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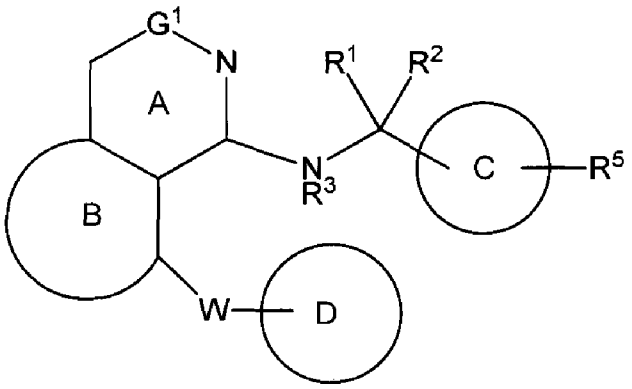
(54) **Title**: HETEROCYCLIC COMPOUNDS AS EP4 RECEPTOR ANTAGONISTS



(I)

(57) **Abstract**: The present invention provides a compound represented by the formula (1) : wherein each symbol is as defined in the specification or a salt thereof has an EP4 receptor antagonistic action, and is useful as an agent for the prophylaxis or treatment of EP4 receptor associated diseases (e.g., rheumatoid arthritis, aortic aneurysm, endometriosis, ankylosing spondylitis, inflammatory breast cancer etc.) and the like.

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DESCRIPTION

HETEROCYCLIC COMPOUNDS AS EP4 RECEPTOR ANTAGONISTS

Technical Field

[0001]

The present invention relates to a novel heterocyclic compound having an EP4 receptor antagonistic action, and is useful an agent for the prophylaxis or treatment of EP4 receptor associated diseases (e.g., rheumatoid arthritis, aortic aneurysm, endometriosis, ankylosing spondylitis, inflammatory breast cancer etc.) and the like.

[0002]

(Background of the Invention)

Prostaglandin E2 (PGE2) is one of the most broadly distributed prostanoids throughout animal species and widely produced within the body by the actions of cyclooxygenases (COX) on arachidonic acid. PGE2 is involved in a number of physiological and pathophysiological responses such as fever, pain, inflammation (non-patent document 1) and elicits its biological functions through four receptor subtypes EP1-4, all G-protein-coupled receptor.

[0003]

Emerging biology has revealed important roles of EP4 receptors in immune system (non-patent documents 2 and 3). For example, EP4 receptor activation stimulates dendritic cells and promotes IL-23 production synergistically with CD40 and Toll-like receptor signaling. PGE2 then enhances the expansion of Th17 cells with IL-23. EP4 receptor activation promotes the differentiation of Th1 from naive T cells synergistically with IL-12. PGE2 synergistically induces IL-6 and IL-1β expression with LPS via EP4 receptors in macrophages. Th1, Th17 and macrophage cells play key roles in the development of autoimmune/inflammatory diseases. Thus, a selective EP4 receptor antagonist is expected to inhibit IL-23 & IL-6 production and suppression of Th1 & Th17 function (non-patent documents 4 and 5), reduce inflammatory pain and offers an

attractive therapeutic approach for rheumatoid arthritis (RA), inflammatory bowel diseases and other autoimmune/ inflammatory diseases.

[0004]

Non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors are clinically proven to relieve inflammation and pain by inhibiting the synthesis of arachidonic acid pathway metabolites including PGE2. However, their use is associated with adverse effects due to pleiotropic function of arachidonic acid pathway metabolites and imbalance in their levels. An imbalance between TXA2 and PGI2, for example, has been implicated in the vasospasm, hyperaggregability and thromboembolism that are associated with many cardiovascular diseases (non-patent document 6). As EP4 selective antagonists specifically block PGE2 function through only EP4 receptor, leaving functions through other receptors intact, it is expected that they will not exhibit the adverse effects similar to that of NSAIDs and COX-2 inhibitors (non-patent document 7). Further, compared to other targeted therapies (e.g. JAK, TNFa, IL-6) for RA, EP4 antagonist has been shown to improve both joint damage and inflammatory pain in animal models. Thus, this mechanism has potential to "complete symptom management" for RA in clinic (non-patent document 8).

[0005]

In addition to autoimmune diseases, endometriosis, aortic aneurysm (e.g. abdominal aortic aneurysm, thoracic aortic aneurysm, thoracoabdominal aortic aneurysm etc.) and ankylosing spondylitis are other indications for EP4 antagonist. Endometriosis (EM) is a chronic, estrogen-dependent inflammatory disease and defined as the presence of functional endometrial tissue at ectopic sites. It is a common disease that 10-20% of women of reproductive age are affected. The most common symptom is a dysmenorrhea. Chronic pelvic pain, dyspareunia, dyschezia (pain on defecation), loin pain, lower abdominal pain or back pain, pain on micturition, pain on

