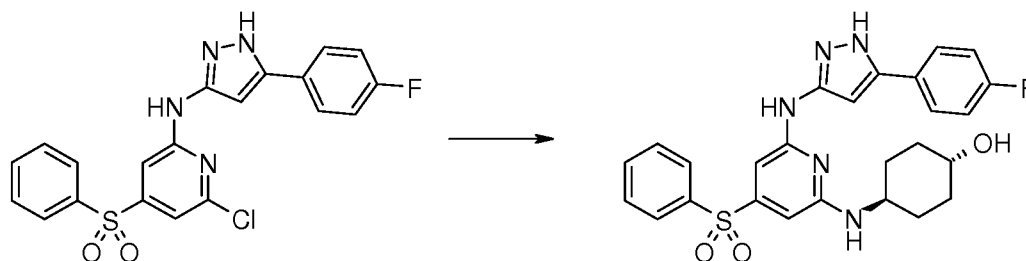
5 To a solution of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-cyclohexyl-1H-pyrazol-3-yl)-amine (130 mg, 0.312 mmol) in anhydrous DMSO (2 mL) was added 3-aminopropanol (0.119 mL, 1.56 mmol) and DIPEA (0.3 mL, 1.56 mmol) and the mixture was stirred at 120°C. More 3-aminopropanol (0.119 mL, 1.56 mmol, 4 times) was added periodically over 10 h. The mixture was allowed to cool to room temperature and it was
 10 partitioned between EtOAc (20 mL) and saturated aq. ammonium chloride solution (10 mL) and the phases were separated. The aqueous was extracted with EtOAc (2x10 mL) and the combined organics were washed with water (40 mL) and brine (40 mL) and then dried (MgSO₄). The crude material was purified by flash chromatography, eluting with a gradient of EtOAc (0 – 100 %) in heptane, followed by a gradient of MeOH (0 – 10 %) in EtOAc to
 15 give the title compound as a pale yellow solid (100 mg, 70%). ¹H NMR (500 MHz, DMSO-d₆) δ 11.80 (s, 1H), 9.14 (s, 1H), 7.87 (d, J=7.5, 2H), 7.73 (t, J=7.4, 1H), 7.66 (t, J=7.6, 2H), 6.84 (s, 1H), 6.79 (s, 1H), 6.19 (s, 1H), 6.14 (s, 1H), 4.45 (s, 1H), 3.53 – 3.43 (m, 2H), 3.32 – 3.27 (m, 2H), 1.96 – 1.85 (m, 2H), 1.81 – 1.71 (m, 2H), 1.70 – 1.62 (m, 3H), 1.42 – 1.26 (m, 4H), 1.26 – 1.16 (m, 1H). MS: m/z = 456.1 (M + H)⁺.

Example 59**(trans)-4-[4-Benzenesulfonyl-6-(5-benzyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-cyclohexanol**

To a solution of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-benzyl-1H-pyrazol-3-yl)-amine (120 mg, 0.282 mmol) in anhydrous DMSO (2 mL) was added *trans*-4-aminocyclohexanol (163 mg, 1.412 mmol) and DIPEA (0.2 mL, 1.412 mmol) and the mixture was stirred at 120°C. More *trans*-4-aminocyclohexanol (163 mg, 1.412 mmol) was added periodically over 14 h. The mixture was allowed to cool to room temperature and it was partitioned between EtOAc (20 mL) and aq. ammonium chloride solution (10 mL) and the phases were separated. The aqueous was extracted with EtOAc (2x10 mL) and the combined organics were washed with water (40 mL) and brine (40 mL) and then dried (MgSO₄). The crude material was purified by flash chromatography, eluting with a gradient of EtOAc (0 - 100 %) in heptane, followed by a gradient of MeOH (0 - 10 %) in EtOAc to give the title compound as a pale yellow solid (56 mg, 39%). ¹H NMR (500 MHz, DMSO-d₆) δ 12.00 (s, 1H), 9.21 (s, 1H), 7.85 (d, J=7.4, 2H), 7.73 (t, J=7.4, 1H), 7.65 (t, J=7.7, 2H), 7.30 (t, J=7.4, 2H), 7.25 (d, J=7.1, 2H), 7.20 (t, J=7.1, 1H), 6.74 (s, 1H), 6.64 (s, 1H), 6.23 (s, 1H), 6.15 (s, 1H), 4.57 (s, 1H), 3.88 (s, 2H), 3.60 (s, 1H), 3.42 (s, 1H), 2.02 - 1.72 (m, 4H), 1.35 - 1.07 (m, 4H). MS: *m/z* = 504.1 (M + H)⁺.

Example 60

(*trans*)-4-{4-Benzenesulfonyl-6-[5-(4-fluoro-phenyl)-1H-pyrazol-3-ylamino]-pyridin-2-ylamino}-cyclohexanol

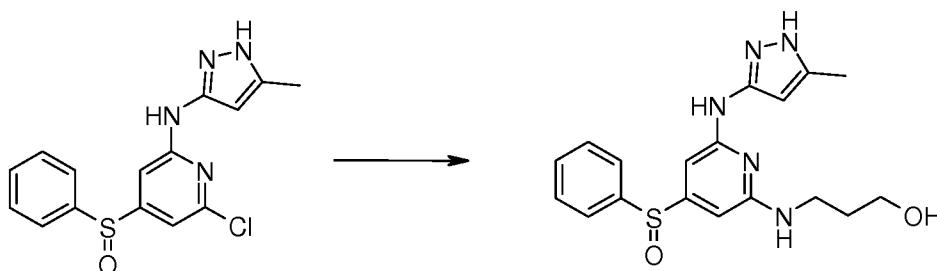


To a solution of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-(4-fluoro-phenyl)-1H-pyrazol-3-yl]-amine (120 mg, 0.28 mmol) in anhydrous DMSO (1.5 mL) was added *trans*-4-aminocyclohexanol (160 mg, 1.4 mmol) and DIPEA (0.2 mL, 1.4 mmol) and the mixture was stirred at 120 °C. More *trans*-4-aminocyclohexanol (160 mg, 1.4 mmol) was added periodically over 12 h. The mixture was allowed to cool to room temperature and it was partitioned between EtOAc (20 mL) and aq. ammonium chloride solution (10 mL) and the phases were separated. The aqueous was extracted with EtOAc (2x10 mL) and the combined organics were washed with water (15 mL) and brine (15 mL) and then dried (MgSO₄). The crude material was purified by flash chromatography, eluting with a gradient of EtOAc (0 - 100 %) in heptane, followed by a gradient of MeOH (0 - 10 %) in EtOAc to give the title

compound as a pale yellow solid (58 mg, 41%). ^1H NMR (500 MHz, CDCl_3) δ 7.96 (d, $J=7.2$, 2H), 7.71 – 7.59 (m, 3H), 7.54 (t, $J=7.6$, 2H), 7.11 (t, $J=8.5$, 2H), 6.83 (s, 1H), 6.53 (s, 1H), 6.30 (s, 1H), 6.17 (s, 1H), 4.61 (s, 1H), 3.70 (s, 1H), 3.58 (s, 1H), 2.27 – 1.96 (m, 4H), 1.40 – 1.16 (m, 4H). MS: m/z = 508.1 ($\text{M} + \text{H}$) $^+$.

5 **Example 61**

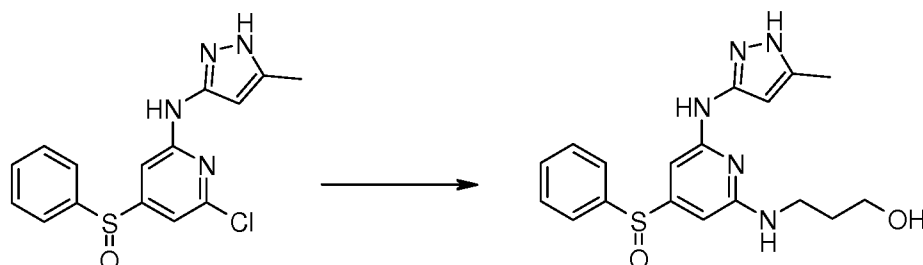
3-[4-Benzenesulfinyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-1-ol



To a solution of (4-benzenesulfinyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (100 mg, 0.3 mmol) in anhydrous DMSO (1.5 mL) was added 3-aminopropanol (115 μL , 1.5 mmol) and DIPEA (0.25 mL, 1.5 mmol) and the mixture was stirred at 120 $^\circ\text{C}$. More 3-aminopropanol (0.115 mL, 1.5 mmol) was added periodically over 14h. The mixture was allowed to cool to room temperature and then it was partitioned between EtOAc (20 mL) and aq. ammonium chloride solution (20 mL). The phases were separated and the aqueous was extracted with EtOAc (2x30 mL). The combined organics were washed with water (20 mL), brine (20 mL) and dried (MgSO_4). The crude material was purified by flash chromatography with a gradient of MeOH (0 - 10%) in DCM followed by a gradient of 7N ammonia in MeOH (0 - 20%). The material isolated was further purified by preparative HPLC (MeCN/Water) on an achiral column and the resulting material was resolved into single enantiomers by chiral HPLC (Column: Chiralcel OD-H; eluent: 85% heptane, 15% EtOH; retention time for 61: 13.65 min).

Enantiomer 1: 12 mg, 11 %

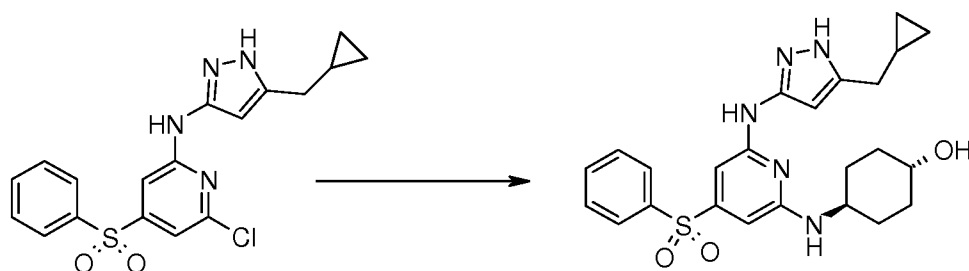
^1H NMR (500 MHz, DMSO-d_6) δ 11.77 (s, 1H), 8.99 (s, 1H), 7.84 – 7.70 (m, 2H), 7.67 – 7.57 (m, 3H), 6.84 – 6.49 (m, 2H), 6.18 (s, 1H), 6.09 (s, 1H), 4.53 (s, 1H), 3.67 – 3.49 (m, 2H), 3.31 (s, 2H), 2.21 (s, 3H), 1.85 – 1.62 (m, 2H). MS: m/z = 372.1 ($\text{M} + \text{H}$) $^+$.

Example 62**3-[4-Benzenesulfinyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-1-ol**

The preparation of this compound was carried out simultaneously with that of Example 61. Retention time: 23.11 min.

Enantiomer 2: 14 mg, 13 %

^1H NMR (500 MHz, DMSO) δ 11.67 (s, 1H), 9.02 (s, 1H), 7.73 – 7.64 (m, 2H), 7.61 – 7.52 (m, 3H), 6.69 (s, 1H), 6.50 (s, 1H), 6.11 – 5.92 (m, 2H), 4.48 (s, 1H), 3.55 – 3.43 (m, 2H), 3.29 – 3.20 (m, 2H), 2.15 (s, 3H), 1.75 – 1.60 (m, 2H). MS: $m/z = 372.1$ ($M + H$) $^+$.

Example 63**(*trans*)-4-[4-Benzenesulfonyl-6-(5-cyclopropylmethyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-cyclohexanol**

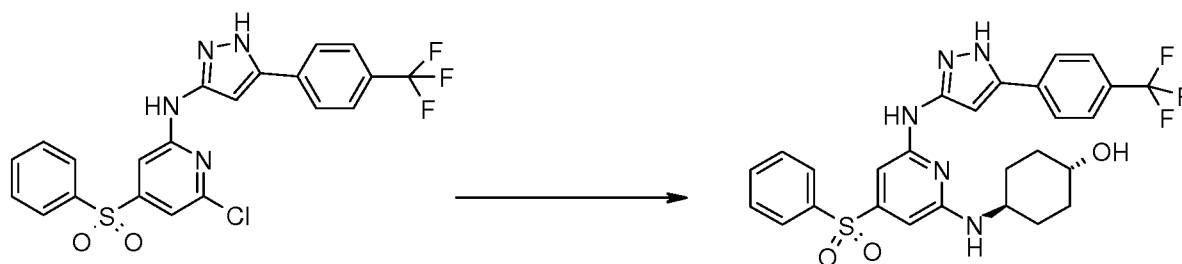
A mixture of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-cyclopropylmethyl-1H-pyrazol-3-yl)-amine (30 mg, 0.08 mmol) and *trans*-4-aminocyclohexanol (80 mg, 0.66 mmol) in anhydrous DMSO (1 mL) was flushed with nitrogen for 5 min and heated at 120°C in a sealed vial. *Trans*-4-aminocyclohexanol (0.08 g, 0.66 mmol) was added while monitoring by LC-MS approximately every 2 h until the amount of product did not increase further (no heating or addition of *trans*-4-aminocyclohexanol overnight). The total heating time was 17.5 h, total amount of *trans*-4-aminocyclohexanol added 42 equivalents. The reaction mixture

was then allowed to cool to room temperature and partitioned between EtOAc (5 mL) and saturated aq. ammonium chloride solution (5 mL). The two phases were separated and the aqueous phase extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried over MgSO₄, filtered and concentrated *in vacuo*.

5 The crude material was purified by flash chromatography (gradient of 1-10% MeOH in DCM) to give the title compound as a dark yellow solid (10 mg, 28 %) ¹H NMR (500 MHz, DMSO-d₆) δ 11.82 (s, 1 H), 9.18 (br. s, 1 H), 7.88 - 7.83 (m, 2 H), 7.77 - 7.70 (m, 1 H), 7.68 - 7.58 (m, 2 H), 6.73 (d, *J* = 7.9 Hz, 1H), 6.68 - 6.58 (m, 1 H), 6.25 (br. s, 1 H), 6.15 (s, 1 H), 4.61 - 4.49 (m, 1 H), 3.66 (br. s, 1 H), 3.41 (br. s, 1 H), 1.99 - 1.75 (m, 4 H), 1.37 - 1.07 (m, 4 H), 1.03 - 0.90 (m, 1 H), 0.56 - 0.38 (m, 2 H), 0.25 - 0.07 (m, 2 H). MS: *m/z* = 468.1 (M+H)⁺.

Example 64

(*trans*)-4-{4-Benzenesulfonyl-6-[5-(4-trifluoromethyl-phenyl)-1*H*-pyrazol-3-ylamino]-pyridin-2-ylamino}-cyclohexanol, formate salt



15

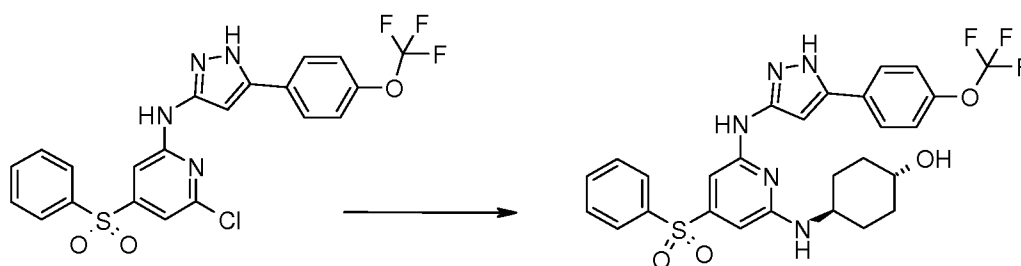
A mixture of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-(4-trifluoromethyl-phenyl)-1*H*-pyrazol-3-yl]-amine (0.28 g, 59% purity, 0.34 mmol), *trans*-4-aminocyclohexanol (0.50 g, 4.35 mmol) and DIPEA (0.72 mL, 4.35 mmol) in anhydrous DMSO (2.8 mL) was flushed with nitrogen and heated at 120 °C in a sealed microwave vial for 3.5h. After this time the reaction mixture was left standing at room temperature for 16h after which more *trans*-4-aminocyclohexanol (0.50 g, 4.35 mmol) was added to the reaction mixture and the reaction heated again at 120 °C. After 2h heating at this temperature more *trans*-4-aminocyclohexanol (0.50 g, 4.35 mmol) was added. The mixture was further heated at the same temperature for 2.5h after which a further addition of *trans*-4-aminocyclohexanol (0.50 g, 4.35 mmol) was carried out. The mixture was heated at the same temperature for 3h more after which it was allowed to stand at room temperature overnight. The reaction mixture was then partitioned between EtOAc (10 mL) and saturated aq. ammonium chloride solution (5 mL), the phases separated and the aqueous phase further extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried

25

over MgSO_4 , filtered and concentrated *in vacuo*. The crude material obtained was purified by automated reverse-phase preparative HPLC (low pH method) to give the title compound as a yellow solid (50 mg, 22 %). ^1H NMR (500 MHz, DMSO-d_6) δ 12.90 (br. s, 1 H), 9.46 (br. s, 1 H), 8.03 - 7.85 (m, 4 H), 7.84 - 7.78 (m, 1 H), 7.77 - 7.71 (m, 2 H) 7.71 - 7.62 (m, 2 H), 6.95 (br. s, 1 H), 6.82 (br. s, 1 H), 6.68 (br. s, 1 H), 6.21 (br. s, 1 H), 4.57 (br. s, 1 H), 3.71 (br. s, 1 H), 3.43 (br. s, 1 H), 2.00 - 1.91 (m, 2 H), 1.90 - 1.79 (m, 2 H), 1.38 - 1.14 (m, 4 H). MS: m/z = 558.0 ($\text{M} + \text{H}$)⁺.

Example 65

(*trans*)-4-{4-Benzenesulfonyl-6-[5-(4-trifluoromethoxy-phenyl)-1*H*-pyrazol-3-ylamino]-pyridin-2-ylamino}-cyclohexanol, formate salt

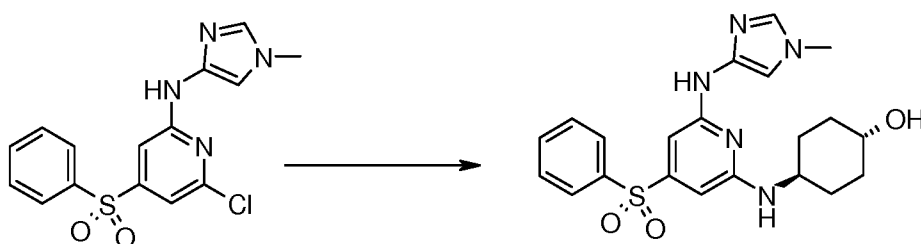


A mixture of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-(4-trifluoromethoxy-phenyl)-1*H*-pyrazol-3-yl]-amine (0.18 g, 0.37 mmol), *trans*-4-aminocyclohexanol (0.32 g, 2.77 mmol) and DIPEA (0.5 mL, 2.77 mmol) in anhydrous DMSO (2.8 mL) was flushed with nitrogen and heated at 120 °C in a sealed microwave vial (plastic lid) for 2h. After this time the reaction mixture was left standing at room temperature for 15.3h after which more *trans*-4-aminocyclohexanol (0.32 g, 2.77 mmol) was added to the reaction mixture and the reaction heated again at 120 °C. After 3.5 h heating at this temperature more *trans*-4-aminocyclohexanol (0.32 g, 2.77 mmol) was added. The mixture was further heated at the same temperature for 3h after which a further addition of *trans*-4-aminocyclohexanol (0.32 g, 2.77 mmol) was carried out. The mixture was heated at the same temperature for 2 h more after which it was allowed to stand at room temperature for 16h. More *trans*-4-aminocyclohexanol (0.20 g, 1.74 mmol) was then added and the reaction mixture heated at 120 °C for 3.5h. The reaction mixture was then partitioned between EtOAc (10 mL) and saturated aq. ammonium chloride solution (5 mL), the phases separated and the aqueous phase further extracted with EtOAc (2 x 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over MgSO_4 , filtered and evaporated *in vacuo*. The crude material obtained was purified by automated reverse-phase preparative HPLC (low

pH method) to give the title compound as a yellow solid (0.06g, 26%). ^1H NMR (500 MHz, DMSO- d_6) δ 12.76 (br. s, 1 H), 9.40 (br. s, 1 H), 7.97 - 7.78 (m, 4 H), 7.77 - 7.71 (m, 1 H), 7.70 - 7.63 (m, 2 H), 7.51 - 7.33 (m, 2 H), 6.92 - 6.58 (m, 2 H), 6.36 - 6.13 (m, 2 H), 4.55 (br. s, 1 H), 3.70 (br. s, 1 H), 3.42 (br. s, 1 H), 1.99 - 1.90 (m, 2 H), 1.89 - 1.78 (m, 2 H), 1.36 - 1.14 (m, 4 H). MS: m/z = 574.0 ($M + H$) $^+$.

Example 66

(*trans*)-4-[4-Benzenesulfonyl-6-(1-methyl-1*H*-imidazol-4-ylamino)-pyridin-2-ylamino]-cyclohexanol

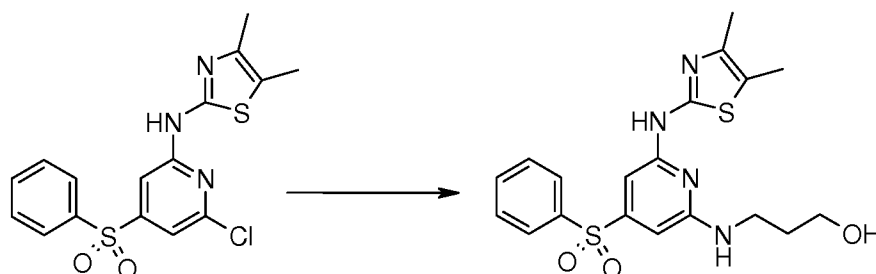


A mixture of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-(1-methyl-1*H*-imidazol-4-yl)-amine (0.14 g, 82% purity, 0.33 mmol), *trans*-4-aminocyclohexanol (0.23 g, 2.01 mmol) and DIPEA (0.3 mL, 2.01 mmol) in anhydrous DMSO (2 mL) was flushed with nitrogen and heated at 120 °C in a sealed microwave vial (plastic lid) for 2.5h. After this time the reaction mixture was left standing at room temperature for 15.5h after which more *trans*-4-aminocyclohexanol (0.35 g, 3.01 mmol) and DIPEA (0.50 mL, 3.01 mmol) were added to the reaction mixture and the reaction heated again at 120 °C. After 3h heating at this temperature more *trans*-4-aminocyclohexanol (0.35 g, 3.01 mmol) was added. The mixture was further heated at the same temperature for 3h after which a further addition of *trans*-4-aminocyclohexanol (0.35 g, 3.01 mmol) was carried out. The mixture was heated at the same temperature for 2.5 h more after which it was allowed to stand at room temperature for 2.5 days. More *trans*-4-aminocyclohexanol (0.35 g, 3.01 mmol) was then added and the reaction mixture heated at 120 °C for 2.5h. After this time, more *trans*-4-aminocyclohexanol (0.35 g, 3.01 mmol) was added and the mixture heated at the same temperature for 3 h more. A final addition of *trans*-4-aminocyclohexanol (0.35 g, 3.01 mmol) was carried out and the mixture heated for a further 2.5h after which it was left standing at room temperature for 1.5 days. The reaction mixture was then partitioned between EtOAc (20 mL) and saturated aqueous ammonium chloride solution (10 mL), the phases separated and the aqueous phase further extracted with EtOAc (1 \times 15 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over MgSO_4 , filtered and evaporated *in vacuo*. The crude material was purified by automated reverse-phase preparative HPLC (low pH method). The

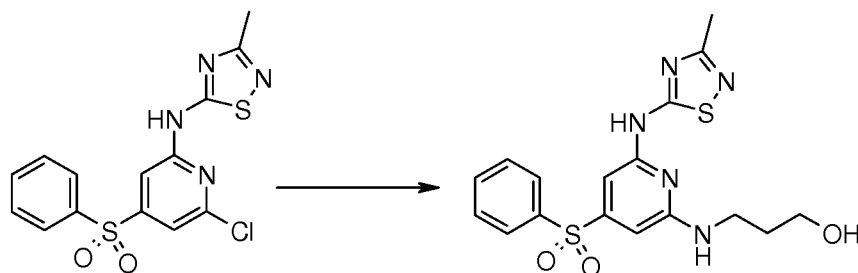
formate salt obtained was free based by passing it through an Isolute flash NH_2 column, eluting with MeOH (50 %) in DCM to give the title compound as a dark yellow solid (0.04 g, 31 %). ^1H NMR (500 MHz, DMSO- d_6) δ 9.29 (s, 1 H), 7.91- 7.81 (m, 2 H), 7.78 - 7.69 (m, 1 H), 7.68 - 7.61 (m, 2 H), 7.33 (s, 1 H), 7.16 (br. s, 1 H), 6.77 (d, J = 6.8 Hz, 1 H), 6.37 (s, 1 H), 6.07 (s, 1 H), 4.58 (br. s, 1 H), 3.66 - 3.52 (m, 4 H), 3.42 (br. s, 1 H), 2.06 - 1.94 (m, 2 H), 1.91 - 1.78 (m, 2 H), 1.39 - 1.09 (m, 4 H). MS: m/z = 428.1 ($\text{M}+\text{H}$) $^+$.

Example 67

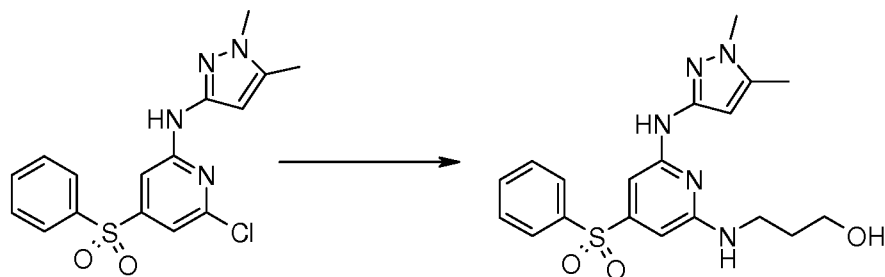
3-[4-Benzenesulfonyl-6-(4,5-dimethyl-thiazol-2-ylamino)-pyridin-2-ylamino]-propan-1-ol, formate salt



A mixture of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-(4,5-dimethyl-thiazol-2-yl)-amine (0.1 g, 0.25 mmol), 3-aminopropanol (60.4 μl , 0.79 mmol), BINAP (0.02 g, 0.04 mmol) and sodium *tert*-butoxide (0.13 g, 1.32 mmol) in anhydrous DME (2 mL) was sonicated under a flow of nitrogen for 10 min before tris(dibenzylideneacetone)dipalladium (0) (0.01 g, 0.01 mmol) was added and the resulting mixture was heated at 85 $^{\circ}\text{C}$ in a sealed tube for 21.3h. The reaction mixture was then allowed to cool down to room temperature, filtered through a pad of Celite and washed with EtOAc. The filtrate was then concentrated *in vacuo*. The crude material obtained was purified by automated reverse-phase preparative HPLC (low pH method) to give the title compound as a yellow solid (0.03 g, 24 %). ^1H NMR (500 MHz, DMSO- d_6) δ 10.94 (br. s, 1 H), 8.18 (br. s, 0.7 H), 7.91 -7.84 (m, 2 H), 7.79 - 7.71 (m, 1 H), 7.70 - 7.62 (m, 2 H), 7.21 (br. s, 1 H), 6.40 (s, 1 H), 6.34 (s, 1 H), 4.47 (br. s, 1 H), 3.54 - 3.41 (m, 4 H), 2.19 (s, 3 H), 2.10 (s, 3 H), 1.70 (quin, J = 6.7 Hz, 2 H). MS: m/z = 419.0 ($\text{M}+\text{H}$) $^+$.

Example 68**3-[4-Benzenesulfonyl-6-(3-methyl-[1,2,4]thiadiazol-5-ylamino)-pyridin-2-ylamino]-propan-1-ol**

5 A mixture of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-(3-methyl-[1,2,4]thiadiazol-5-yl)-amine (0.1 g, 0.27 mmol), 3-aminopropanol (63 μ L, 0.82 mmol), BINAP (0.03 g, 0.04 mmol) and sodium *tert*-butoxide (0.13 g, 1.36 mmol) in anhydrous DME (2 mL) was sonicated under a flow of nitrogen for 10 min before tris(dibenzylideneacetone)dipalladium (0) (0.01 g, 0.01 mmol) was added and the resulting mixture heated at 85 $^{\circ}$ C in a sealed tube
 10 for 17.5 h. The reaction mixture was allowed to cool down to room temperature, filtered through a pad of Celite and washed with EtOAc. The filtrate was then concentrated *in vacuo*. The crude material was purified by flash silica chromatography (eluting with 1-10% MeOH in DCM) to give the title compound as a light yellow solid (0.02 g, 20 %). 1 H NMR (500 MHz, DMSO- d_6) δ 11.89 (br. s, 1 H), 7.93 - 7.87 (m, 2 H), 7.80 - 7.74 (m, 1 H), 7.72 - 7.63 (m, 2 H), 7.42 (br. s, 1 H), 6.56 - 6.45 (m, 2 H), 4.51 (t, J = 4.9 Hz, 1 H), 3.56 - 3.44 (m, 4 H),
 15 2.36 (s, 3 H), 1.72 (quin, J = 6.6 Hz, 2 H). MS: m/z = 406.0 (M+H) $^{+}$.

Example 69**3-[4-Benzenesulfonyl-6-(1,5-dimethyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-propan-1-ol**

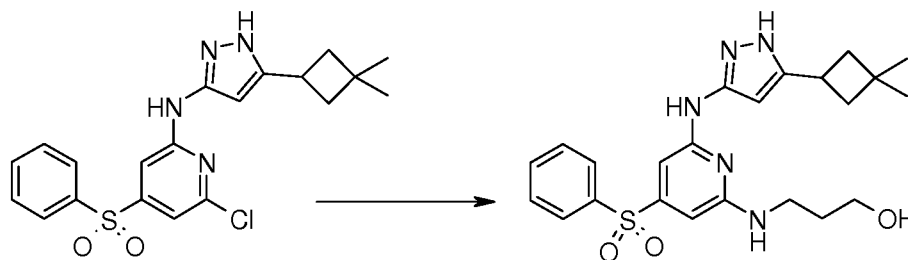
20

A mixture of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-(1,5-dimethyl-1H-pyrazol-3-yl)-amine (0.14 g, 0.39 mmol), 3-aminopropanol (0.2 mL, 2.79 mmol) and DIPEA (0.46 mL, 2.79 mmol) in anhydrous DMSO (2.0 mL) was flushed with nitrogen and heated at 120 $^{\circ}$ C in

a sealed vial for 3h. The mixture was then left standing at room temperature for 15h. More 3-aminopropanol (0.2 mL, 2.79 mmol) was then added and the mixture heated at 120 °C for 2.5h. A final charge of 3-aminopropanol (0.2 mL, 2.79 mmol) was then added and the mixture heated at the same temperature for a further 4.5h. The reaction mixture was then left standing at room temperature for 11h and then partitioned between EtOAc (10 mL) and saturated aq. ammonium chloride solution (5 mL), the phases separated and the aqueous phase extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried (MgSO₄), filtered and evaporated *in vacuo*. The crude material was purified by automated reverse-phase preparative HPLC (low pH method) to give the title compound as a yellow solid (0.07g, 45%). ¹H NMR (500 MHz, DMSO-d₆) δ 9.15 (s, 1 H), 7.90 - 7.85 (m, 2 H), 7.78 - 7.70 (m, 1 H), 7.70 - 7.59 (m, 2 H), 6.86 (br. s, 1 H), 6.61 (br. s, 1 H), 6.21 (br. s, 1 H), 6.16 (s, 1 H), 4.46 (br. s, 1 H), 3.59 (s, 3 H), 3.52 - 3.41 (m, 2 H), 3.31 - 3.21 (m, 2 H), 2.18 (s, 3 H), 1.66 (quin, *J* = 6.7 Hz, 2 H). MS: *m/z* = 402.1 (M+H)⁺.

Example 70

3-{[4-Benzenesulfonyl-6-[5-(3,3-dimethyl-cyclobutyl)-1*H*-pyrazol-3-ylamino]-pyridin-2-ylamino]-propan-1-ol, formate salt

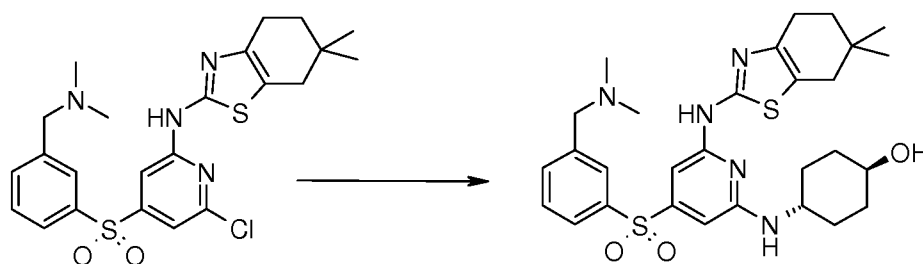


A mixture of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-[5-(3,3-dimethyl-cyclobutyl)-1*H*-pyrazol-3-yl]-amine (140 mg, 80% purity, 0.24 mmol), 3-aminopropanol (179 μL, 2.34 mmol) and DIPEA (0.39 mL, 2.34 mmol) in anhydrous DMSO (1.6 mL) was flushed with nitrogen and heated at 120 °C in a sealed vial for 2.5 h. More 3-aminopropanol (0.18 mL, 2.34 mmol) was then added and the mixture heated at 120 °C for a further 2.75 h. A further addition of 3-aminopropanol (0.2 mL, 2.34 mmol) was then carried out and the mixture heated at the same temperature for a further 2.5 h. The reaction mixture was then allowed to cool down to room temperature and subsequently partitioned between EtOAc (10 mL) and saturated aq. ammonium chloride solution (5 mL). The two phases were separated and the aqueous phase extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried over MgSO₄, filtered and evaporated *in vacuo*. The crude material was purified by automated reverse-phase preparative HPLC under acidic

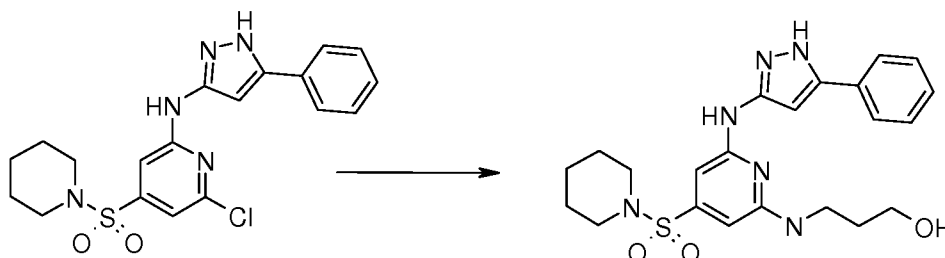
conditions to give the title compound as a yellow solid (50 mg, 39%). ¹H NMR (500 MHz, DMSO-d₆) δ 11.86 (br. s, 1 H), 9.20 (br. s, 1 H), 8.17 (s, 0.4H), 7.92 - 7.81 (m, 2 H), 7.78 - 7.69 (m, 1 H), 7.69 - 7.59 (m, 2 H), 6.88 (br. s, 1 H), 6.71 (br. s, 1 H), 6.19 (s, 2 H), 4.45 (br. s, 1 H), 3.47 (t, *J* = 6.3 Hz, 2 H), 2.11 - 2.02 (m, 2 H), 1.93 - 1.86 (m, 2 H), 1.67 (quin, *J* = 6.7 Hz, 2 H), 1.19 (s, 3 H), 1.09 (s, 3 H). MS: *m/z* = 456.1 (M+H)⁺.

Example 71

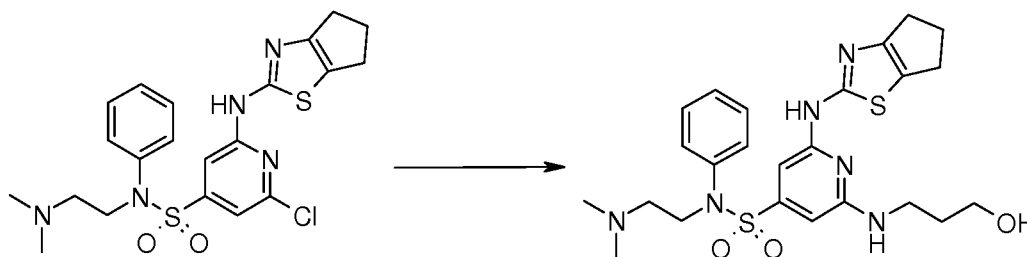
(*trans*)-4-[4-(3-Dimethylaminomethyl-benzenesulfonyl)-6-(6,6-dimethyl-4,5,6,7-tetra hydro-benzothiazol-2-ylamino)-pyridin-2-ylamino]-cyclohexanol



To a solution of [6-Chloro-4-(3-dimethylaminomethyl-benzenesulfonyl)-pyridin-2-yl]-(6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-yl)-amine (150 mg, 0.278 mmol) in DMSO (2.5 mL) was added *trans*-4-aminocyclohexanol (160 mg, 1.39 mmol), and DIPEA (179 mg, 1.39 mmol) and the mixture heated at 140 °C for 1.5h. More *trans*-4-aminocyclohexanol (100 mg, 0.87 mmol) was added and heating continued for a further 1.5h. The cooled mixture was partitioned between saturated ammonium chloride solution (50 mL) and EtOAc (50 mL), and the phases separated. The organic phase was washed with water (2 x 10 mL), dried (Na₂SO₄), filtered, and the filtrate evaporated to dryness to afford a brown oil. The crude was purified by automated reverse-phase HPLC (high pH method) to give the title compound as a brown solid (37 mg, 23 %). ¹H NMR (500MHz, MeOD): δ 7.94 (s, 1 H), 7.89 (d, *J* = 7.9 Hz, 1 H), 7.67- 7.64 (m, 1 H), 7.63 - 7.57 (m, 1 H), 6.44 (s, 1 H), 6.40 (s, 1 H), 4.04 (t, *J* = 10.9 Hz, 1 H), 3.65 - 3.60 (m, 1 H), 3.59 - 3.56 (m, 2 H), 2.60 (t, *J* = 5.8 Hz, 2 H), 2.48 (s, 2 H), 2.25 (s, 6 H), 2.16 (d, *J* = 11.3 Hz, 2 H), 2.02 (d, *J* = 10.6 Hz, 2 H), 1.64 (t, *J* = 6.3 Hz, 2 H), 1.52 - 1.41 (m, 2 H), 1.27 - 1.37 (m, 2 H), 1.05 ppm (s, 6 H). MS: *m/z* = 570.2 (M + H)⁺.

Example 72**3-[6-(5-Phenyl-1H-pyrazol-3-ylamino)-4-(piperidine-1-sulfonyl)-pyridin-2-ylamino]-propan-1-ol**

5 To a solution of [6-Chloro-4-(piperidine-1-sulfonyl)-pyridin-2-yl]-(5-phenyl-1H-pyrazol-3-yl)-amine (70 mg, 60% purity, 0.100 mmol) in DMSO (3 mL) was added 3-aminopropanol (151 mg, 2.01 mmol) and the solution heated at 140 °C for 4h. The cooled mixture was partitioned between water (10 mL) and EtOAc (45 mL), and the phases separated. The organic phase was washed with water (2 x 5 mL), brine (5 mL), dried
 10 (Na₂SO₄), filtered and the filtrate evaporated to dryness to afford an orange oil. The crude was purified by automated reverse phase HPLC (high pH method) to give the title compound as a red solid (11 mg, 23%). ¹H NMR (250MHz, MeOD): δ 7.72 (br. s., 2 H), 7.49 - 7.30 (m, 3 H), 6.60 - 6.20 (m, 1 H), 6.13 (s, 1 H), 3.70 (t, *J* = 6.1 Hz, 2 H), 3.48 (t, *J* = 6.6 Hz, 2 H), 3.11 - 3.02 (m, 4 H), 1.89 (t, *J* = 6.5 Hz, 2 H), 1.65 (br. s., 4 H), 1.50 ppm (d, *J* = 5.3 Hz, 2
 15 H). MS: *m/z* = 457.1 (M + H)⁺.

Example 73**2-(5,6-Dihydro-4H-cyclopentathiazol-2-ylamino)-6-(3-hydroxy-propylamino)-pyridine-4-sulfonic acid (2-dimethylamino-ethyl)-phenyl-amide**

20 To a solution of 2-Chloro-6-(5,6-dihydro-4H-cyclopentathiazol-2-ylamino)-pyridine-4-sulfonic acid (2-dimethylamino-ethyl)-phenyl-amide (188 mg, 0.358 mmol) in DMSO (2 mL) was added 3-aminopropanol (269 mg, 3.58 mmol) and the solution heated at 130 °C for 3h. The cooled mixture was partitioned between saturated aq. ammonium chloride solution (50 mL) and EtOAc (50 mL), and the phases separated. The organic phase was washed with

brine (20 mL), dried (Na_2SO_4), filtered and the filtrate evaporated to dryness to afford a brown oil. The crude was purified by automated reverse phase HPLC (high pH method) to give the title compound as an off-white solid (16 mg, 9 %). ^1H NMR (500 MHz, $\text{MeOD} + \text{CDCl}_3$): δ 7.39 - 7.32 (m, 3 H), 7.19 (d, $J = 6.8$ Hz, 2 H), 6.19 (s, 1 H), 6.07 (s, 1 H), 3.77 - 3.73 (m, 2 H), 3.70 (t, $J = 6.3$ Hz, 2 H), 3.60 (t, $J = 6.7$ Hz, 2 H), 2.87 (t, $J = 6.9$ Hz, 2 H), 2.72 (t, $J = 7.2$ Hz, 2 H), 2.49 - 2.42 (m, 4 H), 2.26 (s, 6 H), 1.88 ppm (quin, $J = 6.5$ Hz, 2 H). MS: $m/z = 517.1$ ($\text{M} + \text{H}$) $^+$.