exercise are also part of the symptoms of EM (non-patent document 9). Current treatments include surgical intervention, pharmacotherapies using NSAIDs, COX-2 inhibitors and hormonal therapies, or a combination of both. NSAIDs or COX-2 inhibitors are effective in relieving pelvic pain, but can cause severe side effects including gastrointestinal injury, nephropathy, and increase cardiovascular risk (non-patent document 10). Hormonal therapy controls disease conditions, but has side effect such as pseudomenopause and decreased bone density due to suppression of estrogen production (non-patent document 11). Development of a safer, but equally efficacious treatment is highly demanded. EP4 receptor proteins were abundantly expressed in human endometriosis tissues (ectopic and eutopic endometrium) during the proliferative phase of the menstrual cycle (non-patent document 12). In human immortalized endometriotic epithelial and stromal cells selective inhibition of EP4 induced apoptosis (non-patent document 12), inhibited proliferation (non-patent document 13), inhibited migration and invasion (non-patent document 14) and inhibited adhesion (non-patent document 15). These studies suggest that inhibition of EP4 signaling is a potential therapeutic option for women with EM (non-patent document 15).

[0006]

Abdominal aortic aneurysm (AAA) is a common, progressive, and life-threatening degenerative vascular disease (non-patent documents 16 and 17). It is an inflammatory disorder characterized by localized connective tissue degeneration and smooth muscle cell apoptosis, leading to aortic dilatation and rupture (non-patent documents 18-20). After rupture occurs, the probability of mortality is greater than 60% (non-patent document 21). No pharmacotherapy has been found to be effective at decreasing the growth rate or rupture rate of AAAs except. In aneurysm walls, COX-2 is widely expressed in macrophages and smooth muscle cells, along with locally synthetized PGE2 (non-patent document 22). EP4 expression is

increased in the aneurysm areas of human AAA tissues, both in human aortic aneurysm smooth muscle cell as well as in macrophages in the lesion (non-patent documents 23 and 24). EP4 receptor antagonist or global gene deletion of the EP4 receptor significantly decreased MMP-2 activation and IL-6 production in human AAA tissues and the rate of AAA formation in preclinical mouse models (non-patent document 23 and 25).

[0007]

Ankylosing spondylitis is the prototypic spondyloarthropathy, one of a group of conditions which also includes psoriatic arthritis, reactive arthritis and arthritis complicating inflammatory bowel disease. Ankylosing spondylitis is highly heritable (non-patent documents 26 and 27) and familial (non-patent document 28). Men are affected 2-3 times more frequently than women. The disease is known to be strongly associated with HLA-B27. Since association between EP4 receptor gene (PTGER4) and ankylosing spondylitis has been also demonstrated (non-patent document 29), EP4 receptor is likely to be involved in disease pathogenesis. There is no cure for ankylosing spondylitis as yet, but the patient's back pain and stiffness usually show good symptomatic response to NSAIDs. Since EP4 antagonists are known to possess analgesic activity at least in animal models (non-patent documents 30 and 31), a safe and chronically-treatable EP4 antagonist may be an alternative symptom-relieving pharmacothetherapy for ankylosing spondylitis.

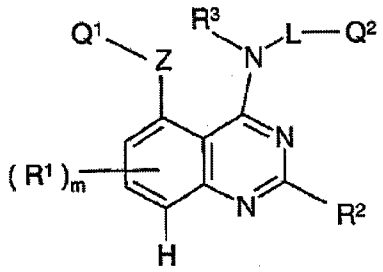
[0008]

Examples of the compound having a structure similar to the compound described in the present specification include the following compounds.

[0009]

(1) Patent document 1 describes a compound represented by the formula:

[0010]



[0011]

wherein

Z is a direct bond, O, S, SO, SO_2, N (R^{11}), CO, CH (OR^{11}), CON (R^{11}), N (R^{11}) CO, SO_2N (R^{11}), N (R^{11}) SO_2, $OC(R^{11})_2$, $SC(R^{11})_2$ or $N(R^{11})C(R^{11})_2$;

R^{11} is hydrogen or C_{1-6} alkyl;

Q^1 is aryl, heteroaryl, etc;

R^1 is halogen, trifluoromethyl, etc;

m is 0, 1 or 2;

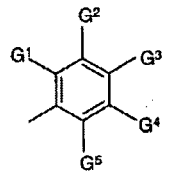
R^2 is hydrogen;

R^3 is hydrogen or C_{1-6} alkyl;

L is a direct bond or $-[C(R^{22})_2]n-$ [n is 1 or 2], and each R^{22} independently is hydrogen or C_{1-4} alkyl;

Q^2 is

[0012]



Ia

[0013]

G^1 and G^5 are each hydrogen;

G^2 and G^4 are each hydrogen, halogen, hydroxy, amino, carboxy, etc.; and

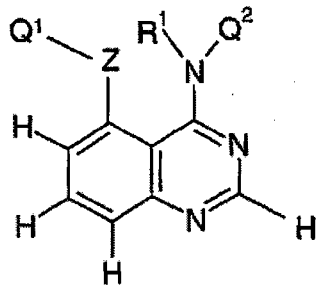
G^3 is hydrogen, halogen, hydroxy, amino, carboxy, etc.,

as an erbB2 receptor inhibitor.