Example 74

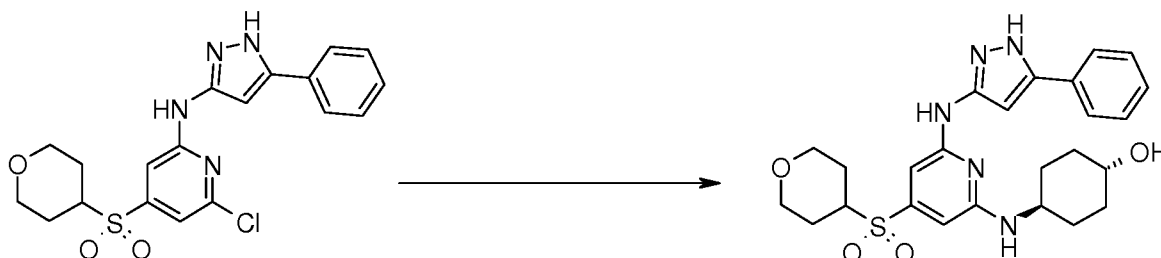
4-Benzenesulfonyl-*N*-(2-methanesulfonyl-ethyl)-*N'*-(1-phenyl-1*H*-imidazol-4-yl)-pyridine-2,6-diamine, formate salt



A mixture of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-(1-phenyl-1*H*-imidazol-4-yl)-amine (0.03 g, 0.05 mmol), methanesulfonyl-ethylamine hydrochloride (0.03 g, 0.16 mmol), BINAP (5 mg, 0.01 mmol) and sodium *tert*-butoxide (37 mg, 0.38 mmol) in anhydrous DME (1 mL) was sonicated under a flow of N_2 for 5 min before tris(dibenzylideneacetone)dipalladium (0) (2.51 mg, 0 mmol) was added and the resulting mixture was heated to 85 °C in a sealed tube for 17h. The reaction mixture was then filtered through a pad of Celite and the Celite washed with EtOAc. The filtrate was concentrated *in vacuo* and the crude material purified by flash chromatography, eluting with MeOH (1 - 20 %) in DCM. The solid obtained was further purified by automated preparative HPLC (low pH method) to give the title compound as a yellow solid (0.01 g, 27 %). ^1H NMR (500 MHz, DMSO-d_6): δ 9.60 (br. s., 1 H), 8.10 (s, 1 H), 7.93 - 7.85 (m, 2 H), 7.78 - 7.71 (m, 1 H), 7.70 - 7.64 (m, 3 H), 7.64 - 7.59 (m, 2 H), 7.52 - 7.44 (m, 2 H), 7.35 - 7.28 (m, 1 H), 7.23 - 7.16 (m, 1 H), 6.56 (s, 1 H), 6.20 (s, 1 H), 3.84 - 3.70 (m, 2 H), 3.00 (s, 3 H). MS: $m/z = 498.0$ ($\text{M} - \text{HCOOH} + \text{H}$) $^+$.

Example 75

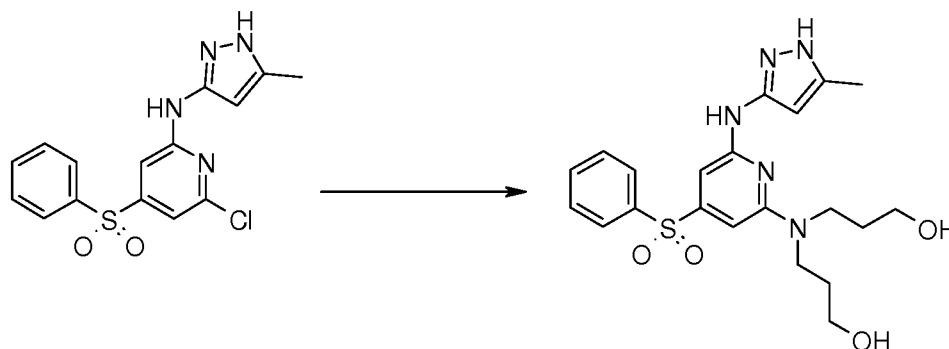
(*trans*)-4-[6-(5-Phenyl-2*H*-pyrazol-3-ylamino)-4-(tetrahydro-pyran-4-sulfonyl)-pyridin-2-ylamino]-cyclohexanol



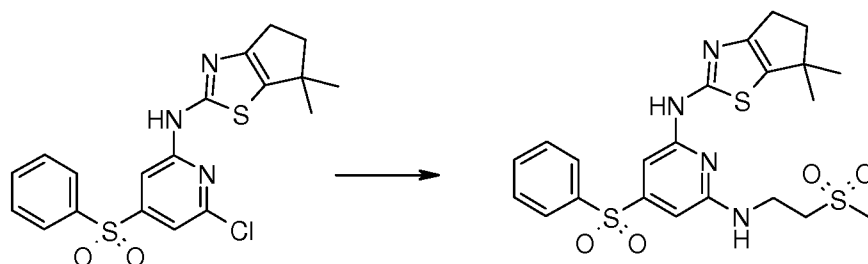
5

A mixture of [6-chloro-4-(tetrahydro-pyran-4-sulfonyl)-pyridin-2-yl]-(5-phenyl-2*H*-pyrazol-3-yl)-amine formate salt (0.1 g, 0.22 mmol), *trans*-4-aminocyclohexanol (0.19 g, 1.61 mmol) and DIPEA (0.27 mL, 1.61 mmol) in anhydrous DMSO (1.0 mL) was flushed with nitrogen and heated to 120 °C in a sealed tube. Further additions of *trans*-4-aminocyclohexanol (0.19 g, 1.61 mmol) were carried out approximately every 2 - 3h while monitoring by LC-MS until the amount of product did not increase further (no heating or addition of *trans*-4-aminocyclohexanol overnight). The total heating time was 24h and the total amount of *trans*-4-aminocyclohexanol added 58.5 equivalents. The reaction mixture was then allowed to cool down to room temperature and partitioned between EtOAc (10 mL) and saturated aq. ammonium chloride solution (5 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried (MgSO₄), filtered and evaporated *in vacuo*. The crude material was purified by flash chromatography eluting with MeOH (0 - 10 %) in DCM to give the title compound as a light brown solid (0.07 g, 68 %). ¹H NMR (500 MHz, DMSO-d₆): δ 12.66 (br. s., 1 H), 9.40 (br. s., 1 H), 7.75 - 7.66 (m, 2 H), 7.51 - 7.41(m, 2 H), 7.38 - 7.29 (m, 1 H), 6.93 - 6.74 (m, 2 H), 6.63 (br. s., 1 H), 6.15 (br. s., 1 H), 4.58 (br. s., 1 H), 3.91 (dd, *J*=11.2, 3.8 Hz, 2 H), 3.76 (br. s., 1 H), 3.44 (br. s., 2 H), 2.09 - 1.94 (m, 2 H), 1.92 - 1.82 (m, 2H), 1.81 - 1.71 (m, 2 H), 1.66 - 1.48 (m, 2 H), 1.38 - 1.11(m, 4 H). MS: *m/z* = 498.1 (M+H)⁺.

25

*Example 76***3-[[4-Benzenesulfonyl-6-(5-methyl-2*H*-pyrazol-3-ylamino)-pyridin-2-yl]-(3-hydroxy-propyl)-amino]-propan-1-ol, formate salt**

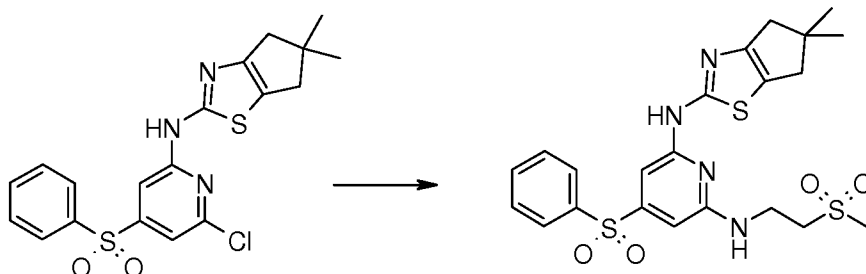
- 5 A mixture of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1*H*-pyrazol-3-yl)-amine (0.15 g, 0.43 mmol), 3-(3-hydroxy-propylamino)-propan-1-ol (0.29 g, 2.15 mmol) (synthesized according to *Tetrahedron* **1995**, 51, 1197-1208) and DIPEA (0.35 mL, 2.15 mmol) in anhydrous DMSO (2.0 mL) was flushed with nitrogen and heated to 120 °C in a sealed tube. Further additions of 3-(3-hydroxy-propylamino)-propan-1-ol (0.29 g, 2.15 mmol) as a solution in DMSO (0.2 mL) were carried out approximately every 3 h while monitoring by LC-MS (no heating or addition of 3-(3-hydroxy-propylamino)-propan-1-ol overnight). The total heating time was 19h and the total amount of 3-(3-hydroxy-propylamino)-propan-1-ol added 30 equivalents. The reaction mixture was then allowed to cool down to room temperature and partitioned between EtOAc (10 mL) and saturated aqueous ammonium chloride solution (5 mL). The phases were separated and the aqueous phase extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried (MgSO₄), filtered and evaporated *in vacuo*. The crude material was purified by automated preparative HPLC (low pH method) to give the title compound as a yellow solid (0.05 g, 21 %). ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.79 (br. s., 1 H), 9.20 (br. s., 1 H), 8.02 - 7.84 (m, 2 H), 7.76 - 7.6 (m, 1 H), 7.68 - 7.60 (m, 2 H), 6.68 (br. s., 1 H), 6.25 (s, 1 H), 6.14 (br. s., 1 H), 4.56 (br. s., 2 H), 3.58 - 3.41 (m, 8 H), 2.16 (s, 3 H), 1.77 - 1.56 (m, 4 H). MS: *m/z* = 446.0 (M + H)⁺.
- 10
- 15
- 20

*Example 77***4-Benzenesulfonyl-N-(6,6-dimethyl-5,6-dihydro-4H-cyclopentathiazol-2-yl)-N'-(2-methanesulfonyl-ethyl)-pyridine-2,6-diamine**

5 To a solution of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(6,6-dimethyl-5,6-dihydro-4H-cyclopenta thiazol-2-yl)-amine and (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5,5-dimethyl-5,6-dihydro-4H-cyclopentathiazol-2-yl)-amine (500 mg, 1.19 mmol) in anhydrous DMSO (6 mL) was added 2-Methanesulfonyl-ethylamine hydrochloride (950 mg, 5.95 mmol) and DIPEA (0.98 mL, 5.95 mmol) and the mixture was heated at 120 °C in a sealed tube for 2 h and then at 150 °C for 10h. A further 2-Methanesulfonyl-ethylamine hydrochloride (380 mg, 2.38 mmol) and DIPEA (0.39 mL, 2.38 mmol) were added and the reaction stirred at 150 °C for another 2 h. The reaction was cooled, was partitioned between EtOAc (20 mL) and aq. ammonium chloride solution (20 mL) and the phases separated. The aqueous was extracted with EtOAc (2 x 30 mL) and the combined organics were washed with water (20 mL), brine (20 mL) and dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100%) in heptane, followed by MeOH (0 - 5%) in EtOAc. The material isolated was further purified by preparative HPLC (MeCN/Water) on an achiral column and the resulting material was resolved into single regio-isomers by chiral HPLC to give the title compound as a yellow solid (43 mg, 7 %). ¹H NMR (500 MHz, CDCl₃): δ 9.83 (br.s, 1H), 7.95 (d, *J* = 7.5 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 2H), 6.57 (s, 1H), 6.42 (s, 1H), 5.30 (t, *J* = 6.3 Hz, 1H), 4.18 (q, *J* = 6.2 Hz, 2H), 3.44 (t, *J* = 6.1 Hz, 2H), 2.84 (t, *J* = 7.0 Hz, 2H), 2.29 (t, *J* = 7.0 Hz, 2H), 1.36 (s, 6H). MS: *m/z* = 507.0 (M + H)⁺.

Example 78

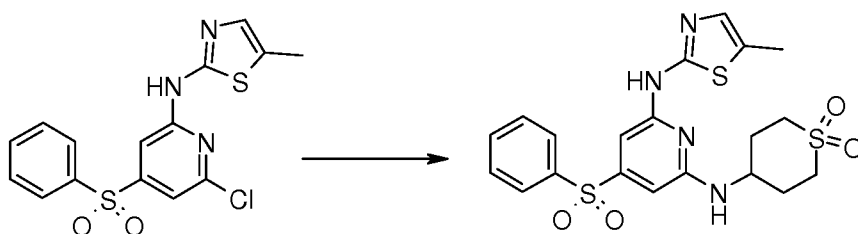
4-Benzenesulfonyl-N-(5,5-dimethyl-5,6-dihydro-4H-cyclopentathiazol-2-yl)-N'-(2-methanesulfonyl-ethyl)-pyridine-2,6-diamine



5 The preparation of this compound was carried out simultaneously with that of Example 77. The title compound was a yellow solid (9 mg, 1.5 %). ¹H NMR (500 MHz, CDCl₃): δ 7.87 (d, J = 7.7 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 6.51 (s, 1H), 6.36 (s, 1H), 5.35 – 5.26 (m, 1H), 4.13 – 4.04 (m, 2H), 3.36 (t, J = 5.7 Hz, 2H), 2.90 (s, 3H), 2.66 – 2.58 (m, 4H), 1.22 (s, 6H). MS: *m/z* = 507.0 (M + H)⁺.

10 **Example 79**

4-Benzenesulfonyl-N-(1,1-dioxo-hexahydro-1λ6-thiopyran-4-yl)-N'-(5-methyl-thiazol-2-yl)-pyridine-2,6-diamine

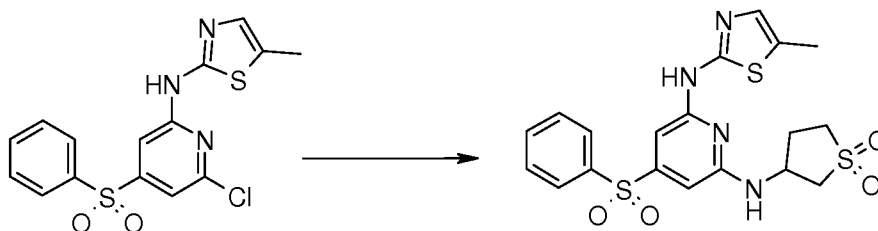


15 A mixture of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-thiazol-2-yl)-amine (135 mg, 0.35 mmol), 1,1-Dioxo-hexahydro-1λ6-thiopyran-4-ylamine hydrochloride (197 mg, 1.06 mmol), BINAP (33 mg, 0.05 mmol) and sodium *tert*-butoxide (204 mg, 2.13 mmol) in DME (1.5 ml) was sonicated under a flow of nitrogen for 10 minutes before tris(dibenzylideneacetone)dipalladium(0) (16 mg, 0.02 mmol) was added and the resulting mixture was heated to 85 °C in a sealed tube for 18h. The reaction mixture was cooled,
 20 filtered through a pad of Celite and the pad washed with EtOAc. The filtrate was concentrated and the residue purified by flash chromatography, eluting with EtOAc (40 - 100 %) in heptane to give the title compound as a yellow solid (134 mg, 77%). ¹H NMR (500MHz, DMSO-d₆): δ 11.06 (s, 1H), 7.95 – 7.85 (m, 2H), 7.83 – 7.74 (m, 1H), 7.73 – 7.65 (m, 2H), 7.37 (d, J = 7.3 Hz, 1H), 7.03 (d, J = 1.2 Hz, 1H), 6.52 (d, J = 1.0 Hz, 1H), 6.39 (d, J = 1.2

Hz, 1H), 4.33 – 4.18 (m, 1H), 3.31 – 3.24 (m, 2H), 3.24 – 3.15 (m, 2H), 2.41 – 2.24 (m, 5H), 2.07 – 1.92 (m, 2H). MS: m/z = 479.0 (M + H)⁺.

Example 80

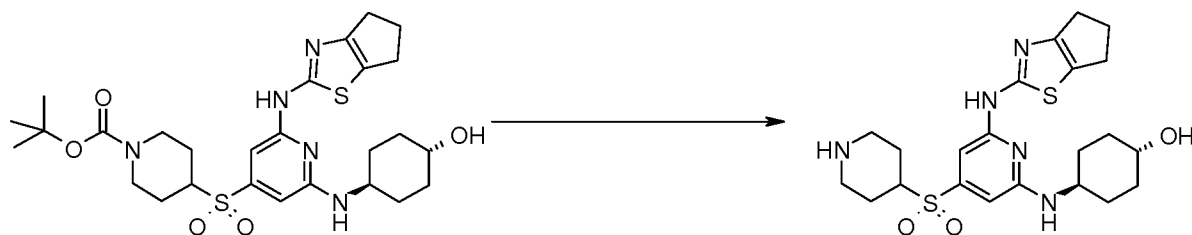
5 (+/-)-4-Benzenesulfonyl-N-(1,1-dioxo-tetrahydro-1λ6-thiophen-3-yl)-N'-(5-methyl-thiazol-2-yl)-pyridine-2,6-diamine



The title compound was synthesized according to Example 79 by substituting 1,1-Dioxo-hexahydro-1λ6-thiopyran-4-ylamine hydrochloride with (+/-)-1,1-Dioxo-tetrahydro-1λ6-thiophen-3-ylamine hydrochloride. ¹H NMR (500MHz, DMSO-d₆): δ 7.92 – 7.85 (m, 2H), 7.61 – 7.54 (m, 1H), 7.53 – 7.46 (m, 2H), 6.98 (s, 1H), 6.51 (s, 1H), 6.36 (s, 1H), 5.09 – 5.00 (m, 1H), 5.00 – 4.94 (m, 1H), 3.66 (dd, J = 13.2, 6.4 Hz, 1H), 3.33 – 3.23 (m, 1H), 3.22 – 3.10 (m, 1H), 2.90 (dd, J = 13.3, 6.1 Hz, 1H), 2.66 – 2.53 (m, 1H), 2.34 (s, 3H), 2.32 – 2.22 (m, 1H). MS: m/z = 465.0 (M + H)⁺.

Example 81

15 (*trans*)-4-[6-(5,6-Dihydro-4H-cyclopentathiazol-2-ylamino)-4-(piperidine-4-sulfonyl)-pyridin-2-ylamino]-cyclohexanol

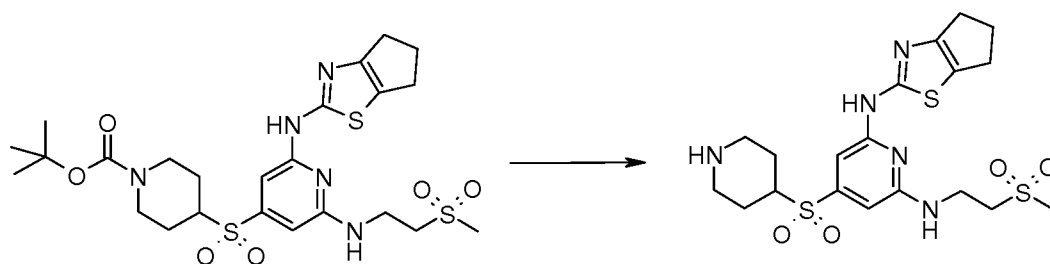


A solution of tert-butyl 4-[2-({4H,5H,6H-cyclopenta[d][1,3]thiazol-2-yl}amino)-6-
20 {[(*trans*)-4-hydroxycyclohexyl]amino}pyridine-4-sulfonyl]piperidine-1-carboxylate (100 mg, 0.173 mmol) in MeOH (1 mL) and 4M HCl in dioxane (2 mL, 8 mmol) was stirred at room temperature for 1.5h. The solvent was evaporated and the residue passed through an SCX-2 column, eluting with 7 N ammonia in MeOH in DCM to produce crude material as a free base, which was purified by flash chromatography, eluting with 7 N ammonia in MeOH (0 -
25 10 %) in DCM, followed by preparative HPLC (high pH method) to give the title compound

as a yellow solid (24 mg, 28 %). ¹H NMR (500 MHz, MeOD) δ 6.44 (s, 1H), 6.36 (s, 1H), 4.18 – 4.02 (m, 1H), 3.96 – 3.84 (m, 1H), 3.63 (dd, J = 12.7, 8.8 Hz, 2H), 3.07 – 3.00 (m, 1H (+ 1H)), 2.92 – 2.87 (m, 2H), 2.79 – 2.70 (m, 2H), 2.55 – 2.43 (m, 2H), 2.26 (d, J = 12.8 Hz, 2H), 2.22 – 2.15 (m, 2H), 2.10 – 2.00 (m, 2H), 1.98 – 1.87 (m, 2H), 1.55 – 1.42 (m, 2H + 2H), 1.35 (dd, J = 25.7, 12.8 Hz, 2H). MS: *m/z* = 478.1 (M + H)⁺.

Example 82

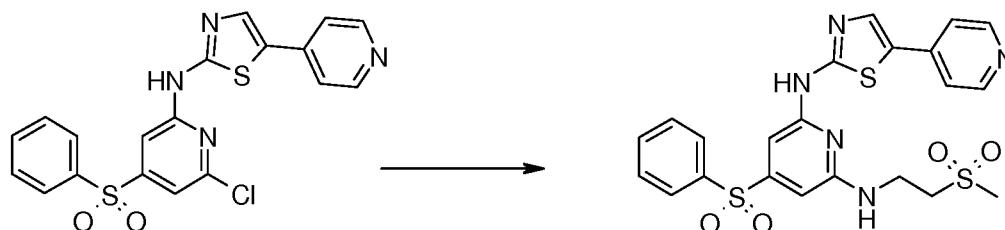
N-(5,6-Dihydro-4H-cyclopentathiazol-2-yl)-N'-(2-methanesulfonyl-ethyl)-4-(piperidine-4-sulfonyl)-pyridine-2,6-diamine



The title compound was synthesized according to Example 81 by substitution of tert-butyl 4-[2-({4H,5H,6H-cyclopenta[d][1,3]thiazol-2-yl}amino)-6-{{(trans)-4-hydroxycyclohexyl}amino}pyridine-4-sulfonyl]piperidine-1-carboxylate with 4-[2-(5,6-Dihydro-4H-cyclopentathiazol-2-ylamino)-6-(2-methanesulfonyl-ethylamino)-pyridine-4-sulfonyl]-piperidine-1-carboxylic acid *tert*-butyl ester. ¹H NMR (500 MHz, MeOD) δ 6.56 (s, 1H), 6.43 (d, J = 1.1 Hz, 1H), 4.10 (t, J = 6.7 Hz, 2H), 3.54 (t, J = 6.6 Hz, 2H), 3.31 – 3.22 (m, 1H), 3.13 (d, J = 12.7 Hz, 2H), 3.03 (s, 3H), 2.89 (t, J = 7.0 Hz, 2H), 2.74 (t, J = 7.3 Hz, 2H), 2.58 (t, J = 11.4 Hz, 2H), 2.51 – 2.42 (m, 2H), 1.98 (d, J = 12.3 Hz, 2H), 1.69 – 1.57 (m, 2H). MS: *m/z* = 486.1 (M + H)⁺.

Example 83

4-Benzenesulfonyl-N-(2-methanesulfonyl-ethyl)-N'-(5-pyridin-4-yl-thiazol-2-yl)-pyridine-2,6-diamine

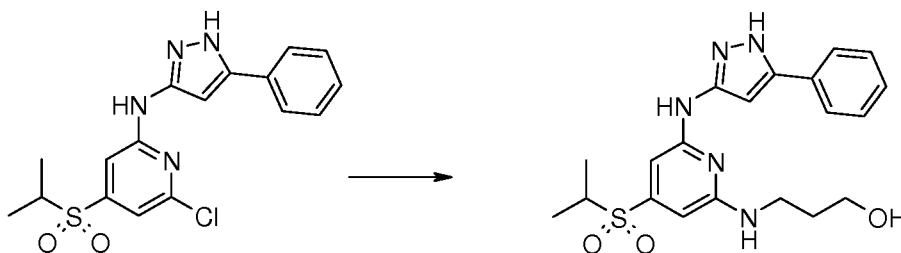


A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-pyridin-4-yl-thiazol-2-yl)-amine (70 mg, 0.163 mmol), 2-methanesulfonylethan-1-amine hydrochloride (78 mg, 0.49

mmol), BINAP (15 mg, 0.024 mmol) and sodium *tert*-butoxide (78 mg, 0.816 mmol) in anhydrous DME (2 mL) was sonicated under a flow of N₂ for 10 min before tris(dibenzylideneacetone)dipalladium (0) (8 mg, 0.008 mmol) was added and the resulting mixture was heated to 85 °C in a sealed tube for 24h. The reaction mixture was filtered
 5 through a pad of Celite, washed with EtOAc (50 mL) and concentrated to dryness. The crude material was purified by flash chromatography with a gradient of MeOH (0 - 10%) in EtOAc followed by 7N ammonia in MeOH. The material isolated was further purified by preparative HPLC (low pH method) to afford the title compound as a yellow solid (40 mg, 48 %). ¹H NMR (500MHz, DMSO-d₆): δ 11.63 (s, 1H), 8.48 (d, *J* = 6.1, 2H), 8.14 (s, 1H), 7.94 – 7.88
 10 (m, 2H), 7.77 (t, *J* = 7.5, 1H), 7.70 (t, *J* = 7.7, 2H), 7.66 – 7.58 (m, 3H), 6.62 (s, 1H), 6.54 (d, *J* = 1.2, 1H), 4.04 – 3.94 (m, 2H), 3.50 (t, *J* = 7.0, 2H), 3.06 (s, 3H). MS: *m/z* = 516.0 (M + H)⁺.

Example 84

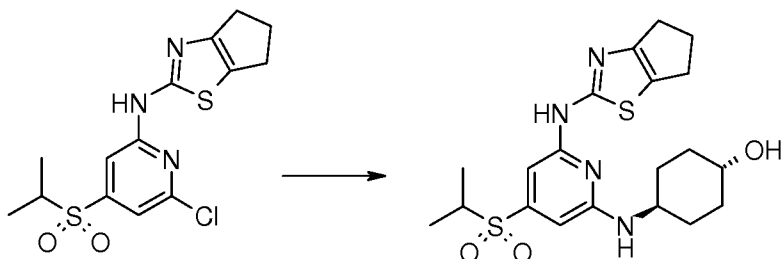
3-[6-(5-Phenyl-1H-pyrazol-3-ylamino)-4-(propane-2-sulfonyl)-pyridin-2-ylamino]-propan-1-ol



A mixture of [6-Chloro-4-(propane-2-sulfonyl)-pyridin-2-yl]-(5-phenyl-1H-pyrazol-3-yl)-amine (235 mg, 0.62 mmol), 3-aminopropan-1-ol (234 mg, 3.12 mmol) and DIPEA (0.52 ml, 3.12 mmol) in DMSO (2 mL) was heated to 120 °C in a sealed tube for 4h before a further
 20 3-aminopropan-1-ol (234 mg, 3.12 mmol) was added and heating continued for another 4h. The reaction was cooled, partitioned between EtOAc (25 mL) and saturated aq. ammonium chloride solution (25 mL) and the aqueous extracted with EtOAc (2 x 25 mL). The combined organics were washed with water (2 x 20 mL), brine (2 x 20 mL), dried (MgSO₄) and then concentrated. The crude was purified by flash chromatography, eluting with EtOAc (0 - 100
 25 %) in heptane to give the title compound as a brown solid (178 mg, 68 %). ¹H NMR (500 MHz, CDCl₃) δ 7.56 (d, *J* = 7.3 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.25 (m, 1H), 6.55 (s, 1H), 6.25 (s, 1H), 6.20 (s, 1H), 3.75 (t, *J* = 5.6 Hz, 2H), 3.52 – 3.44 (m, 2H), 3.17 – 3.09 (m, 1H), 1.85 – 1.78 (m, 2H), 1.26 (d, *J* = 6.9 Hz, 6H). MS: *m/z* = 416.1 (M+H)⁺.

Example 85

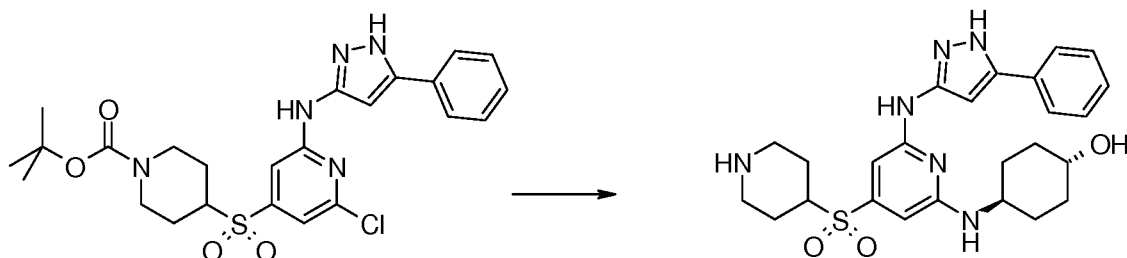
(trans)-4-[6-(5,6-Dihydro-4H-cyclopentathiazol-2-ylamino)-4-(propane-2-sulfonyl)-pyridin-2-ylamino]-cyclohexanol



5 A mixture of [6-Chloro-4-(propane-2-sulfonyl)-pyridin-2-yl]-(5,6-dihydro-4H-cyclopentathiazol-2-yl)-amine (116 mg, 0.32 mmol), trans 4-amino cyclohexanol (112 mg, 0.97 mmol), BINAP (30 mg, 0.05 mmol) and sodium *tert*-butoxide (15g mg, 1.62 mmol) in DME (1 ml) was sonicated under a flow of nitrogen for 10 minutes before tris(dibenzylideneacetone)dipalladium(0) (15 mg, 0.02 mmol) was added and the resulting
10 mixture was heated to 85 °C in a sealed tube for 18h. The reaction mixture was cooled, filtered through a pad of Celite and the pad washed with EtOAc (25 mL). The filtrate was concentrated and the crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane to give the title compound as a brown solid (29 mg, 20 %). ¹H
15 NMR (500 MHz, CDCl₃) δ 6.36 (s, 1H), 6.22 (s, 1H), 4.53 (d, J = 7.9 Hz, 1H), 3.85 (br.s, 1H), 3.71 – 3.61 (m, 1H), 3.12 (dt, J = 13.7, 6.9 Hz, 1H), 2.82 (t, J = 7.0 Hz, 2H), 2.74 (t, J = 7.2 Hz, 2H), 2.47 – 2.37 (m, 2H), 2.17 (d, J = 11.4 Hz, 2H), 1.99 (d, J = 12.9 Hz, 3H), 1.44 (td, J = 13.2, 3.2 Hz, 2H), 1.26 (d, J = 6.9 Hz, 6H), 1.25 – 1.16 (m, 2H). MS: *m/z* = 437.1 (M+H)⁺.

Example 86

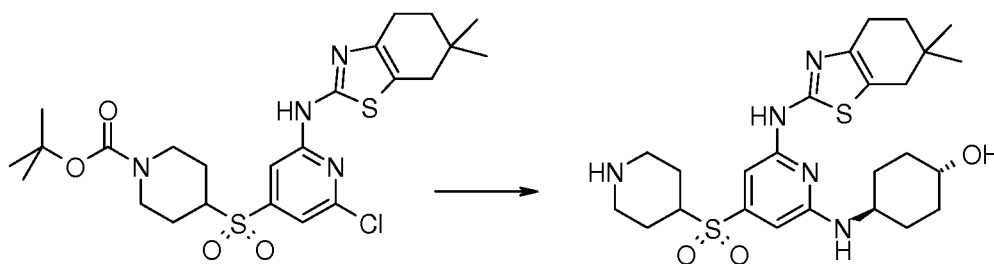
20 **(trans)-4-[4-(4-Methyl-piperidine-4-sulfonyl)-6-(5-phenyl-1H-pyrazol-3-ylamino)-pyridin-2-ylamino]-cyclohexanol**



A mixture of 4-[2-Chloro-6-(5-phenyl-1H-pyrazol-3-ylamino)-pyridine-4-sulfonyl]-4-methyl-piperidine-1-carboxylic acid *tert*-butyl ester (150 mg, 0.29 mmol), *trans* 4-amino cyclohexanol (167 mg, 1.45 mmol) and DIPEA (0.24 mL, 1.45 mmol) in DMSO (2 mL) was heated to 120 °C in a sealed tube with a further *trans* 4-amino cyclohexanol (19 eq. in total) added in portions over 28h (no heating or addition overnight). The reaction was cooled, partitioned between EtOAc (25 mL) and water (25 mL) and the aqueous extracted twice with EtOAc (2 x 20 mL). The combined organics were washed with water (2 x 10 mL) and brine (2 x 10 mL) and then dried (MgSO₄). The crude material was purified by flash chromatography, eluting with EtOAc (0 - 100 %) in heptane to give 4-[2-(4-Hydroxy-cyclohexylamino)-6-(5-phenyl-1H-pyrazol-3-ylamino)-pyridine-4-sulfonyl]-4-methyl-piperidine-1-carboxylic acid *tert*-butyl ester as a brown solid (243 mg, 63 %). MS: $m/z = 416.1$ (M+H)⁺. This was taken up in DCM (3 mL) and to the resulting solution, TFA (1 mL) was added and the reaction stirred for 1h. The reaction was cooled on ice, diluted with DCM (15 mL), neutralized to pH 9 with sodium bicarbonate solution and extracted with DCM (20 mL). The aqueous was re-extracted with DCM (4 x 20 mL) and the combined organics washed with brine (20 mL) and dried (hydrophobic frit). to give the title compound as an orange solid (71 mg, 34 %). ¹H NMR (500 MHz, MeOD) δ 7.80 – 7.66 (m, 2H), 7.49 – 7.40 (m, 2H), 7.38 – 7.30 (m, 1H), 6.69 (d, $J = 154.8$ Hz, 2H), 6.21 (s, 1H), 3.94 – 3.70 (m, 1H), 3.67 – 3.55 (m, 1H), 3.31 – 3.20 (m, 1H), 3.12 (d, $J = 12.9$ Hz, 2H), 2.57 (t, $J = 11.6$ Hz, 2H), 2.14 (d, $J = 11.4$ Hz, 2H), 2.07 – 1.94 (m, 4H), 1.63 (qd, $J = 12.5, 4.1$ Hz, 2H), 1.54 – 1.27 (m, 4H). MS: $m/z = 497.1$ (M+H)⁺.

Example 87

(*trans*)-4-[6-(6,6-Dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-ylamino)-4-(4-methyl-piperidine-4-sulfonyl)-pyridin-2-ylamino]-cyclohexanol

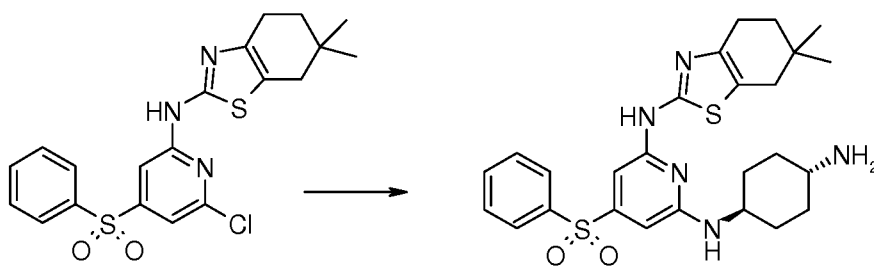


A mixture of 4-[2-Chloro-6-(6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-ylamino)-pyridine-4-sulfonyl]-4-methyl-piperidine-1-carboxylic acid *tert*-butyl ester (146 mg, 0.27 mmol), *trans*-4-amino cyclohexanol (93 mg, 0.81 mmol), BINAP (25 mg, 0.04 mmol) and sodium *tert*-butoxide (130 mg, 1.35 mmol) in DME (2 mL) was sonicated under a

flow of nitrogen for 10 minutes before tris(dibenzylideneacetone)dipalladium(0) (12 mg, 0.01 mmol) was added and the resulting mixture was heated to 85 °C in a sealed tube for 18h. The reaction mixture was cooled and filtered through a pad of Celite and the pad washed with EtOAc (20 mL). The filtrate was concentrated and the crude was purified by flash chromatography, eluting with EtOAc (40 - 100 %) in heptane to give 4-[2-(6,6-Dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-ylamino)-6-(4-hydroxy-cyclohexylamino)-pyridine-4-sulfonyl]-4-methyl-piperidine-1-carboxylic acid *tert*-butyl ester as a yellow solid (120 mg, 69 %). MS: m/z = 620.2 (M+H)⁺. This was dissolved in DCM (2 mL) and to the resulting solution was added TFA (0.5 mL). The reaction was stirred for 20 min before being cooled on ice, diluted with DCM (10 mL), taken up to pH 9 with sodium bicarbonate and extracted with DCM (20 mL). The aqueous phase was further extracted with EtOAc (3 x 20 mL). The organics were combined, dried (hydrophobic frit) and concentrated. The crude was passed through an SCX-2 column, eluting with 7N ammonia in MeOH (20 %) in DCM to give the title compound as a yellow solid (76 mg, 77 %). ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.99 (s, 1H), 7.09 (d, *J* = 7.4 Hz, 1H), 6.31 (s, 1H), 6.27 (s, 1H), 4.62 (d, *J* = 4.4 Hz, 1H), 3.92 (br.s, 1H), 3.49 – 3.41 (m, 1H), 3.22 – 3.14 (m, 1H), 2.99 (d, *J* = 12.3 Hz, 2H), 2.47 – 2.40 (m, 4H), 2.03 (d, *J* = 11.9 Hz, 2H), 1.88 (d, *J* = 11.7 Hz, 2H), 1.78 (d, *J* = 11.9 Hz, 2H), 1.56 (t, *J* = 6.4 Hz, 2H), 1.44 – 1.33 (m, 2H), 1.32 – 1.20 (m, 4H), 1.01 (s, 6H). MS: m/z = 520.2 (M+H)⁺.

Example 88

2-N-(6,6-dimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)-4-(1-methylidenecyclohexa-2,4-diene-1-sulfonyl)-6-N-[(*trans*)-4-aminocyclohexyl]pyridine-2,6-diamine

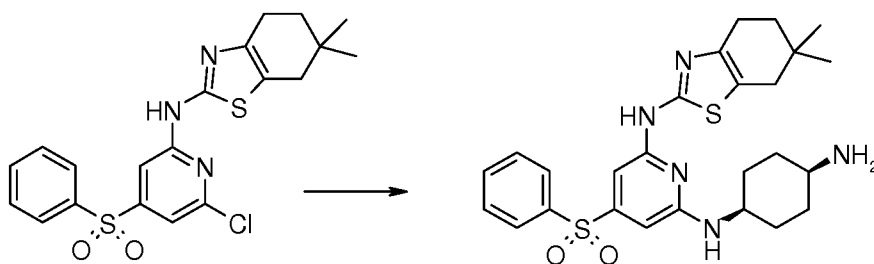


A mixture of (4-Benzenesulfonyl-6-chloro-pyridin-2-yl)-(6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazol-2-yl)-amine (200 mg, 0.46 mmol), *tert*-butyl N-[(*trans*)-4-aminocyclohexyl]carbamate (296 mg, 1.38 mmol), BINAP (43 mg, 0.07 mmol) and sodium *tert*-butoxide (221 mg, 2.3 mmol) in DME (2 ml) was sonicated under a flow of nitrogen for 10 minutes before tris(dibenzylideneacetone)dipalladium(0) (21 mg, 0.02 mmol) was added and the resulting mixture was heated to 85 °C in a sealed tube for 20 h. The reaction mixture

was cooled, filtered through a pad of Celite and the pad washed with EtOAc (25 mL). The filtrate was concentrated and the residue purified by flash chromatography, eluting with MeOH (0 - 10 %) in DCM, followed by 7 N ammonia in MeOH solution (0 - 20 %) in DCM. A further purification was achieved by preparative HPLC (low pH method) to give the title compound as an orange solid (50 mg, 21 %). ¹H NMR (500 MHz, MeOD) δ 8.47 (br.s, 2H), 7.96 (d, J = 7.5 Hz, 2H), 7.71 (t, J = 7.4 Hz, 1H), 7.63 (t, J = 7.7 Hz, 2H), 6.47 (d, J = 1.1 Hz, 1H), 6.42 (d, J = 1.1 Hz, 1H), 4.12 – 4.02 (m, 1H), 3.22 – 3.13 (m, 1H), 2.61 (t, J = 6.3 Hz, 2H), 2.49 (s, 2H), 2.30 (d, J = 11.8 Hz, 2H), 2.14 (d, J = 11.9 Hz, 2H), 1.65 (t, J = 6.5 Hz, 2H), 1.62 – 1.52 (m, 2H), 1.39 (q, J = 10.2 Hz, 2H), 1.06 (s, 6H). MS: *m/z* = 512.1 (M+H)⁺.