[0014]

(2) Patent document 2 describes a compound represented by the formula:

[0015]



[0016]

wherein

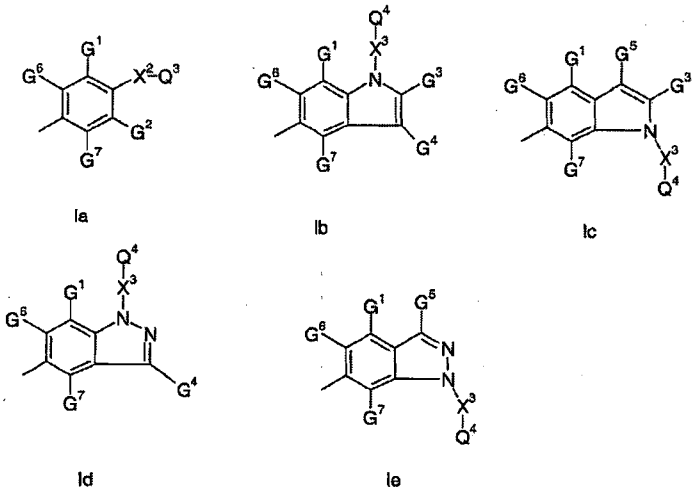
Z is a direct bond, O, S, N(R^2) wherein R^2 is hydrogen or C_{1-6} alkyl;

Q^1 is C_{3-7} cycloalkyl, heterocyclyl, etc.;

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

Q^2 is

[0017]



[0018]

G^1, G^2, G^3, G^4 and G^5 are each hydrogen, halogen, hydroxy, amino, carboxy, etc.;

X^2 is a direct bond, O, S, SO, SO_2, CH(OR^6), CON(R^6), etc.;

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

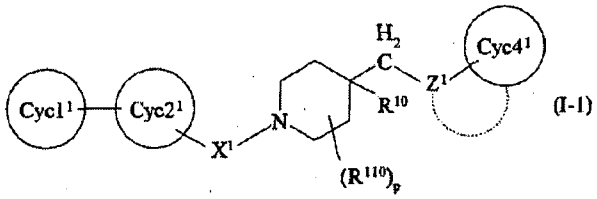
Q^3 is aryl or heteroaryl,

as an erbB2 receptor inhibitor.

[0019]

(3) Patent document 3 describes a compound represented by the formula:

[0020]



[0021]

wherein

$Cycl^1$ is a 5- to 6-membered mono-cyclic carbocyclic ring optionally having substituent(s), or a 5- to 6-membered mono-cyclic heterocyclic ring optionally having substituent(s);

$Cyc2^1$ is a 5-membered mono-cyclic heterocyclic ring optionally having substituent(s);

$Cyc4^1$ is a 5- to 10-membered mono-cyclic or bi-cyclic carbocyclic ring optionally having substituent(s), or a 5- to 10-membered mono-cyclic or bi-cyclic heterocyclic ring optionally having substituent(s);

X^1 is $-CH_2-$, $-CO-$ or $-SO_2-$;

Z^1 is bond, $-N(R^{51})-CO-$, $-CO-N(R^{51})-$, $-N(R^{51})-$ or $-O-$;

R^{51} is H, C_{1-4} alkyl optionally having substituent(s), or R^{51} and the substituent of $Cyc4^1$ is taken together to form a C_{1-4} alkylene optionally having substituent(s) or a C_{2-4} alkenylene optionally having substituent(s);

R^{10} is H or a substituent;

R^{110} is a substituent; and

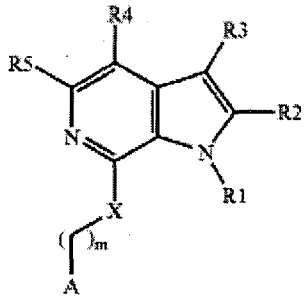
p is 0-8,

as an agent for the prophylaxis or treatment of metabolic disease (diabetes), cerebrovascular disease (stroke) etc.

[0022]

(4) Patent document 4 describes a compound represented by the formula:

[0023]



[0024]

wherein

A is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;

m is 0, 1 or 2;

X is a bond, O, S, CH_2, etc.;

R1 is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted acyl group, an optionally substituted carbamoyl group, or a substituted sulfonyl group;

R2 is an optionally substituted hydrocarbon group, or an alkoxycarbonyl group;

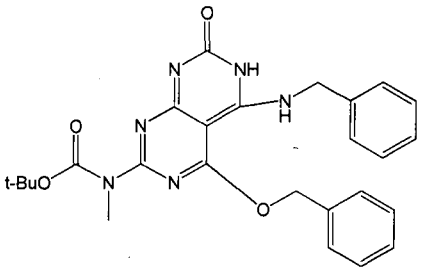
R3 is a hydrogen atom, an optionally substituted hydrocarbon group, a formyl group, an alkylcarbonyl group, a halogen atom, a cyano group, or R2 and R3 optionally form a ring structure together with the carbon atoms bonded thereto; and

R4 and R5 are each a hydrogen atom, a halogen atom, a cyano group, a nitro group, an optionally substituted hydrocarbon group, an optionally substituted hydrocarbon oxy group, an optionally substituted hydrocarbon thio group, an alkylcarbonyl group, carbamoyl group, a mono- or di-alkylcarbamoyl group optionally substituted by hydroxy or benzyloxy, an acyloxy group, a substituted sulfonyl group, a substituted sulfinyl group, an optionally substituted amino group, or a heterocyclyl-carbonyl group,

as a proton pump inhibitor.