Example 89

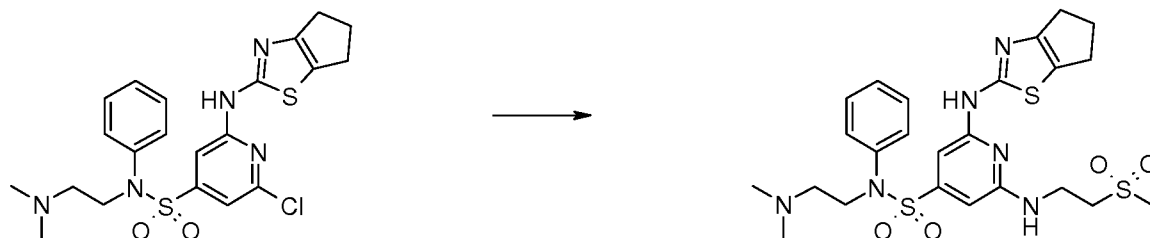
4-(benzenesulfonyl)-2-N-(6,6-dimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)-6-N-[(*cis*)-4-aminocyclohexyl]pyridine-2,6-diamine



The title compound was synthesized according to Example 88 by substituting *tert*-butyl N-[(*trans*)-4-aminocyclohexyl] carbamate with *tert*-butyl N-[(*cis*)-4-aminocyclohexyl] carbamate and then passing the formate salt through an Isolute SCX-2 column, eluting with 7 N ammonia in MeOH (20 %) in DCM. ¹H NMR(500 MHz, MeOD) δ 7.99 – 7.92 (m, 2H), 7.74 – 7.65 (m, 1H), 7.65 – 7.57 (m, 2H), 6.48 (d, J = 1.2 Hz, 1H), 6.44 (d, J = 1.3 Hz, 1H), 4.28 – 4.19 (m, 1H), 2.95 – 2.85 (m, 1H), 2.57 (t, J = 6.3 Hz, 2H), 2.42 (s, 2H), 1.84 – 1.70 (m, 6H), 1.61 (t, J = 6.5 Hz, 2H), 1.58 – 1.51 (m, 2H), 1.03 (s, 6H). MS: *m/z* = 512.0 (M+H)⁺.

Example 90

2-(5,6-Dihydro-4H-cyclopentathiazol-2-ylamino)-6-(2-methanesulfonyl-ethylamino)-pyridine-4-sulfonic acid (2-dimethylamino-ethyl)-phenyl-amide, formate salt



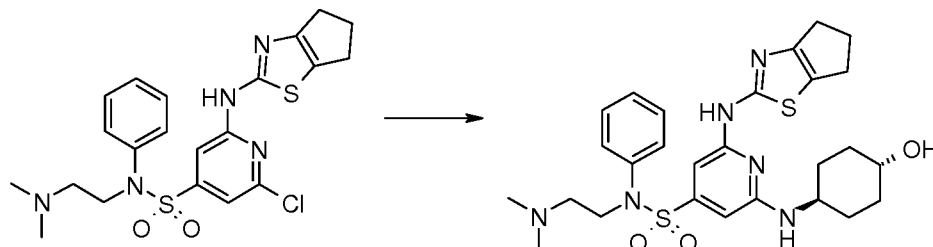
5

A mixture of 2-Chloro-6-(5,6-dihydro-4H-cyclopentathiazol-2-ylamino)-pyridine-4-sulfonic acid (2-dimethylamino-ethyl)-phenyl-amide (165 mg, 0.345 mmol), 2-Methanesulfonyl-ethylamine hydrochloride (165 mg, 1.035 mmol), BINAP (32 mg, 0.052 mmol), sodium *tert*-butoxide (199 mg, 2.071 mmol) and tris(dibenzylideneacetone)dipalladium (0) (16 mg, 0.017 mmol) in DME (5 mL) was heated at 85 °C in a pressure tube for 3h. The reaction was cooled, filtered and the filtrate evaporated. The crude material was purified by flash chromatography, eluting with DCM:MeOH:c.NH₃ (100:10:1) and then by preparative HPLC (low pH) to afford the title compound as a yellow solid (16 mg, 8 %). ¹H NMR (250 MHz, MeOD): δ 8.23 (s, 1 H), 7.39 - 7.32 (m, 3 H), 7.16 (dd, *J* = 7.2, 2.4 Hz, 2 H), 6.23 (d, *J* = 1.2 Hz, 1 H), 6.10 (d, *J* = 1.2 Hz, 1 H), 4.05 (t, *J* = 6.4 Hz, 2 H), 3.83 (t, *J* = 6.7 Hz, 2 H), 3.47 (t, *J* = 6.4 Hz, 2 H), 2.96 (s, 3 H), 2.81 - 2.89 (m, 2 H), 2.66 - 2.78 (m, 4 H), 2.50 (s, 6 H), 2.38 - 2.48 ppm (m, 2H). MS: *m/z* = 565.1 (M+H)⁺.

20

Example 91

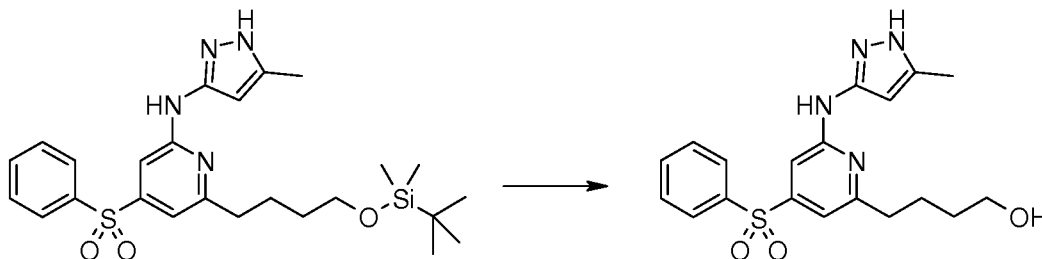
2-({4H,5H,6H-cyclopenta[d][1,3]thiazol-2-yl}amino)-N-[2-(dimethylamino)ethyl]-N-phenyl-6-[(*trans*)-4-hydroxycyclohexyl]amino}pyridine-4-sulfonamide, formate salt



A mixture of 2-Chloro-6-(5,6-dihydro-4H-cyclopentathiazol-2-ylamino)-pyridine-4-sulfonic acid (2-dimethylamino-ethyl)-phenyl-amide (165 mg, 0.345 mmol), *trans*-4-aminocyclohexanol (239 mg, 2.071 mmol) and DIPEA (445 mg, 3.452 mmol) in anhydrous DMSO (5 mL) was heated at 135 °C with more *trans*-4-aminocyclohexanol (600 mg, 5.210 mmol) added portion wise over 6h. The reaction mixture was cooled and partitioned between EtOAc (80 mL) and saturated aq. ammonium chloride solution (20 mL). The phases were separated and the organic phase washed with brine (20 mL), dried (Na₂SO₄) and concentrated. The crude material was purified by flash chromatography, eluting with DCM:MeOH:cNH₃ (100:10:1) and then by automated reverse-phase HPLC (low pH method) to afford the title compound as a tan solid (4 mg, 2 %). ¹H NMR (500 MHz, MeOD): δ 8.54 (s, 1 H), 7.43 - 7.34 (m, 3 H), 7.26 - 7.21 (m, 2 H), 6.18 (d, *J* = 0.9 Hz, 1 H), 6.08 (s, 1 H), 4.03 (br. s., 1 H), 3.83 (t, *J* = 6.9 Hz, 2 H), 3.67 - 3.58 (m, 1 H), 2.89 (t, *J* = 6.9 Hz, 2 H), 2.75 - 2.70 (m, 2 H), 2.57 (t, *J* = 6.7 Hz, 2 H), 2.52 - 2.45 (m, 2 H), 2.37 (s, 6 H), 2.16 (d, *J* = 11.2 Hz, 2 H), 2.02 (d, *J* = 11.3 Hz, 2 H), 1.53 - 1.42 (m, 2 H), 1.39 - 1.26 ppm (m, 2 H). MS: *m/z* = 557.1 (M+H)⁺.

Example 92

4-[4-Benzenesulfonyl-6-(5-methyl-1H-pyrazol-3-ylamino)-pyridin-2-yl]-butan-1-ol

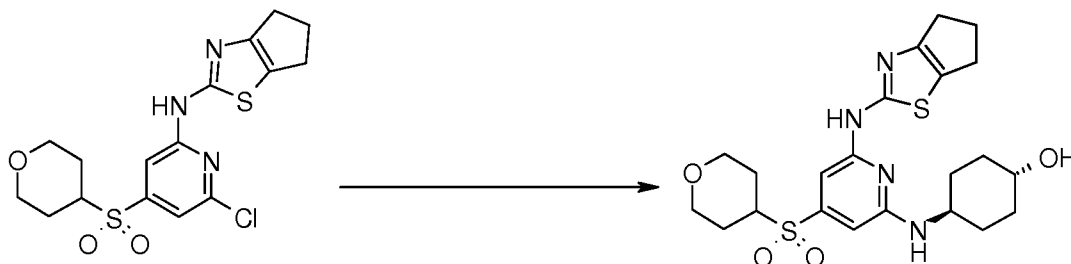


To a solution of {4-Benzenesulfonyl-6-[4-(*tert*-butyl-dimethyl-silanyloxy)-butyl]-pyridin-2-yl}-(5-methyl-1H-pyrazol-3-yl)-amine (238 mg, 0.475 mmol) in THF (15 mL) was added tetra-*n*-butylammonium fluoride (150 mg, 0.475 mmol) and the mixture stirred at room temperature for 2h. More tetra-*n*-butylammonium fluoride (300 mg, 0.95 mmol) was added and stirring continued for 18h. EtOAc (50 mL) and water (25 mL) were added and the phases separated. The organic phase was washed with brine (20 mL), dried (Na₂SO₄) and concentrated. The crude material was purified by flash chromatography, eluting with EtOAc (50 %) in heptane and then by automated reverse-phase HPLC (low pH method) to afford the title compound as a yellow oil (33 mg, 18 %). ¹H NMR (250 MHz, MeOD): δ 8.01 - 7.94 (m, 2 H), 7.71 - 7.57 (m, 3 H), 7.36 (s, 1 H), 6.98 (d, *J* = 1.4 Hz, 1 H), 6.08 (s, 1 H), 3.56 (t, *J* = 6.4

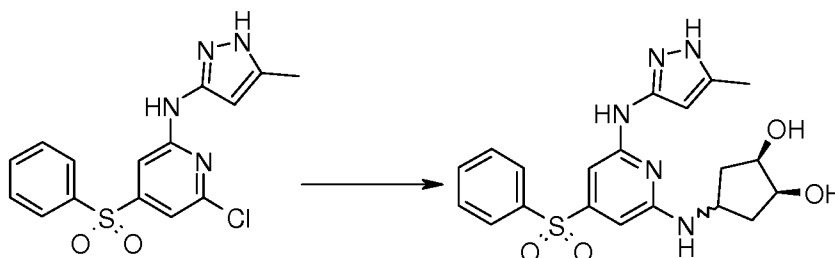
Hz, 2 H), 2.74(t, $J=7.5$ Hz, 2 H), 1.78 (quin, $J=7.6$ Hz, 2 H), 1.62 - 1.49 ppm (m, 2 H). MS: $m/z=387.1$ (M+H)⁺.

Example 93

5 (trans)-4-[6-(5,6-Dihydro-4H-cyclopentathiazol-2-ylamino)-4-(tetrahydro-pyran-4-sulfonyl)-pyridin-2-ylamino]-cyclohexanol, formate salt



A mixture of [6-chloro-4-(tetrahydro-pyran-4-sulfonyl)-pyridin-2-yl]-(5,6-dihydro-4H-cyclopentathiazol-2-yl)-amine, formate salt (0.01 g, 0.03 mmol), *trans*-4-aminocyclohexanol (0.01 g, 0.09 mmol), BINAP (3 mg, 0.01 mmol) and sodium *tert*-butoxide (21 mg, 0.22 mmol) in anhydrous DME (2.0 mL) was sonicated under a flow of nitrogen for 5 minutes before tris(dibenzylideneacetone)dipalladium (5 mg, 0.01 mmol) was added and the resulting mixture was heated to 85 °C in a sealed tube for 19h. The reaction mixture was then allowed to cool down to room temperature and the volatiles evaporated *in vacuo*. The crude material was purified by flash chromatography eluting with MeOH (1 – 10 %) in DCM. The material obtained was further purified by automated preparative HPLC (low pH method) to give the title compound as a white/light yellow solid (2 mg, 88 % purity, 11 %). ¹H NMR (500 MHz, CDCl₃): δ 6.43 (s, 1 H), 6.26 (s, 1 H), 4.63 (d, $J=7.7$ Hz, 1 H), 4.08 (dd, $J=11.7$, 3.2 Hz, 2 H), 4.00 - 3.88 (m, 1 H), 3.78 - 3.69 (m, 1 H), 3.35 (td, $J=11.7$, 2.2 Hz, 2 H), 3.22 - 3.10 (m, 1 H), 2.90 (t, $J=6.9$ Hz, 2 H), 2.81 (t, $J=7.1$ Hz, 2 H), 2.49 (quin, $J=7.2$ Hz, 2 H), 2.30 - 2.21 (m, 2 H), 2.11 - 2.03 (m, 2 H), 1.97 - 1.80 (m, 4 H), 1.58 - 1.46 (m, 2 H), 1.37 - 1.24 (m, 2 H). MS: $m/z=479.0$ (M-HCOOH+H)⁺.

Examples 94**(1R,2S)-4-{[4-(benzenesulfonyl)-6-[(5-methyl-1H-pyrazol-3-yl)amino]pyridin-2-yl]amino}cyclopentane-1,2-diol**

5 To a solution of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (0.18 g, 0.5 mmol) in anhydrous DMSO (2 mL) was added a mixture of *cis* and *trans*-4-amino-*cis*-1,2-cyclopentanediol (0.18 g, 1.51 mmol) in DMSO (0.2 mL) and DIPEA (0.25 mL, 1.51 mmol) and the reaction mixture flushed with nitrogen and heated to 120 °C in a sealed tube. Further additions of *cis* and *trans*-4-amino-*cis*-1,2-cyclopentanediol (0.18 g, 1.51 mmol) as a solution in DMSO (0.2 mL) were carried out approximately every 3h while monitoring by LC-MS (no heating or addition of *cis* and *trans*-4-amino-*cis*-1,2-cyclopentanediol overnight). The total heating time was 18.5h and the total amount of *cis* and *trans*-4-amino-*cis*-1,2-cyclopentanediol added 15 equivalents. The reaction was then allowed to cool down to room temperature and partitioned between EtOAc (15 mL) and saturated aq. ammonium chloride solution (5 mL). The two phases were separated and the aqueous phase extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried (MgSO₄), filtered and evaporated *in vacuo*. The crude mixture of isomers was purified by automated preparative HPLC (Column: XBridge Prep C18, 5 um OBD; eluent: 10-100% ACN (+0.2% NH₄OH) in H₂O (+0.2% NH₄OH)).

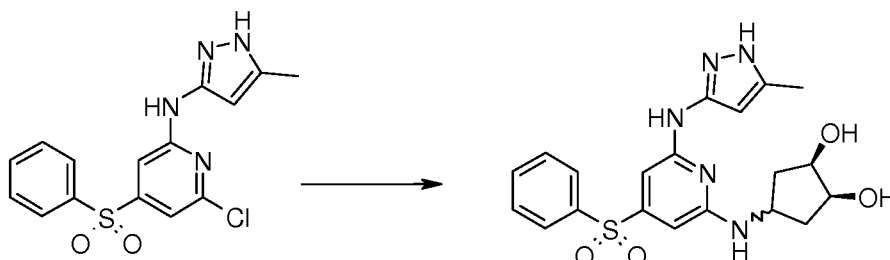
20 **Isomer 1:** yellow solid (0.04 g, 20 %)

¹H NMR (500MHz, DMSO-d₆): δ 11.77 (br. s., 1 H), 9.11 (br. s., 1 H), 7.91 - 7.81 (m, 2 H), 7.77 - 7.70 (m, 1 H), 7.68 - 7.60 (m, 2 H), 6.84 (br. s., 1 H), 6.76 (br. s., 1 H), 6.15 (br. s., 1 H), 6.11 (br. s., 1 H), 4.42 (br. s., 2 H), 4.37 - 4.26 (m, 1 H), 4.00 - 3.91 (m, 2 H), 2.16 (br. s., 3 H), 2.04 - 1.93 (m, 2 H), 1.67 - 1.45 (m, 2 H). MS: *m/z* = 430.0 (M+H)⁺.

25

Examples 95

(1R,2S)-4-{[4-(benzenesulfonyl)-6-[(5-methyl-1H-pyrazol-3-yl)amino]pyridin-2-yl]amino}cyclopentane-1,2-diol



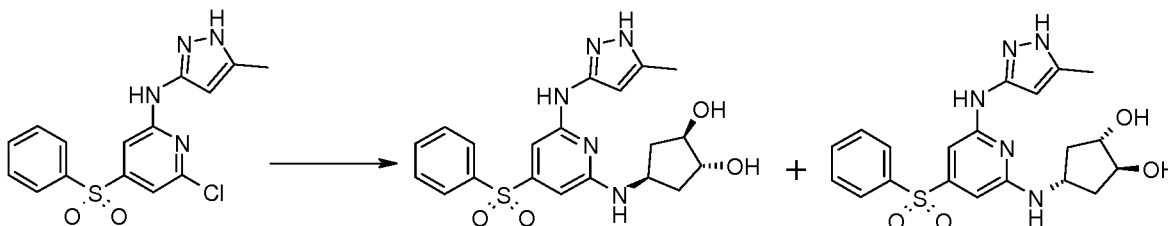
5 The preparation of this compound was carried out simultaneously with that of Example 94.

Isomer 2: yellow solid (0.03 g, 16 %)

¹H NMR (500MHz, DMSO-d₆): δ 11.76 (br. s., 1 H), 9.08 (br. s., 1 H), 7.99 - 7.81(m, 2 H), 7.77 - 7.69 (m, 1 H), 7.69 - 7.61 (m, 2 H), 6.80 (br. s., 2 H), 6.20 (br. s., 1 H), 6.13 - 6.01 (m, 1 H), 4.46 (br. s., 2 H), 4.06 - 3.98 (m, 1 H), 3.84 - 3.73 (m, 2 H), 2.26 - 2.10 (m, 5 H), 1.51 - 1.39 (m, 2 H). MS: *m/z* = 430.0 (M+H)⁺.

Examples 96 and 97

(1R,2R)-4-{[4-(benzenesulfonyl)-6-[(5-methyl-1H-pyrazol-3-yl)amino]pyridin-2-yl]amino}cyclopentane-1,2-diol and (1S,2S)-4-{[4-(benzenesulfonyl)-6-[(5-methyl-1H-pyrazol-3-yl)amino]pyridin-2-yl]amino}cyclopentane-1,2-diol

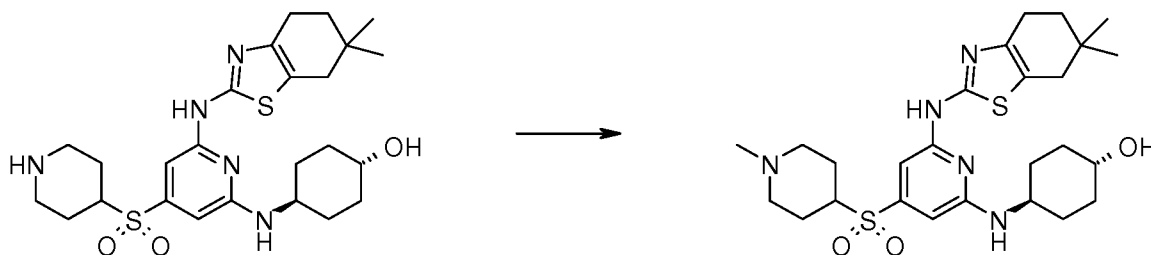


A mixture of (4-benzenesulfonyl-6-chloro-pyridin-2-yl)-(5-methyl-1H-pyrazol-3-yl)-amine (0.18 g, 0.5 mmol), (+/-)-4-amino-(*trans*)-1,2-cyclopentanediol (synthesized according to *J. Med. Chem.* **1992**, 35, 2191-2195) (80%, 0.18 g, 1.2 mmol) and DIPEA (0.25 mL, 1.51 mmol) in anhydrous DMSO (2.0 mL) was flushed with nitrogen and heated to 120 °C in a sealed tube. Further additions of (+/-)-4-amino-(*trans*)-1,2-cyclopentanediol (80%, 0.18 g, 1.2 mmol) as a solution in DMSO (0.2 mL) were carried out approximately every 3 h while monitoring by LC-MS (no heating or addition of (+/-)-4-amino-(*trans*)-1,2-cyclopentanediol

overnight). The total heating time was 17h and the total amount of (+/-)-4-amino-(*trans*)-1,2-cyclopentanediol added 12 equivalents. The reaction was allowed to cool down to room temperature and partitioned between EtOAc (10 mL) and saturated aq. ammonium chloride solution (5 mL), the phases separated and the aqueous phase extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried (MgSO₄), filtered and evaporated *in vacuo*. The enantiomers were resolved by chiral SFC (22% MeOH: 88% CO₂; column = Chiralcel OJ-H; retention time for 97: 6.06 min; retention time for 98: 7.76 min. ¹H NMR (500 MHz, DMSO-d₆): δ 11.75 (br. s., 1 H), 9.14 (br. s., 1 H), 7.92 - 7.81 (m, 2 H), 7.77 - 7.69 (m, 1 H), 7.68 - 7.61 (m, 2 H), 6.84 (br. s., 1 H), 6.73 (br. s., 1 H), 6.24 - 6.05 (m, 2 H), 4.76 (br. s., 1 H), 4.67 (br. s., 1 H), 4.37 - 4.19 (m, 1 H), 3.88 - 3.81 (m, 1 H), 3.80 - 3.73 (m, 1 H), 2.41 - 2.30 (m, 1H), 2.15 (s, 3 H), 1.94 - 1.82 (m, 1 H), 1.75 - 1.62 (m, 1 H), 1.36 - 1.18 (m, 1 H). MS: *m/z*= 430.0 (M + H)⁺.