(5) Non-Patent Document 32 describes the following compound:

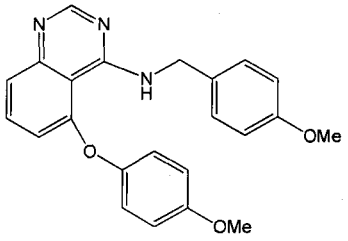
[0025]

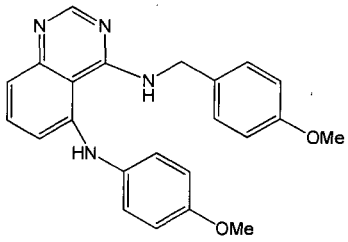


[0026]

(6) Non-Patent Document 33 describes the following compounds:

[0027]





Document List

Patent Document

[0028]

[Patent Document 1] WO 2003/040109

[Patent Document 2] WO 2003/040108

[Patent Document 3] WO 2010/080864

[Patent Document 4] WO 2006/011670

Non-Patent Document

[0029]

[Non-Patent Document 1] Pharmacol. Rev., 2011. 63(3): p. 471-538

[Non-Patent Document 2] Trends Pharmacol. Sci., 2012. 33(6): p. 304-11

[Non-Patent Document 3] J. Allergy Clin. Immunol., 2013. 131(2): p. 532-40 e1-2

[Non-Patent Document 4] Immunity, 2010. 33(2): p. 279-88

[Non-Patent Document 5] Immunity, 2010. 33(2): p. 150-2

[Non-Patent Document 6] Thromb. Res., 2013. 132(1): p. 56-62

[Non-Patent Document 7] Postepy Hig. Med. Dosw., (Online), 2012. 66: p. 287-94

[Non-Patent Document 8] Br. J. Pharmacol., 2010. 160(2): p.

292-310

[Non-Patent Document 9] BMJ, 2001. 323(7304): p. 93-5

[Non-Patent Document 10] J. Pharm. Pharm. Sci., 2013. 16(5): p. 821-47

[Non-Patent Document 11] N. Engl. J. Med., 2008. 359(11): p. 1136-42

[Non-Patent Document 12] Mol. Endocrinol., 2009. 23(8): p. 1291-305

[Non-Patent Document 13] Fertil Steril, 2010. 93(8): p. 2498-506

[Non-Patent Document 14] Mol. Cell Endocrinol., 2011. 332(1-2): p. 306-13

[Non-Patent Document 15] Biol. Reprod, 2013. 88(3): p. 77

[Non-Patent Document 16] Arterioscler. Thromb. Vasc. Biol., 1996. 16(8): p. 963-70

[Non-Patent Document 17] N. Engl. J. Med., 1993. 328(16): p. 1167-72

[Non-Patent Document 18] J. Clin. Invest., 1998. 102(11): p. 1900-10

[Non-Patent Document 19] J. Clin. Invest., 2002. 110(5): p. 625-32

[Non-Patent Document 20] J. Immunol., 2004. 172(4): p. 2607-12

[Non-Patent Document 21] World J. Surg., 2008. 32(6): p. 976-86

[Non-Patent Document 22] Circulation, 1999. 100(1): p. 48-54

[Non-Patent Document 23] PLoS One, 2012. 7(5): p. e36724

[Non-Patent Document 24] J. Vasc. Surg., 2003. 38(2): p. 354-9

[Non-Patent Document 25] Am. J. Pathol., 2012. 181(1): p. 313-21

[Non-Patent Document 26] Scand. J. Rheumatol., 2008. 37: p. 120-126

[Non-Patent Document 27] Arthritis Rheum., 1997. 40: p. 1823-1828

[Non-Patent Document 28] Ann. Rheum. Dis., 2000. 59: p. 883-886

[Non-Patent Document 29] Nature Genetics., 2011. 43: p. 761-767

[Non-Patent Document 30] Eur J Pharmacol., 2008, 580: p. 116-121

[Non-Patent Document 31] Bioorg Med Chem Lett., 2010. 15: p. 3760-3 [Non-Patent Document 32] Tetrahedron Letters, vol.52, (2011), pages 661-664

[Non-Patent Document 33] Am. Chem. Soc. Med. Chem. Lett., 2010, Vol.1, pages 54-58

Summary of the Invention

Problems to be Solved by the Invention

[0030]

The present invention aims to provide a novel heterocyclic compound having an EP4 receptor antagonistic action, and is useful as an agent for the prophylaxis or treatment of EP4 receptor associated diseases (e.g., rheumatoid arthritis, aortic aneurysm (e.g. abdominal aortic aneurysm, thoracic aortic aneurysm, thoracoabdominal aortic aneurysm etc.), endometriosis, ankylosing spondylitis, inflammatory breast cancer etc.) and the like.

Means of Solving the Problems

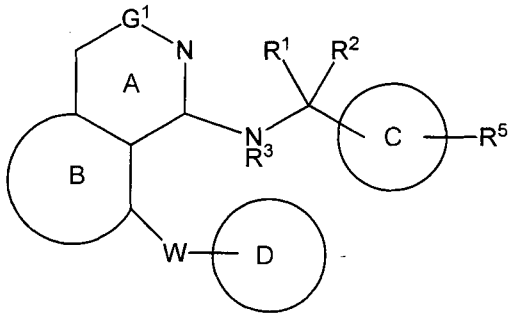
[0031]

The present inventors have conducted intensive studies, and have found that a compound represented by the below-mentioned formula (1) unexpectedly has an EP4 receptor antagonistic action, and therefore, is useful as an agent for the prophylaxis or treatment of EP4 receptor associated diseases (e.g., rheumatoid arthritis, aortic aneurysm (e.g. abdominal aortic aneurysm, thoracic aortic aneurysm, thoracoabdominal aortic aneurysm etc.), endometriosis, ankylosing spondylitis, inflammatory breast cancer etc.) and the like, and completed the present invention based on these findings.

Accordingly, the present invention provides the following.

[1] A compound represented by the formula (I):

[0032]



(I)

[0033]

wherein

Ring A is an optionally further substituted pyridine or an optionally further substituted pyridazine,

G^1 is N or CR^4,

R^4 is a hydrogen atom or a substituent,

Ring B is an optionally substituted 6-membered aromatic ring,

R^1 and R^2 are each independently a hydrogen atom or an optionally substituted C_{1-6} alkyl group, or R^1 and R^2 are joined together to form a cycloalkane or a heterocycle, each of which is optionally substituted,

R^3 is a hydrogen atom or a substituent,

Ring C is an optionally further substituted ring,

R^5 is a substituent,

Ring D is an optionally substituted ring, and

W is a bond, or a spacer in which the number of atoms in the main chain is 1 to 4,

or a salt thereof (hereinafter to be referred to as compound (I).

[2] The compound or salt of the above-mentioned [1], wherein

Ring A is pyridine optionally further having one substituent, on the carbon atom adjacent to G^1, selected from

(1) a halogen atom,

(2) an optionally halogenated C_{1-6} alkyl group, and

(3) a C_{3-10} cycloalkyl group,

G^1 is CR^4,

R^4 is a hydrogen atom,

Ring B is a 6-membered aromatic ring optionally having 1 to 3

substituents selected from

(1) a halogen atom,

(2) an optionally halogenated C_{1-6} alkyl group,

(3) an optionally halogenated C_{1-6} alkoxy group, and

(4) a C_{3-10} cycloalkyl group,

R^1 and R^2 are each independently a hydrogen atom or a C_{1-6} alkyl group, or R^1 and R^2 are joined together to form a cycloalkane,

R^3 is a hydrogen atom,

Ring C is a C_{6-14} aromatic hydrocarbon ring or a 5- or 6-membered monocyclic aromatic heterocycle, each optionally having 1 to 3 substituents, in addition to R^5, selected from

(1) a halogen atom, and

(2) an optionally halogenated C_{1-6} alkyl group,

R^5 is

(1) a carboxy group,

(2) a C_{1-6} alkoxy-carbonyl group,

(3) a cyano group,

(4) a C_{1-6} alkyl group optionally having 1 to 3 substituents selected from

(a) a halogen atom,

(b) a hydroxy group, and

(c) a carboxy group,

(5) a carbamoyl group optionally having 1 or 2 substituents selected from

(a) a C_{1-6} alkyl group,

(b) a C_{1-6} alkoxy group,

(c) a C_{7-16} aralkyloxy group, and

(d) a C_{1-6} alkylsulfonyl group, or

(6) a sulfamoyl group,

Ring D is a C_{6-14} aromatic hydrocarbon ring or a 5- or 6-membered monocyclic aromatic heterocycle, each optionally having 1 to 3 substituents selected from

(1) a halogen atom,

(2) a cyano group,

(3) an optionally halogenated C_{1-6} alkyl group, and

(4) an optionally halogenated C_{1-6} alkoxy group, and

W is -O- or -O-CH_2- (wherein the left bond is bonded to Ring B, and the right bond is bonded to Ring D).

[3] 4-[(1S)-1-[[8-(3-Fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid or a salt thereof.

[4] 4-[(1S)-1-[[5-Chloro-8-(4-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid or a salt thereof.

[5] 4-[(1S)-1-[[8-(3-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid or a salt thereof.

[6] A medicament comprising the compound or salt of the above-mentioned [1].

[7] The medicament of the above-mentioned [6], which is an EP4 receptor antagonist.

[8] The medicament of the above-mentioned [6], which is an agent for the prophylaxis or treatment of EP4 receptor associated diseases.