Example 98

(*trans*)-4-({6-[(6,6-dimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)amino]-4-(1-methylpiperidine-4-sulfonyl)pyridin-2-yl}amino)cyclohexan-1-ol



To a solution of (*trans*)-4-({6-[(6,6-dimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)amino]-4-(piperidine-4-sulfonyl)pyridin-2-yl}amino)cyclohexan-1-ol (30 mg, 0.058 mmol) in methanol (2 mL) and acetic acid (0.035 mL, 0.58 mmol) was added formaldehyde (37% solution in water)(0.025 mL, 0.289 mmol) and the mixture was stirred at room temperature for 30 minutes before Na(CN)BH₃ (18 mg, 0.289 mmol) was added. The mixture was stirred at room temperature for 1 hour 15 minutes, after which it was quenched with sat. NaHCO₃ (10 mL) and extracted with EtOAc (3x 20 mL). The combined organic phases were washed with water (10 mL), brine (10 mL) and dried over MgSO₄. The crude material obtained after filtration and concentration of the solvent was purified by automated reverse-phase HPLC (low pH method), then it was applied to a SCX cartridge, washed with methanol and eluted with 7N NH₃ in methanol to recover the free base of the title compound as a yellow solid (23 mg, 75%). ¹H NMR (500 MHz, CDCl₃): δ 6.35 (s, 1H), 6.25 (s, 1H),

4.66 (d, $J=7.8$, 1H), 3.98 (s, 1H), 3.84 – 3.68 (m, 1H), 2.99 (d, $J=11.5$, 2H), 2.95 – 2.83 (m, 1H), 2.69 (t, $J=6.1$, 2H), 2.50 (s, 2H), 2.34 – 2.22 (m, 5H), 2.17 – 2.01 (m, 4H), 2.01 – 1.92 (m, 2H), 1.90 – 1.75 (m, 3H), 1.64 (t, $J=6.3$, 2H), 1.59 – 1.45 (m, 2H), 1.38 – 1.26 (m, 2H), 1.07 (s, 6H). MS: $m/z=534.2$ (M+H)⁺.

5 BIOLOGICAL EXAMPLES

Compounds of Formula I, II or III or any variation thereof described herein may be assayed for the ability to modulate the activity of protein kinases, tyrosine kinases, additional serine/threonine kinases, and/or dual specificity kinases *in vitro* and *in vivo*. *In vitro* assays include biochemical and cell-based assays that determine inhibition of the kinase activity. Alternate *in vitro* assays quantify the ability of a compound described herein to bind to kinases and may be measured either by radiolabelling the compound prior to binding, isolating the compound /kinase complex and determining the amount of radiolabel bound, or by running a competition experiment where a compound is incubated with known radiolabeled ligands. These and other useful *in vitro* assays are well known to those of skill in the art.

In an embodiment, the compounds described herein can be used to control, modulate or inhibit tyrosine kinase activity, for example ITK kinase activity, additional serine/threonine kinases, and/or dual specificity kinases. Thus, they are useful as pharmacological standards for use in the development of new biological tests, assays and in the search for new pharmacological agents.

Example 99

ITK Biochemical Assay

GST-ITK full-length enzyme was from Invitrogen (PV3875) and the substrate was BLK peptide (Ac-EFPIYDFLPK^{KK}-NH₂). Reactions were carried out in a final volume of 51 μ L with 50 mM HEPES (pH 7.2), 15 mM MgCl₂, 2 mM DTT, 0.015% Brij-35, 1 nM ITK, 2 μ M substrate, 20 μ M ATP, and 2% DMSO. After 35 min incubation at room temperature, reactions were stopped upon addition of 10 μ L of 30% TCA. Samples were centrifuged (4350 rpm, 4 °C, 5 min) and subjected to LC/MS analysis on a Waters Acquity UPLC/TQD system equipped with a Waters Acquity UPLC BEH C18 (2.1 x 50 mm) 1.7 μ m column (injection volume: 5 μ L; column temperature: 60 °C; flow rate: 1 mL/min; solvent A: 0.1% formic acid in LC/MS grade water; solvent B: 0.1% formic acid in LC/MS grade ACN). Analytes were separated by applying a gradient from 15% to 32% solvent B within 0.7 min and detected in positive mode ESI-MS/MS by MRM (multiple reaction monitoring) of transitions 819.8/84.8 (BLK substrate) and 859.0/84.8 as well as 859.0/120.7 (phosphorylated BLK product).

Examples 1-98 were tested in the above assay and found to have the activities given in in Table 2.

Table 2

Example No.	ITK Ki (nM)
1	8.4
2	20
3	67
4	1300
5	7.1
6	3.3
7	0.3
8	130
9	330
10	68
11	5.6
12	81
13	310
14	270
15	140
16	140
17	550
18	27

Example No.	ITK Ki (nM)
19	54
20	110
21	820
22	34
23	35
24	220
25	57
26	80
27	200
28	89
29	43
30	25
31	110
32	27
33	73
34	14
35	64
36	65

Example No.	ITK Ki (nM)
37	27
38	35
39	1.2
40	2.3
41	5.9
42	0.2
43	5.3
44	28
45	1.6
46	4000
47	0.2
48	450
49	3.0
50	6.1
51	300
52	300
53	41
54	3.7
55	23
56	4.2

Example No.	ITK Ki (nM)
57	0.4
58	6.3
59	16
60	1.8
61	1400
62	83
63	0.6
64	20
65	61
66	14
67	450
68	280
69	4000
70	4.3
71	3.0
72	21
73	720
74	2.2
75	5.5
76	150

Example No.	ITK Ki (nM)
77	26
78	4000
79	14
80	3.6
81	8.5
82	52
83	0.2
84	31
85	25
86	2.8
87	4.5
88	360

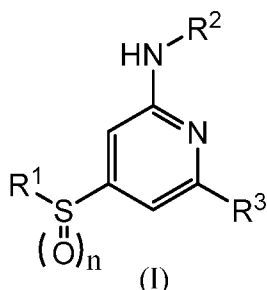
Example No.	ITK Ki (nM)
89	170
90	170
91	62
92	92
93	19
94	15
95	7.7
96	9.2
97	6.5
98	9.7

All references throughout, such as publications, patents, patent applications and published patent applications, are incorporated herein by reference in their entireties.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is apparent to those skilled in the art that certain minor changes and modifications will be practiced. Therefore, the description and examples should not be construed as limiting the scope of the invention.

CLAIMS

1. A compound of Formula I:



or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein:

R^1 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, C_6 - C_{14} aryl, 5-10-membered heteroaryl, 3-10-membered heterocyclyl or $-NR^4R^5$, wherein R^1 is optionally substituted by R^{10} ;

n is 1 or 2;

R^2 is 5-10-membered heteroaryl optionally substituted by R^{10} ;

R^3 is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_8 cycloalkyl, 3-10-membered heterocyclyl or $-NR^6R^7$, wherein R^3 is optionally substituted by R^{10} ;

R^4 and R^5 are each independently C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_6 - C_{14} aryl or $-(C_1-C_3 \text{ alkylene})NR^8R^9$; or

R^4 and R^5 are taken together with the nitrogen to which they attached to form 3-10-membered heterocyclyl optionally substituted by R^{10} ;

R^6 and R^7 are each independently hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl and heterocyclyl are independently optionally substituted by halogen, oxo, $-OR^8$, $-NR^8R^9$, $-S(O)R^9$, $-S(O)_2R^9$ or 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1 - C_6 alkyl optionally substituted by oxo or halogen; or

R^6 and R^7 are taken together with the nitrogen to which they attached to form 3-10-membered heterocyclyl optionally substituted by R^{10} ;

R^8 and R^9 are each independently hydrogen or C_1 - C_6 alkyl optionally substituted by oxo or halogen;

each R^{10} is independently hydrogen, oxo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, halogen, $-CN$, $-OR^{11}$, $-SR^{11}$, $-NR^{11}R^{12}$, $-NO_2$, $-C=NH(OR^{11})$, $-C(O)R^{11}$, $-C(O)OR^{11}$,

-C(O)NR¹¹R¹², -NR¹¹C(O)R¹², -S(O)R¹¹, -S(O)₂R¹¹, -NR¹¹S(O)R¹², -NR¹¹S(O)₂R¹², -S(O)NR¹¹R¹², -S(O)₂NR¹¹R¹², C₃-C₆ cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, C₆-C₁₄ aryl, -(C₁-C₃ alkylene)CN, -(C₁-C₃ alkylene)OR¹¹, -(C₁-C₃ alkylene)SR¹¹, -(C₁-C₃ alkylene)NR¹¹R¹², -(C₁-C₃ alkylene)CF₃, -(C₁-C₃ alkylene)NO₂, -C=NH(OR¹¹), -(C₁-C₃ alkylene)C(O)R¹¹, -(C₁-C₃ alkylene)C(O)OR¹¹, -(C₁-C₃ alkylene)C(O)NR¹¹R¹², -(C₁-C₃ alkylene)NR¹¹C(O)R¹², -(C₁-C₃ alkylene)S(O)R¹¹, -(C₁-C₃ alkylene)S(O)₂R¹¹, -(C₁-C₃ alkylene)NR¹¹S(O)R¹², -(C₁-C₃ alkylene)NR¹¹S(O)₂R¹², -(C₁-C₃ alkylene)S(O)NR¹¹R¹², -(C₁-C₃ alkylene)S(O)₂NR¹¹R¹², -(C₁-C₃ alkylene)(C₃-C₆ cycloalkyl), -(C₁-C₃ alkylene)(3-10-membered heterocyclyl), -(C₁-C₃ alkylene)(5-10-membered heteroaryl) or -(C₁-C₃ alkylene)(C₆-C₁₄ aryl), wherein each R¹⁰ is independently optionally substituted by halogen, oxo, -OR¹³, -NR¹³R¹⁴, -C(O)R¹³, -S(O)R¹³, -S(O)₂R¹³, -(C₁-C₃ alkylene)OR¹³, -(C₁-C₃ alkylene)NR¹³R¹⁴, -(C₁-C₃ alkylene)C(O)R¹³, -(C₁-C₃ alkylene)S(O)R¹³, -(C₁-C₃ alkylene)S(O)₂R¹³ or C₁-C₆ alkyl optionally substituted by oxo, -CN or halogen;

R¹¹ and R¹² are each independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₆-C₁₄ aryl, 5-6 membered heteroaryl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are independently optionally substituted by halogen, oxo, -CN, -OR¹⁶, -NR¹⁶R¹⁷ or C₁-C₆ alkyl optionally substituted by halogen, -CN or oxo; or

R¹¹ and R¹² are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, -OR¹⁶, -NR¹⁶R¹⁷ or C₁-C₆ alkyl optionally substituted by halogen, oxo or OH;

R¹³ and R¹⁴ are each independently hydrogen, C₁-C₆ alkyl optionally substituted by halogen or oxo, C₂-C₆ alkenyl optionally substituted by halogen or oxo, or C₂-C₆ alkynyl optionally substituted by halogen or oxo; or

R¹³ and R¹⁴ are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C₁-C₆ alkyl optionally substituted by halogen or oxo; and

R¹⁶ and R¹⁷ are each independently hydrogen, C₁-C₆ alkyl optionally substituted by halogen or oxo, C₂-C₆ alkenyl optionally substituted by halogen or oxo, or C₂-C₆ alkynyl optionally substituted by halogen or oxo; or

R¹⁶ and R¹⁷ are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C₁-C₆ alkyl optionally substituted by oxo or halogen.

2. The compound of claim 1, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein n is 2.

3. The compound of claim 1 or 2, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 is C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{14} aryl, 5-10-membered heteroaryl, 3-10-membered heterocyclyl or $-NR^4R^5$, wherein R^1 is optionally substituted by R^{10} .

4. The compound of claim 3, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 is C_6 - C_{14} aryl optionally substituted by R^{10} .

5. The compound of claim 3, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 is phenyl optionally substituted by C_1 - C_6 alkyl or $-(C_1$ - C_3 alkylene) $NR^{11}R^{12}$.

6. The compound of claim 3, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 is 3-10-membered heterocyclyl optionally substituted by R^{10} .

7. The compound of claim 3, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 is C_1 - C_6 alkyl or C_3 - C_8 cycloalkyl.

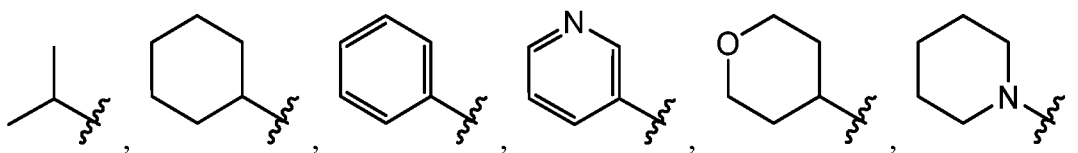
8. The compound of claim 3, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 is 5-10-membered heteroaryl.

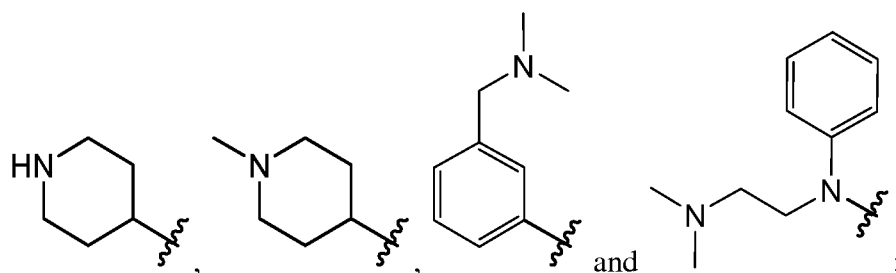
9. The compound of claim 3, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 is $-NR^4R^5$.

10. The compound of any one of claims 1-9, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^4 is C_6 - C_{14} aryl and R^5 is $-(C_1$ - C_3 alkylene) NR^8R^9 .

11. The compound of any one of claims 1-9, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^4 and R^5 are taken together with the nitrogen to which they attached to form 3-10-membered heterocyclyl optionally substituted by R^{10} .

12. The compound of claim 1 or 2, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 is selected from the group consisting of:

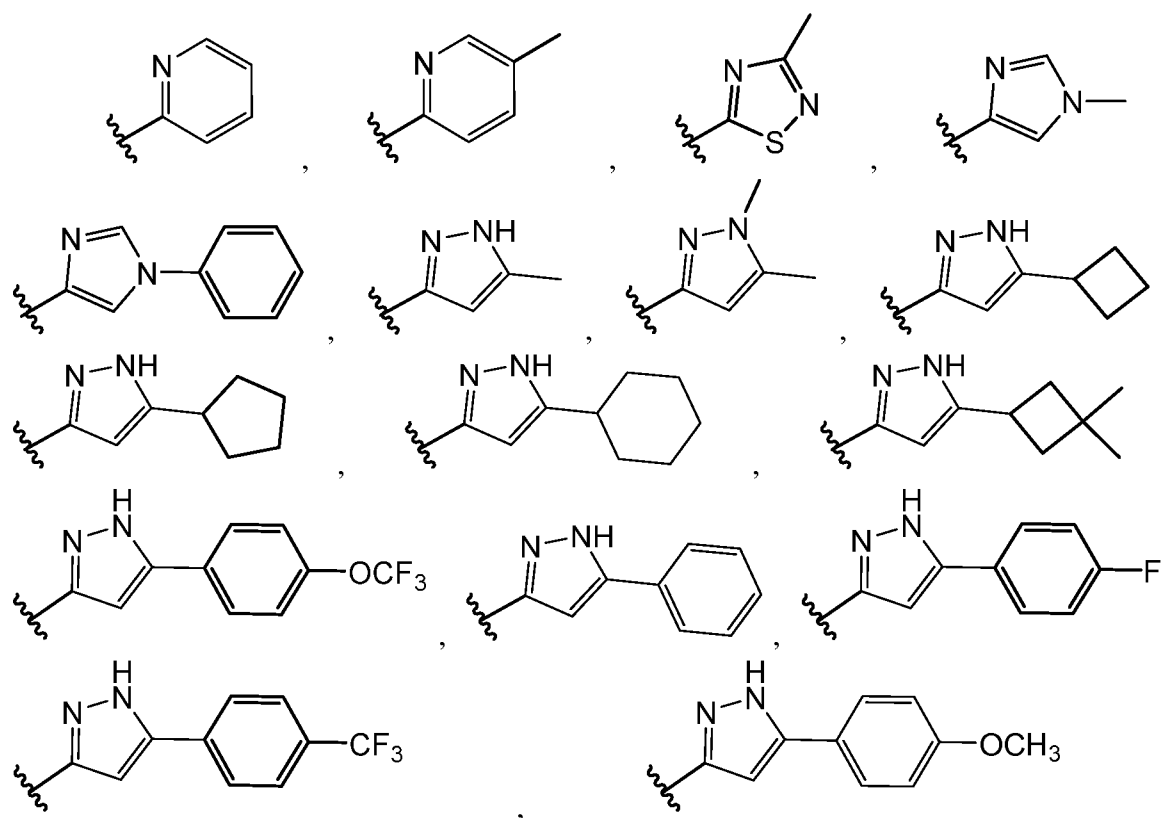


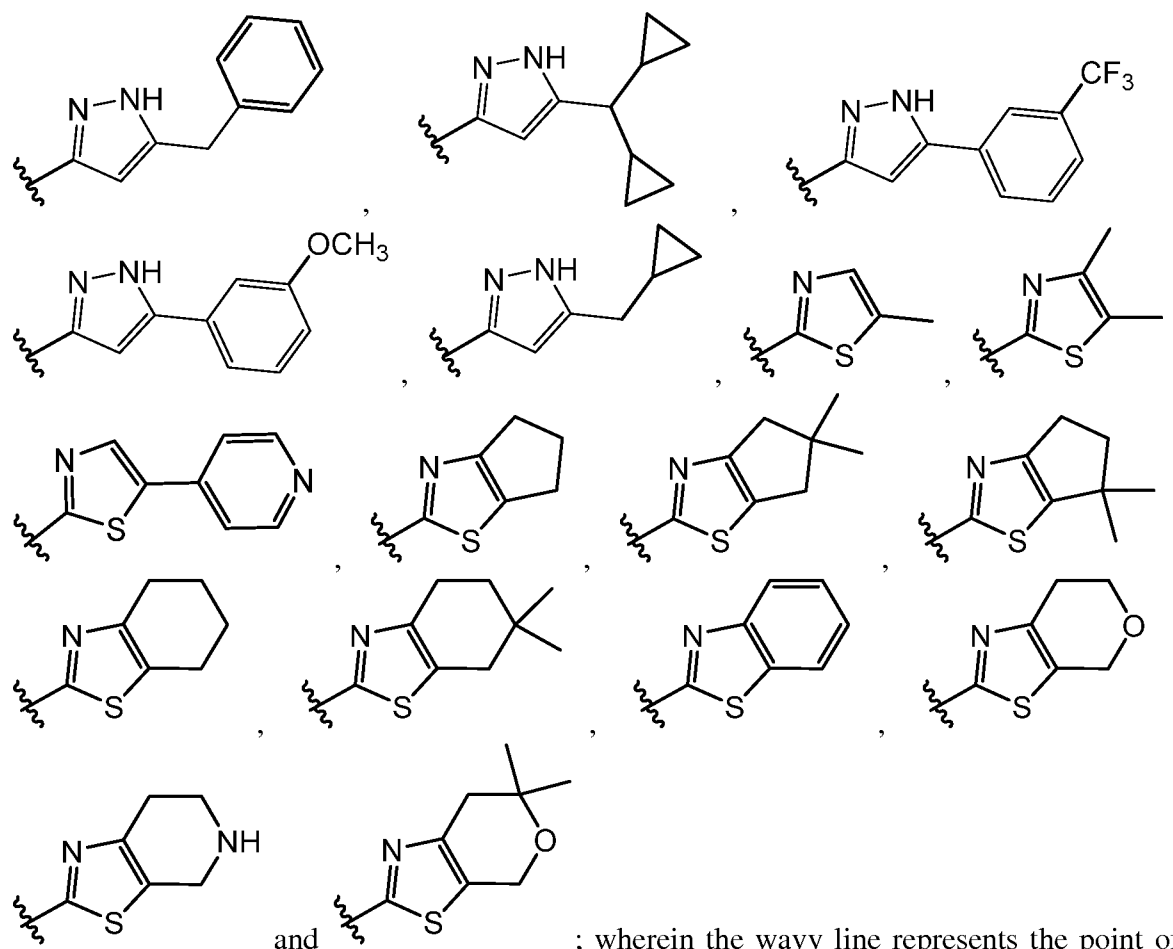


wherein the wavy line represents the point of attachment of R^1 in Formula I.

13. The compound of any one of claims 1 to 12, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^2 is 5-6-membered monocyclic heteroaryl optionally substituted by R^{10} or 5-10-membered fused heteroaryl optionally substituted by R^{10} .