[9] The medicament of the above-mentioned [6], which is an agent for the prophylaxis or treatment of rheumatoid arthritis, aortic aneurysm, endometriosis, ankylosing spondylitis or inflammatory breast cancer.

[10] The compound or salt the above-mentioned [1] for use in the prophylaxis or treatment of EP4 receptor associated diseases.

[11] The compound or salt the above-mentioned [10], wherein the EP4 receptor associated diseases is selected from rheumatoid arthritis, aortic aneurysm, endometriosis, ankylosing spondylitis and inflammatory breast cancer.

[12] A method of inhibiting EP4 in a mammal, which comprises administering an effective amount of the compound or salt of the above-mentioned [1] to the mammal.

[13] A method for the prophylaxis or treatment of EP4 receptor associated diseases in a mammal, which comprises administering an effective amount of the compound or salt of the above-mentioned [1] to the mammal.

[14] The method of the above-mentioned [13], wherein the EP4

receptor associated diseases is selected from rheumatoid arthritis, aortic aneurysm, endometriosis, ankylosing spondylitis and inflammatory breast cancer.

[15] Use of the compound or salt of the above-mentioned [1] for the production of an agent for the prophylaxis or treatment of EP4 receptor associated diseases.

[16] Use of the above-mentioned [15], wherein the EP4 receptor associated diseases is selected from rheumatoid arthritis, aortic aneurysm, endometriosis, ankylosing spondylitis and inflammatory breast cancer.

Effect of the Invention

[0034]

Compound (I) has a superior EP4 receptor antagonistic action, which is useful as an agent for the prophylaxis or treatment of EP4 receptor associated diseases (e.g., rheumatoid arthritis, aortic aneurysm, endometriosis, ankylosing spondylitis, inflammatory breast cancer etc.) and the like.

[0035]

[Detailed Description of the Invention]

The definition of each substituent used in the present specification is described in detail in the following. Unless otherwise specified, each substituent has the following definition.

In the present specification, examples of the "halogen atom" include fluorine, chlorine, bromine and iodine.

In the present specification, examples of the "C_{1-6} alkyl group" include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl and 2-ethylbutyl.

In the present specification, examples of the "optionally halogenated C_{1-6} alkyl group" include a C_{1-6} alkyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include methyl, chloromethyl,

difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, tetrafluoroethyl, pentafluoroethyl, propyl, 2,2-difluoropropyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl and 6,6,6-trifluorohexyl.

In the present specification, examples of the "C_{2-6} alkenyl group" include ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl and 5-hexenyl.

In the present specification, examples of the "C_{2-6} alkynyl group" include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl and 4-methyl-2-pentynyl.

In the present specification, examples of the "C_{3-10} cycloalkyl group" include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl and adamantyl.

In the present specification, examples of the "optionally halogenated C_{3-10} cycloalkyl group" include a C_{3-10} cycloalkyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include cyclopropyl, 2,2-difluorocyclopropyl, 2,3-difluorocyclopropyl, cyclobutyl, difluorocyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

In the present specification, examples of the "C_{3-10} cycloalkenyl group" include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

In the present specification, examples of the "C_{6-14} aryl group" include phenyl, 1-naphthyl, 2-naphthyl, 1-anthryl, 2-anthryl and 9-anthryl.

In the present specification, examples of the "C_{7-16} aralkyl group" include benzyl, phenethyl, naphthylmethyl and

phenylpropyl.

[0036]

In the present specification, examples of the "C_{1-6} alkoxy group" include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy and hexyloxy.

In the present specification, examples of the "optionally halogenated C_{1-6} alkoxy group" include a C_{1-6} alkoxy group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy and hexyloxy.

In the present specification, examples of the "C_{3-10} cycloalkyloxy group" include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and cyclooctyloxy.

In the present specification, examples of the "C_{1-6} alkylthio group" include methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, pentylthio and hexylthio.

In the present specification, examples of the "optionally halogenated C_{1-6} alkylthio group" include a C_{1-6} alkylthio group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include methylthio, difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentylthio and hexylthio.

In the present specification, examples of the "C_{1-6} alkyl-carbonyl group" include acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 3-methylbutanoyl, 2-methylbutanoyl, 2,2-dimethylpropanoyl, hexanoyl and heptanoyl.

In the present specification, examples of the "optionally halogenated C_{1-6} alkyl-carbonyl group" include a C_{1-6} alkyl-carbonyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include acetyl,

chloroacetyl, trifluoroacetyl, trichloroacetyl, propanoyl, butanoyl, pentanoyl and hexanoyl.

In the present specification, examples of the "C_{1-6} alkoxy-carbonyl group" include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl and hexyloxycarbonyl.

In the present specification, examples of the "C_{6-14} aryl-carbonyl group" include benzoyl, 1-naphthoyl and 2-naphthoyl.

In the present specification, examples of the "C_{7-16} aralkyl-carbonyl group" include phenylacetyl and phenylpropionyl.

In the present specification, examples of the "5- to 14-membered aromatic heterocyclylcarbonyl group" include nicotinoyl, isonicotinoyl, thenoyl and furoyl.

In the present specification, examples of the "3- to 14-membered non-aromatic heterocyclylcarbonyl group" include morpholinylcarbonyl, piperidinylcarbonyl and pyrrolidinylcarbonyl.

In the present specification, examples of the "mono- or di-C_{1-6} alkyl-carbamoyl group" include methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl and N-ethyl-N-methylcarbamoyl.

In the present specification, examples of the "mono- or di-C_{7-16} aralkyl-carbamoyl group" include benzylcarbamoyl and phenethylcarbamoyl.

In the present specification, examples of the "C_{1-6} alkylsulfonyl group" include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, sec-butylsulfonyl and tert-butylsulfonyl.

In the present specification, examples of the "optionally halogenated C_{1-6} alkylsulfonyl group" include a C_{1-6} alkylsulfonyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include methylsulfonyl, difluoromethylsulfonyl,

trifluoromethylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, 4,4,4-trifluorobutylsulfonyl, pentylsulfonyl and hexylsulfonyl.

In the present specification, examples of the "C_{6-14} arylsulfonyl group" include phenylsulfonyl, 1-naphthylsulfonyl and 2-naphthylsulfonyl.

[0037]

In the present specification, examples of the "substituent" include a halogen atom, a cyano group, a nitro group, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an acyl group, an optionally substituted amino group, an optionally substituted carbamoyl group, an optionally substituted thiocarbamoyl group, an optionally substituted sulfamoyl group, an optionally substituted hydroxy group, an optionally substituted sulfanyl (SH) group and an optionally substituted silyl group.

In the present specification, examples of the "hydrocarbon group" (including "hydrocarbon group" of "optionally substituted hydrocarbon group") include a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, a C_{3-10} cycloalkyl group, a C_{3-10} cycloalkenyl group, a C_{6-14} aryl group and a C_{7-16} aralkyl group.

[0038]

In the present specification, examples of the "optionally substituted hydrocarbon group" include a hydrocarbon group optionally having substituent(s) selected from the following substituent group A.

[substituent group A]

(1) a halogen atom,
(2) a nitro group,
(3) a cyano group,
(4) an oxo group,
(5) a hydroxy group,
(6) an optionally halogenated C_{1-6} alkoxy group,
(7) a C_{6-14} aryloxy group (e.g., phenoxy, naphthoxy),

(8) a C_{7-16} aralkyloxy group (e.g., benzyloxy),

(9) a 5- to 14-membered aromatic heterocyclyloxy group (e.g., pyridyloxy),

(10) a 3- to 14-membered non-aromatic heterocyclyloxy group (e.g., morpholinyloxy, piperidinyloxy),

(11) a C_{1-6} alkyl-carbonyloxy group (e.g., acetoxy, propanoyloxy),

(12) a C_{6-14} aryl-carbonyloxy group (e.g., benzoyloxy, 1-naphthoyloxy, 2-naphthoyloxy),

(13) a C_{1-6} alkoxy-carbonyloxy group (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy),

(14) a mono- or di-C_{1-6} alkyl-carbamoyloxy group (e.g., methylcarbamoyloxy, ethylcarbamoyloxy, dimethylcarbamoyloxy, diethylcarbamoyloxy),

(15) a C_{6-14} aryl-carbamoyloxy group (e.g., phenylcarbamoyloxy, naphthylcarbamoyloxy),

(16) a 5- to 14-membered aromatic heterocyclylcarbonyloxy group (e.g., nicotinoyloxy),

(17) a 3- to 14-membered non-aromatic heterocyclylcarbonyloxy group (e.g., morpholinylcarbonyloxy, piperidinylcarbonyloxy),

(18) an optionally halogenated C_{1-6} alkylsulfonyloxy group (e.g., methylsulfonyloxy, trifluoromethylsulfonyloxy),

(19) a C_{6-14} arylsulfonyloxy group optionally substituted by a C_{1-6} alkyl group (e.g., phenylsulfonyloxy, toluenesulfonyloxy),

(20) an optionally halogenated C_{1-6} alkylthio group,

(21) a 5- to 14-membered aromatic heterocyclic group,

(22) a 3- to 14-membered non-aromatic heterocyclic group,

(23) a formyl group,

(24) a carboxy group,

(25) an optionally halogenated C_{1-6} alkyl-carbonyl group,

(26) a C_{6-14} aryl-carbonyl group,

(27) a 5- to 14-membered aromatic heterocyclylcarbonyl group,

(28) a 3- to 14-membered non-aromatic heterocyclylcarbonyl group,

(29) a C_{1-6} alkoxy-carbonyl group,

(30) a C_{6-14} aryloxy-carbonyl group (e.g., phenyloxycarbonyl, 1-naphthyloxycarbonyl, 2-naphthyloxycarbonyl),

(31) a C_{7-16} aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, phenethyloxycarbonyl),

(32) a carbamoyl group,

(33) a thiocarbamoyl group,

(34) a mono- or di-C_{1-6} alkyl-carbamoyl group,

(35) a C_{6-14} aryl-carbamoyl group (e.g., phenylcarbamoyl),

(36) a 5- to 14-membered aromatic heterocyclylcarbamoyl group (e.g., pyridylcarbamoyl, thienylcarbamoyl),