14. The compound of claim 13, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^2 is selected from the group consisting of:



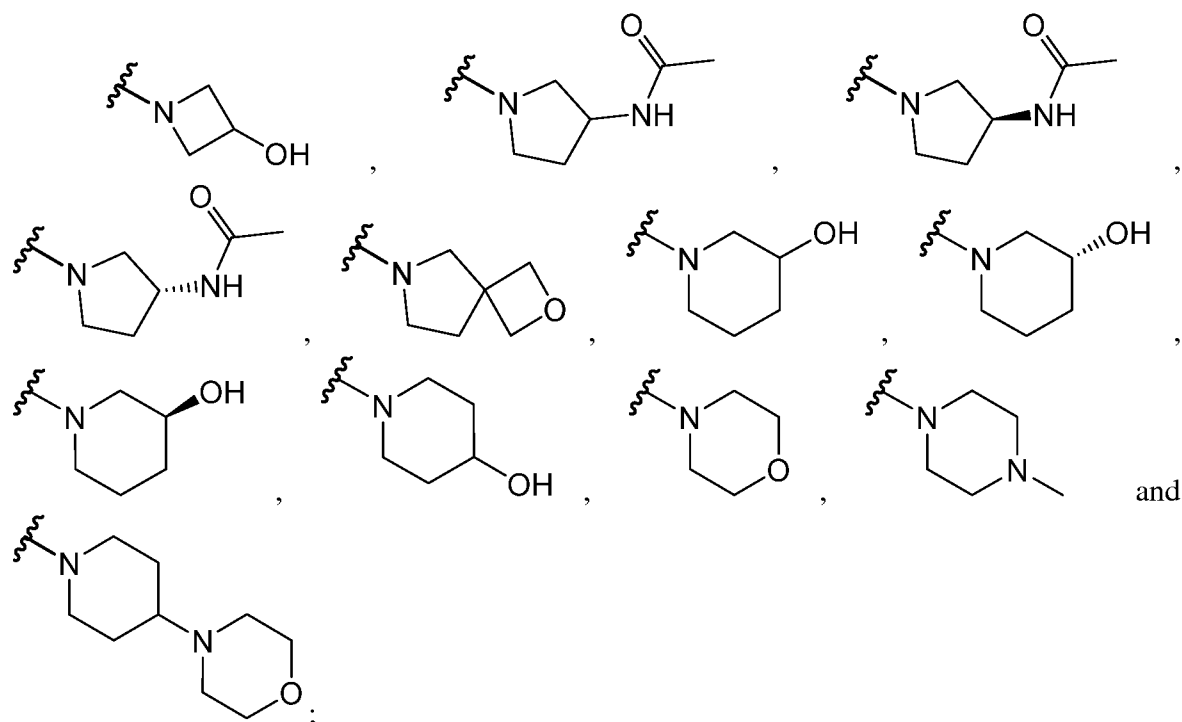


15. The compound of any one of claims 1 to 14, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^3 is C_1 - C_6 alkyl optionally substituted by R^{10} or C_3 - C_8 cycloalkyl optionally substituted by R^{10} .

16. The compound of claim 15, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^3 is 4-hydroxybutyl.

17. The compound of any one of claims 1 to 14, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^3 is 3-10-membered heterocyclyl optionally substituted by R^{10} .

18. The compound of claim 17, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^3 is selected from the group consisting of:



wherein the wavy line represents the point of attachment of R^3 in Formula I.

19. The compound of any one of claims 1 to 14, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^3 is $-NR^6R^7$.

20. The compound of claim 19, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^6 is C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl or 3-6 membered heterocyclyl, wherein the alkyl, cycloalkyl and heterocyclyl are independently optionally substituted by halogen, oxo, $-OR^8$, $-NR^8R^9$, $-S(O)R^9$, $-S(O)_2R^9$, or 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1 - C_6 alkyl optionally substituted by oxo or halogen.

21. The compound of claim 19, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^6 is C_1 - C_6 alkyl optionally substituted by $-OR^8$, $-NR^8R^9$, $-S(O)R^9$, $-S(O)_2R^9$, or 3-6 membered heterocyclyl optionally substituted by C_1 - C_6 alkyl.

22. The compound of claim 21, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein each R^8 is hydrogen and each R^9 is methyl.

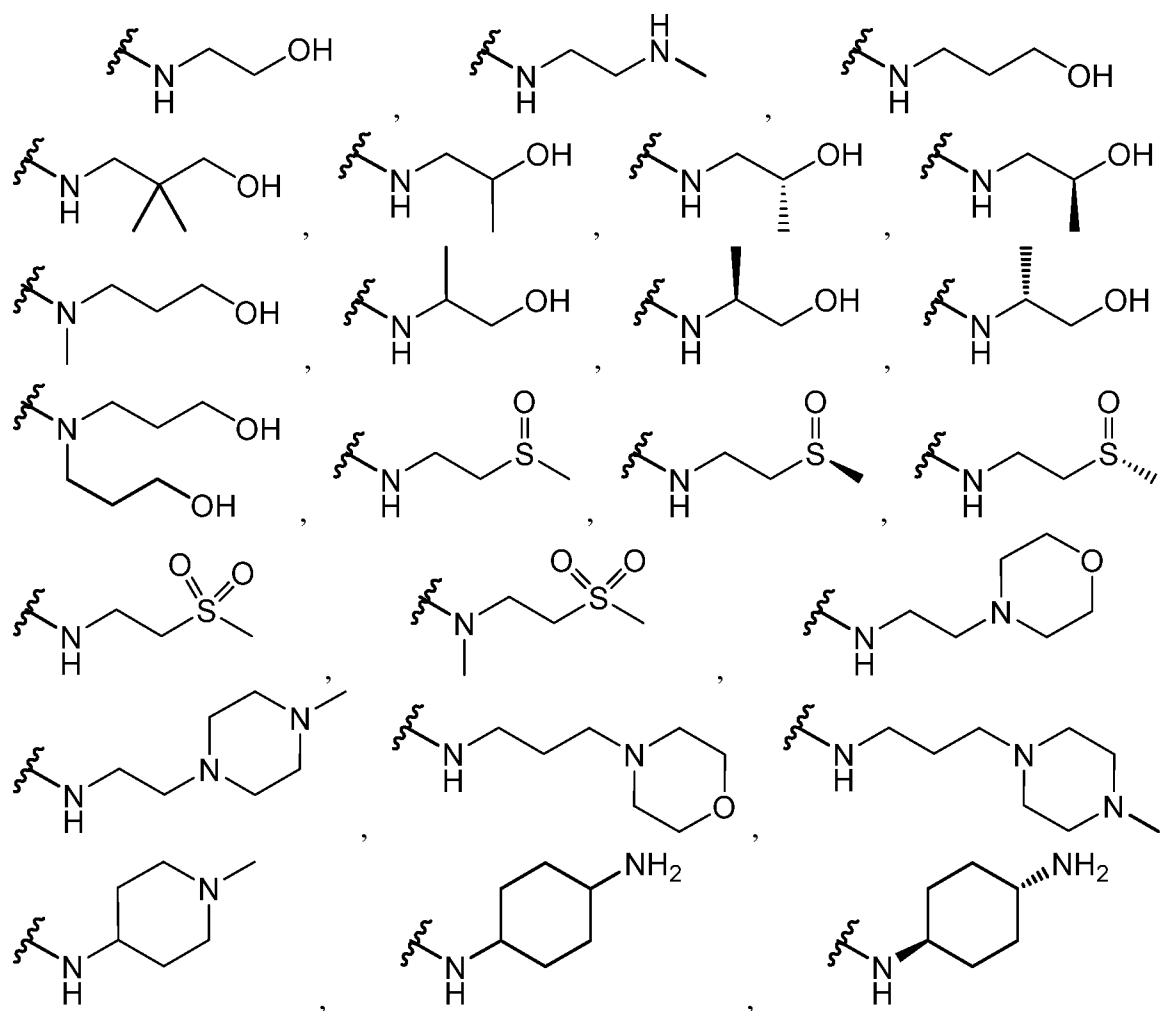
23. The compound of claim 19, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^6 is C_3 - C_6 cycloalkyl optionally substituted by $-OR^8$, $-NR^8R^9$ or 3-6 membered heterocyclyl.

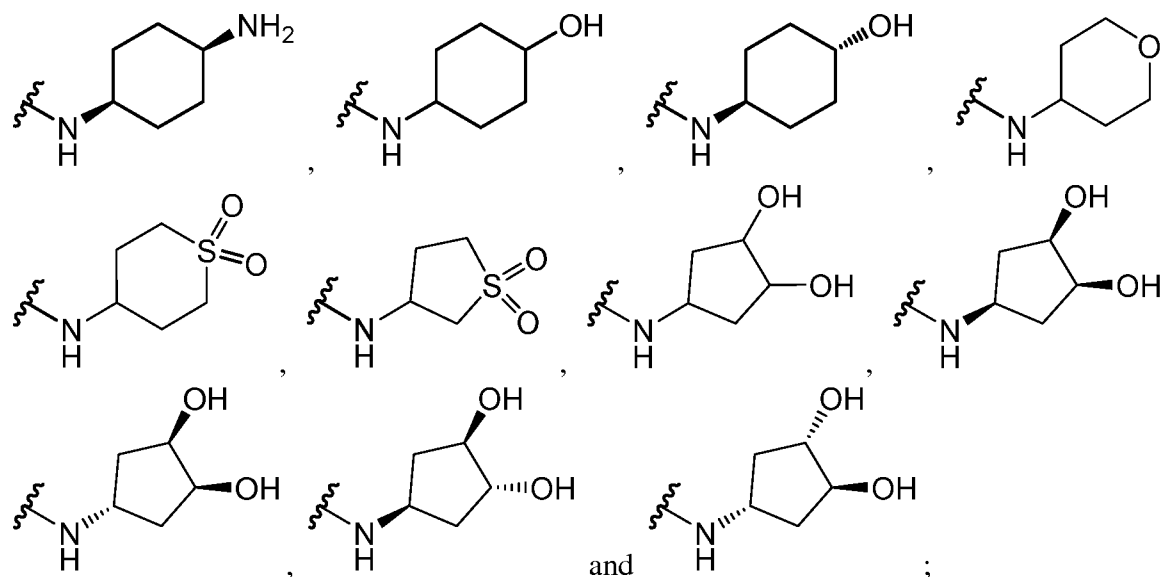
24. The compound of claim 19, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^6 is C_3 - C_6 cycloalkyl optionally substituted by $-OR^8$ where R^8 is hydrogen.

25. The compound of any one of claims 19 to 24, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^7 is hydrogen or C_1 - C_6 alkyl optionally substituted by $-OR^8$ where R^8 is hydrogen.

26. The compound of claim 25, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^7 is hydrogen.

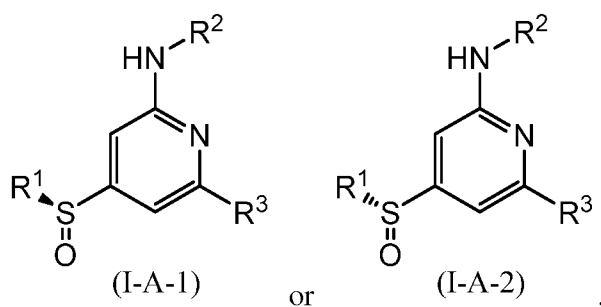
27. The compound of claim 19, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^3 is selected from the group consisting of:





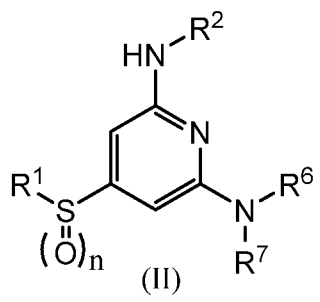
wherein the wavy line represents the point of attachment of R^3 in Formula I.

28. The compound of any one of claims 1-27, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein the compound is of the Formula (I-A-1) or (I-A-2):



wherein R^1 , R^2 and R^3 are as defined for Formula (I).

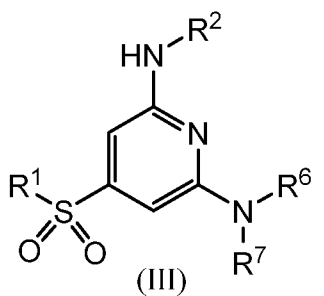
29. The compound of any one of claims 1-27, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein the compound is of the Formula (II):



wherein R^1 , R^2 , R^6 , R^7 and n are as defined for Formula (I).

30. The compound of claim 29, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1 is C_3 - C_8 cycloalkyl, C_6 - C_{14} aryl, 5-10-membered monocyclic heteroaryl, 3-10-membered monocyclic heterocyclyl or $-NR^4R^5$, wherein R^1 is optionally substituted by R^{10} .

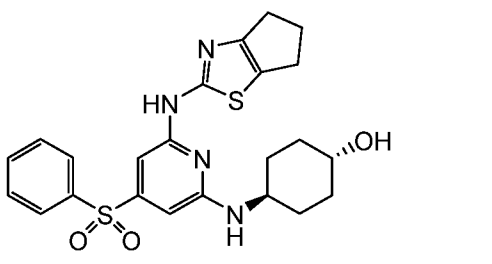
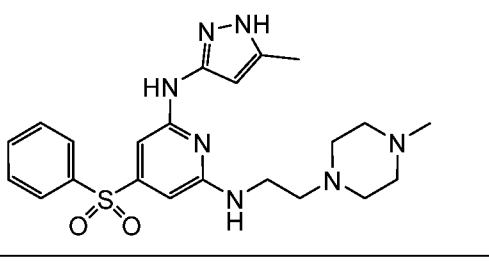
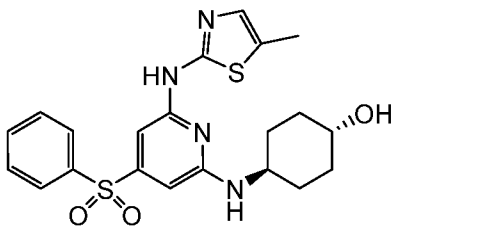
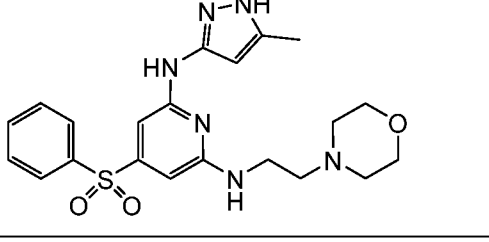
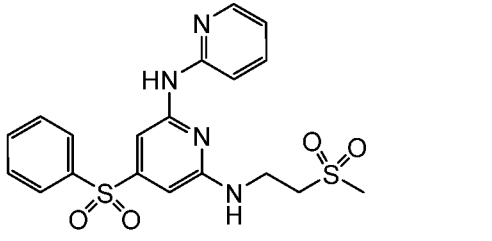
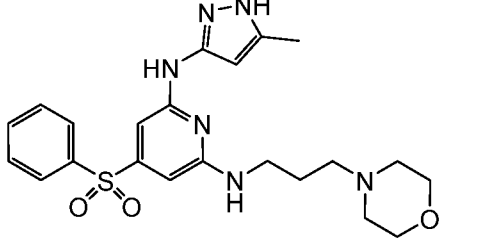
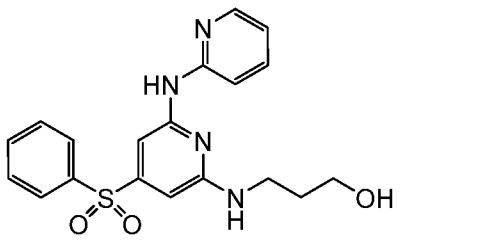
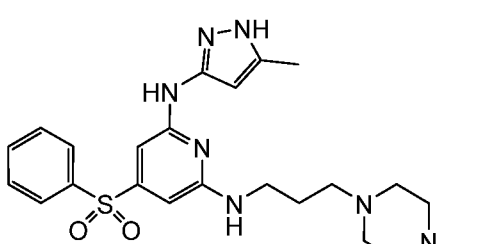
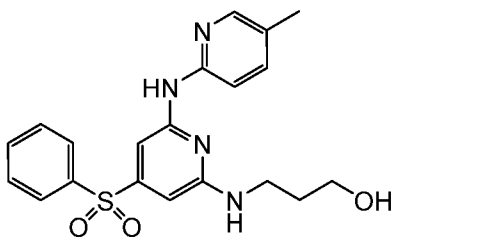
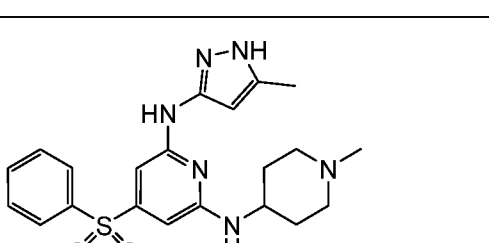
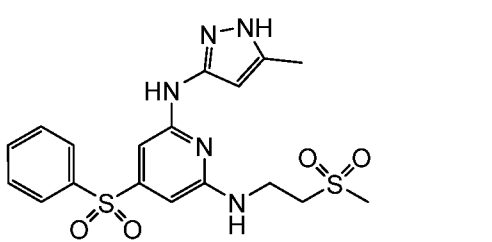
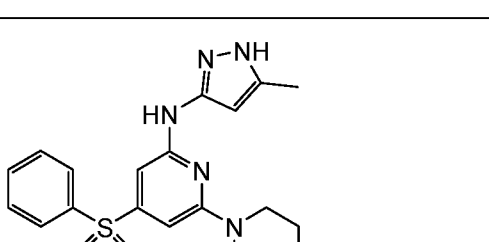
31. The compound of any one of claims 1-27, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein the compound is of the Formula III:

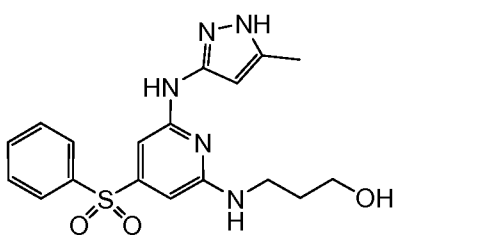
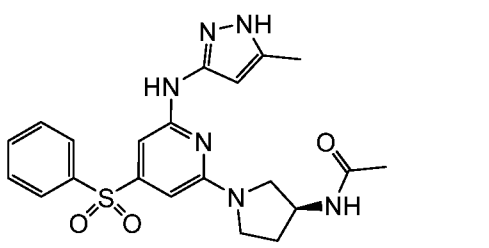
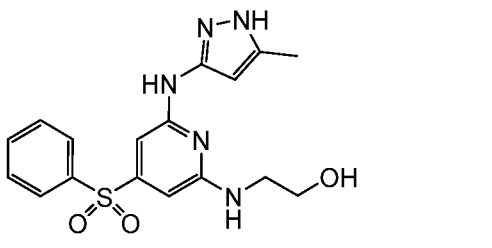
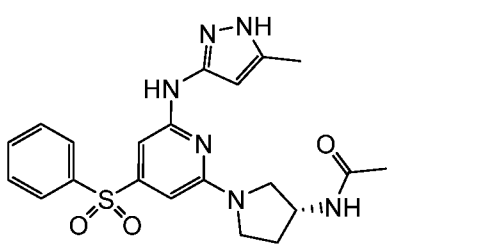
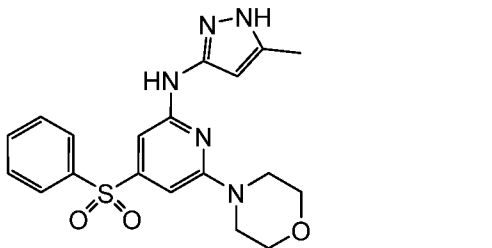
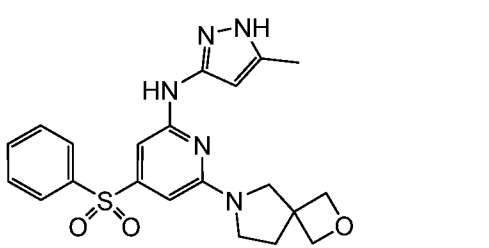
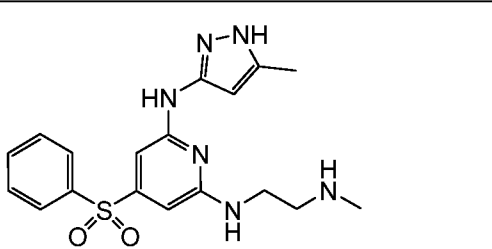
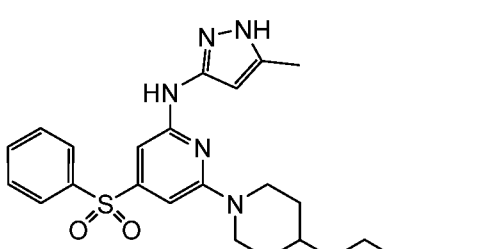
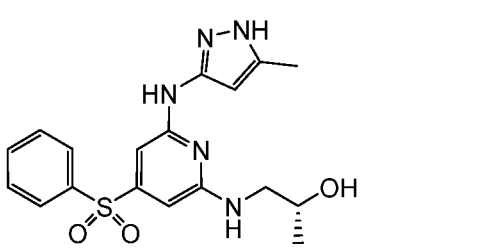
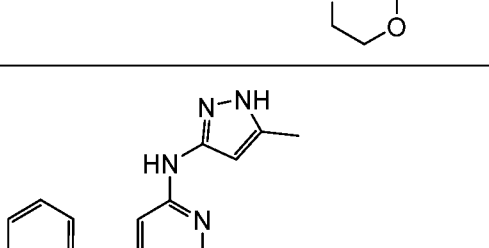
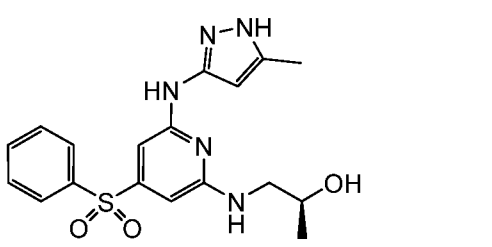


wherein R^1 , R^2 , R^6 and R^7 are as defined for Formula (I).

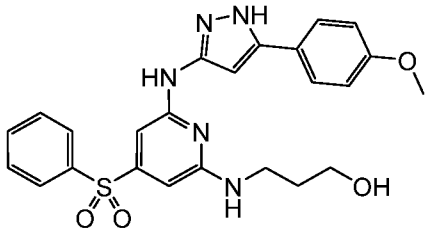
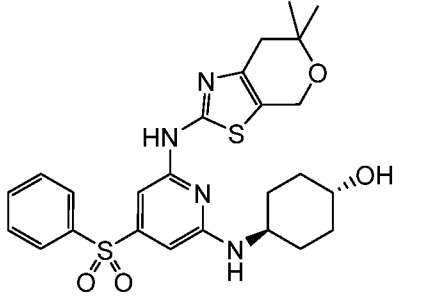
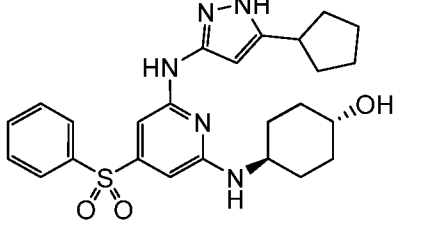
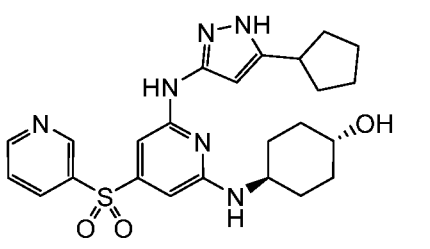
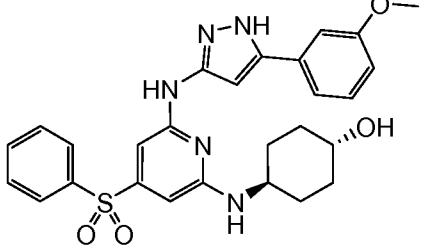
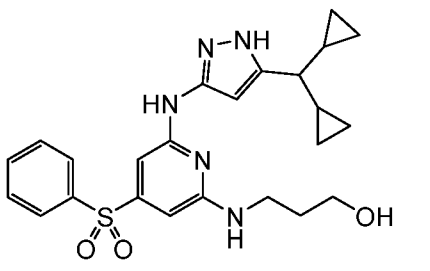
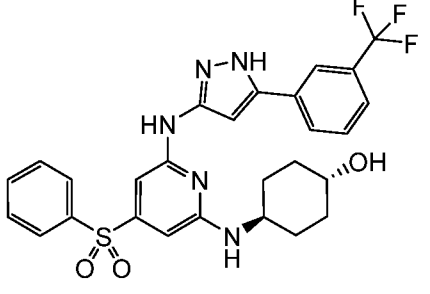
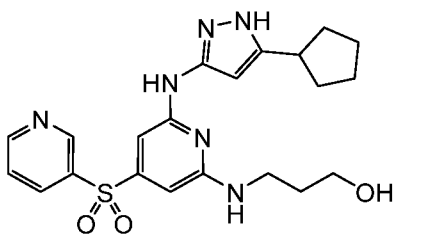
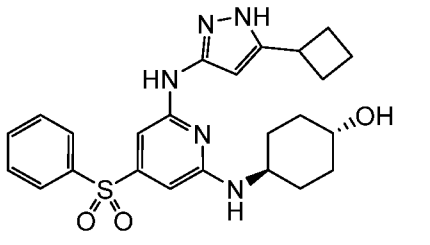
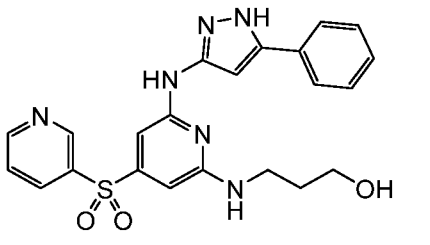
32. The compound of any one of claims 1-31, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein the compound is selected from:

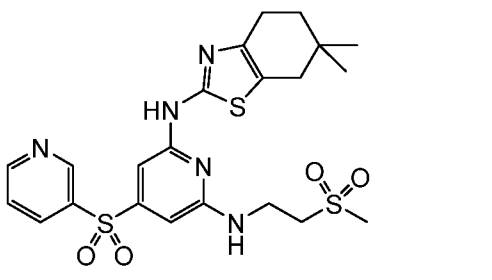
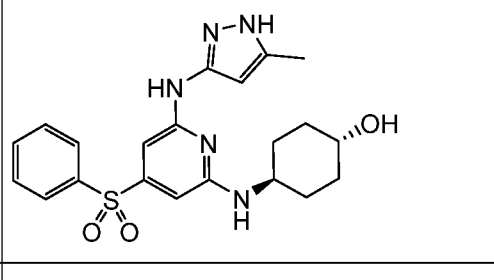
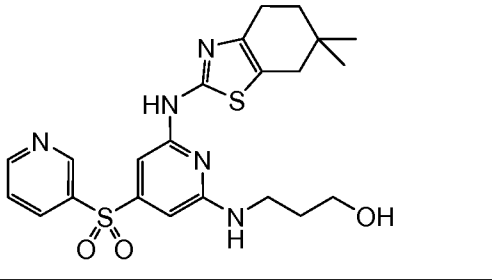
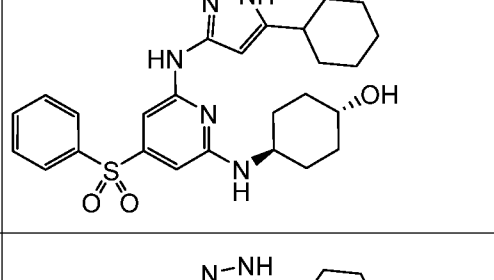
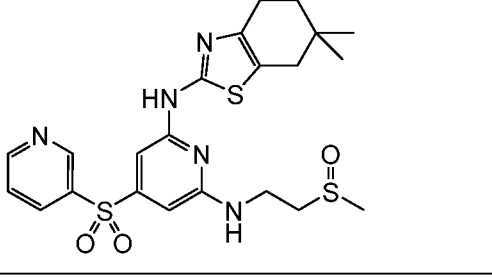
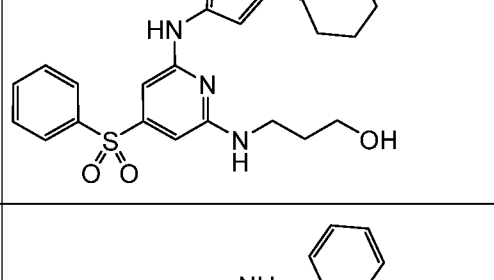
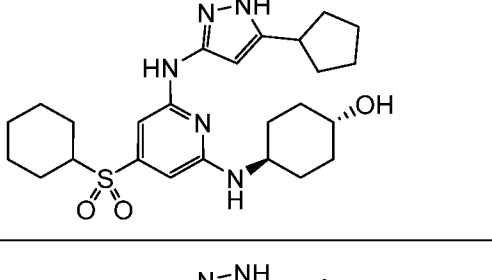
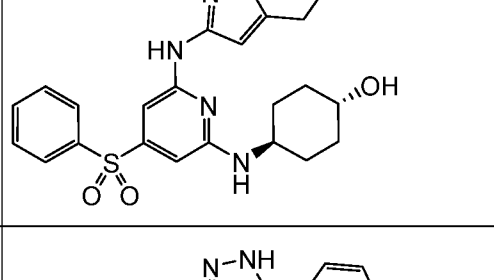
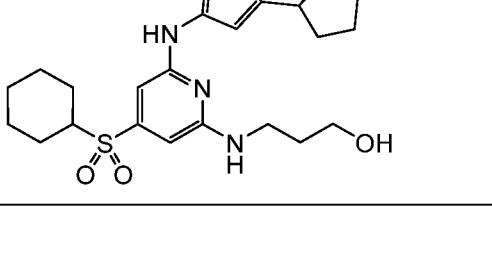
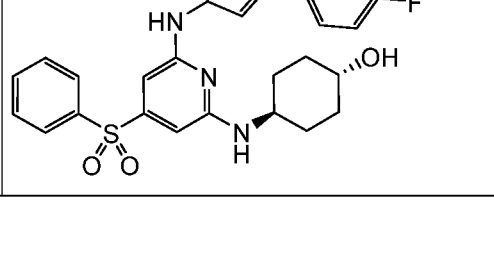
Exam. No.	Structure
1	
2	
3	
4	
5	

6		12	
7		13	
8		14	
9		15	
10		16	
11		17	

18		24	
19		25	
20		26	
21		27	
22		28	
23			

29		35	
30		36	
31		37	
32		38	
33		39	
34		40	

41		46	
42		47	
43		48	
44		49	
45		50	

51		56	
52		57	
53		58	
54		59	
55		60	

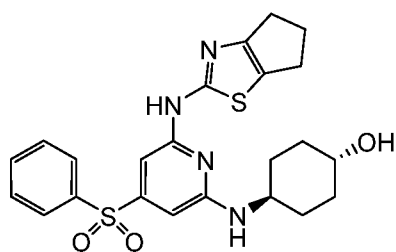
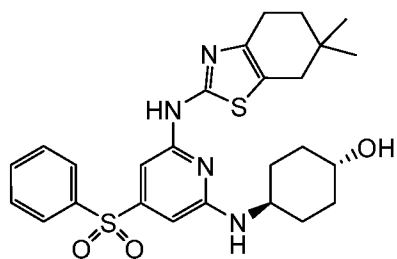
61 or 62		66	
61 or 62		67	
63		68	
64		69	
65		70	

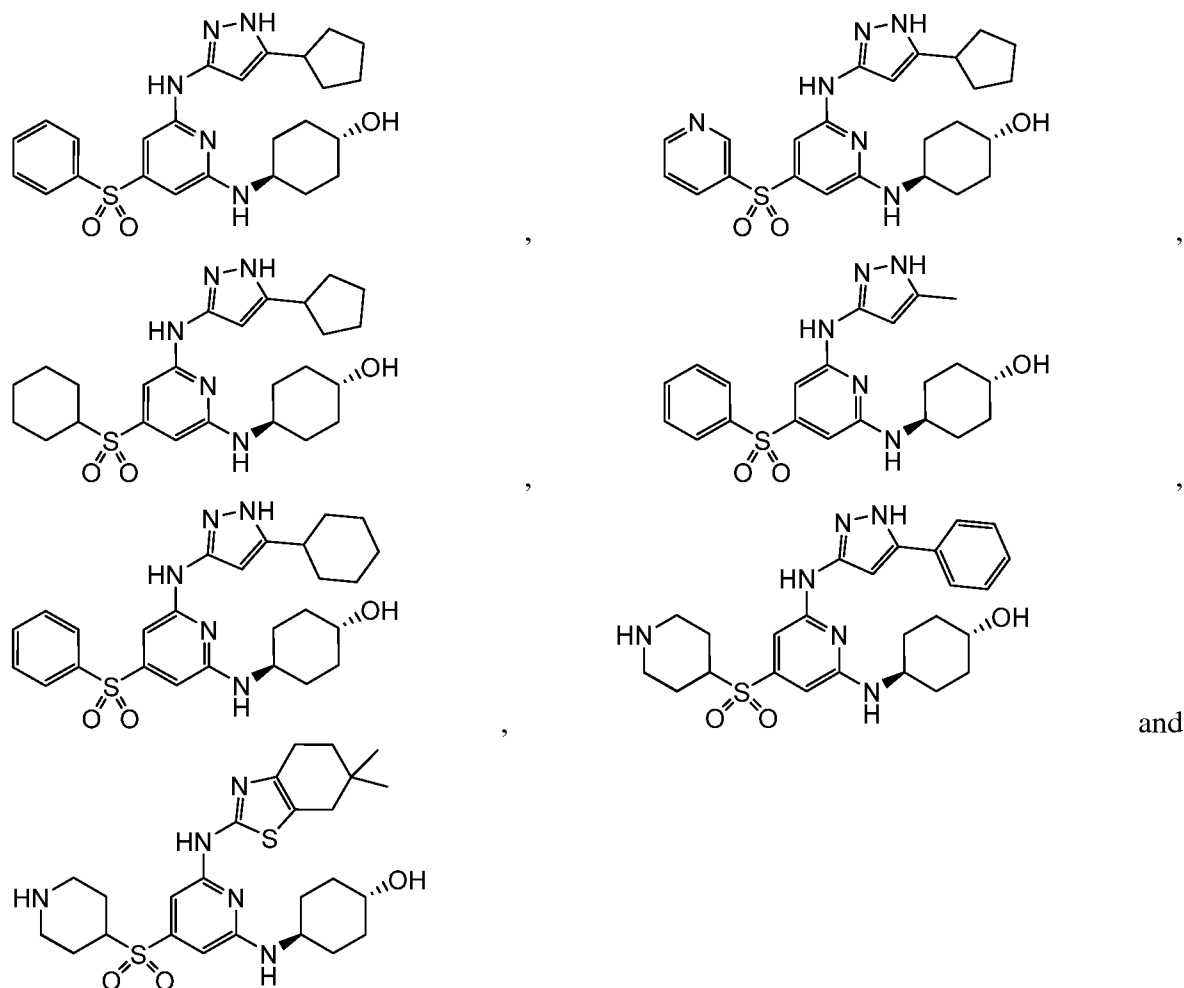
71	
72	
73	
74	
75	
76	
77	
78	
79	
80	

81		87	
82		88	
83		89	
84		90	
85		91	
86			

92		96	
93		97	
94 or 95		98	
94 or 95			

33. The compound of any one claims 1-27, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein the compound is selected from:





34. A pharmaceutical composition comprising a compound of any one of claims 1-33, or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof.

35. The composition of claim 34, further comprising a pharmaceutically acceptable carrier, adjuvant or vehicle.

36. A method of treating a disease responsive to the inhibition of ITK kinase activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition of claim 35.

37. The method of claim 36, wherein the disease is an inflammatory disease.

38. The method of claim 37, wherein the disease is asthma, allergic rhinitis, atopic dermatitis, rheumatoid arthritis, psoriasis, contact dermatitis or delayed hypersensitivity reactions.

39. The method of claim 36, wherein the disease is cancer.
40. The method of claim 39, wherein the cancer is T-cell related cancer.
41. The method of claim 36, further comprising administering a second therapeutic agent.
42. A kit comprising a pharmaceutical composition of claim 35 and instructions for use.
43. A compound of any one of claims 1-33 for use as a therapeutic agent.
44. The use of a compound of any one of claims 1-33 in the manufacture of a medicament for the treatment of an inflammatory disease or cancer.
45. The use of a compound of any one of claims 1-33 in the treatment of an inflammatory disease or cancer.
46. A compound of any one of claims 1-33 for use in the treatment of an inflammatory disease or cancer.
47. The invention as hereinabove described.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2015/065052

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/14 C07D401/12 C07D417/12 C07D417/14 C07D491/107
 C07D513/04 A61K31/44 A61P29/00 A61P35/00

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/084786 A1 (NOVARTIS AG [CH]; BURGER MATTHEW [US]; NI ZHI-JIE [US]; PECCHI SABINA) 26 July 2007 (2007-07-26) claims 36, 40; examples 78, 109 -----	1-3,7, 13,34, 35,39, 41-46
X	WO 2014/074660 A1 (SQUIBB BRISTOL MYERS CO [US]) 15 May 2014 (2014-05-15) claim 14; example 282 -----	1-3,7, 13,34,35
X	WO 2011/014515 A1 (IRM LLC [US]; CHE JIANWEI [US]; CHEN BEI [US]; DING QIANG [US]; HAO XU) 3 February 2011 (2011-02-03) claims 30, 35-37; compound 699 ----- -/-	1-3,7, 13,34, 35,37, 38,43-46



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

4 September 2015

Date of mailing of the international search report

18/09/2015

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040,
 Fax: (+31-70) 340-3016

Authorized officer

Bakboord, Joan

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/065052

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/089512 A1 (ARRAY BIOPHARMA INC [US]; AICHER THOMAS DANIEL [US]; BOYD STEVEN ARMEN) 9 August 2007 (2007-08-09) claims 17, 18; examples 28, 29 -----	1-5, 12, 13, 34, 35, 43, 44
X,P	TRANI G ET AL: "Design, synthesis and structure-activity relationships of a novel class of sulfonylpyridine inhibitors of Interleukin-2-inducible T-cell kinase (ITK)", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 24, 12 October 2014 (2014-10-12), pages 5818-5823, XP002743987, compounds 6a, 34a -----	1-46
A	WO 2014/041518 A1 (GLENMARK PHARMACEUTICALS SA [CH]) 20 March 2014 (2014-03-20) abstract -----	1-46
A	WO 2014/024119 A1 (GLENMARK PHARMACEUTICALS SA [CH]) 13 February 2014 (2014-02-13) abstract -----	1-46

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2015/065052

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007084786	A1	26-07-2007	AR 059087 A1 12-03-2008
			AT 478064 T 15-09-2010
			AU 2007206048 A1 26-07-2007
			BR PI0707189 A2 26-04-2011
			CA 2636993 A1 26-07-2007
			CN 101389622 A 18-03-2009
			CR 10163 A 17-09-2008
			CY 1111091 T1 11-06-2015
			DK 1984350 T3 15-11-2010
			DK 2261223 T3 23-09-2013
			EA 200801680 A1 30-12-2008
			EC SP088630 A 29-08-2008
			EP 1984350 A1 29-10-2008
			EP 2261223 A1 15-12-2010
			ES 2351172 T3 01-02-2011
			ES 2427624 T3 31-10-2013
			GE P20115147 B 25-01-2011
			GT 200800143 A 11-06-2009
			HK 1122031 A1 31-12-2010
			HN 2008001144 A 08-04-2011
			HR P20100603 T1 31-12-2010
			HR P20130796 T1 30-09-2013
			IL 192763 A 30-04-2013
			JO 2660 B 17-06-2012
			JP 5161110 B2 13-03-2013
			JP 2009527464 A 30-07-2009
			KR 20080096776 A 03-11-2008
			MA 30208 B1 02-02-2009
			ME P3908 A 10-02-2010
			MY 144233 A 15-08-2011
			NZ 569771 A 29-07-2011
			PE 13222007 A1 27-01-2008
			PT 1984350 E 11-11-2010
			PT 2261223 E 16-09-2013
			RS 51548 B 30-06-2011
			RS 52928 B 28-02-2014
			SI 1984350 T1 31-12-2010
			SI 2261223 T1 30-10-2013
			SM AP200800048 A 13-08-2008
			SV 2008002984 A 17-08-2010
			TW 200808786 A 16-02-2008
			TW 201315723 A 16-04-2013
			UA 96284 C2 25-10-2011
			US 2010249126 A1 30-09-2010
			US 2012225859 A1 06-09-2012
			WO 2007084786 A1 26-07-2007
			ZA 200806017 A 27-01-2010
WO 2014074660	A1	15-05-2014	AU 2013341185 A1 02-07-2015
			CA 2890929 A1 15-05-2014
			CN 104781252 A 15-07-2015
			EP 2922841 A1 30-09-2015
			KR 20150081338 A 13-07-2015
			TW 201422587 A 16-06-2014
			WO 2014074660 A1 15-05-2014
WO 2011014515	A1	03-02-2011	AR 077507 A1 31-08-2011
			CN 102548992 A 04-07-2012

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2015/065052

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
		EP 2459556 A1	06-06-2012	
		JP 2013500972 A	10-01-2013	
		TW 201105669 A	16-02-2011	
		US 2011053897 A1	03-03-2011	
		UY 32809 A	28-02-2011	
		WO 2011014515 A1	03-02-2011	

WO 2007089512	A1	09-08-2007	AT 539748 T	15-01-2012
			CA 2637172 A1	09-08-2007
			CN 101437512 A	20-05-2009
			EP 1986645 A1	05-11-2008
			ES 2378704 T3	17-04-2012
			JP 5236499 B2	17-07-2013
			JP 2009524670 A	02-07-2009
			US 2009247526 A1	01-10-2009
			WO 2007089512 A1	09-08-2007

WO 2014041518	A1	20-03-2014	NONE	

WO 2014024119	A1	13-02-2014	NONE	