(37) a 3- to 14-membered non-aromatic heterocyclylcarbamoyl group (e.g., morpholinylcarbamoyl, piperidinylcarbamoyl),

(38) an optionally halogenated C_{1-6} alkylsulfonyl group,

(39) a C_{6-14} arylsulfonyl group,

(40) a 5- to 14-membered aromatic heterocyclylsulfonyl group (e.g., pyridylsulfonyl, thienylsulfonyl),

(41) an optionally halogenated C_{1-6} alkylsulfinyl group,

(42) a C_{6-14} arylsulfinyl group (e.g., phenylsulfinyl, 1-naphthylsulfinyl, 2-naphthylsulfinyl),

(43) a 5- to 14-membered aromatic heterocyclylsulfinyl group (e.g., pyridylsulfinyl, thienylsulfinyl),

(44) an amino group,

(45) a mono- or di-C_{1-6} alkylamino group (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, N-ethyl-N-methylamino),

(46) a mono- or di-C_{6-14} arylamino group (e.g., phenylamino),

(47) a 5- to 14-membered aromatic heterocyclylamino group (e.g., pyridylamino),

(48) a C_{7-16} aralkylamino group (e.g., benzylamino),

(49) a formylamino group,

(50) a C_{1-6} alkyl-carbonylamino group (e.g., acetylamino, propanoylamino, butanoylamino),

(51) a (C_{1-6} alkyl)(C_{1-6} alkyl-carbonyl)amino group (e.g., N-acetyl-N-methylamino),

(52) a C_{6-14} aryl-carbonylamino group (e.g., phenylcarbonylamino, naphthylcarbonylamino),

(53) a C_{1-6} alkoxy-carbonylamino group (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, tert-butoxycarbonylamino),

(54) a C_{7-16} aralkyloxy-carbonylamino group (e.g., benzyloxycarbonylamino),

(55) a C_{1-6} alkylsulfonylamino group (e.g., methylsulfonylamino, ethylsulfonylamino),

(56) a C_{6-14} arylsulfonylamino group optionally substituted by a C_{1-6} alkyl group (e.g., phenylsulfonylamino, toluenesulfonylamino),

(57) an optionally halogenated C_{1-6} alkyl group,

(58) a C_{2-6} alkenyl group,

(59) a C_{2-6} alkynyl group,

(60) a C_{3-10} cycloalkyl group,

(61) a C_{3-10} cycloalkenyl group and

(62) a C_{6-14} aryl group.

[0039]

The number of the above-mentioned substituents in the "optionally substituted hydrocarbon group" is, for example, 1 to 5, preferably 1 to 3. When the number of the substituents is two or more, the respective substituents may be the same or different.

In the present specification, examples of the "heterocyclic group" (including "heterocyclic group" of "optionally substituted heterocyclic group") include (i) an aromatic heterocyclic group, (ii) a non-aromatic heterocyclic group and (iii) a 7- to 10-membered bridged heterocyclic group, each containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

[0040]

In the present specification, examples of the "aromatic

heterocyclic group" (including "5- to 14-membered aromatic heterocyclic group") include a 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

Preferable examples of the "aromatic heterocyclic group" include 5- or 6-membered monocyclic aromatic heterocyclic groups such as thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, triazolyl, tetrazolyl, triazinyl and the like; and

8- to 14-membered fused polycyclic (preferably bi or tricyclic) aromatic heterocyclic groups such as benzothiophenyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzotriazolyl, imidazopyridinyl, thienopyridinyl, furopyridinyl, pyrrolopyridinyl, pyrazolopyridinyl, oxazolopyridinyl, thiazolopyridinyl, imidazopyrazinyl, imidazopyrimidinyl, thienopyrimidinyl, furopyrimidinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, oxazolopyrimidinyl, thiazolopyrimidinyl, pyrazolotriazinyl, naphtho[2,3-b]thienyl, phenoxathiinyl, indolyl, isoindolyl, 1H-indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl and the like.

[0041]

In the present specification, examples of the "non-aromatic heterocyclic group" (including "3- to 14-membered non-aromatic heterocyclic group") include a 3- to 14-membered (preferably 4- to 10-membered) non-aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom

and an oxygen atom.

Preferable examples of the "non-aromatic heterocyclic group" include 3- to 8-membered monocyclic non-aromatic heterocyclic groups such as aziridinyl, oxiranyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, tetrahydrothienyl, tetrahydrofuranyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, oxazolinyl, oxazolidinyl, pyrazolinyl, pyrazolidinyl, thiazolinyl, thiazolidinyl, tetrahydroisothiazolyl, tetrahydrooxazolyl, tetrahydroisooxazolyl, piperidinyl, piperazinyl, tetrahydropyridinyl, dihydropyridinyl, dihydrothiopyranyl, tetrahydropyrimidinyl, tetrahydropyridazinyl, dihydropyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, morpholinyl, thiomorpholinyl, azepanyl, diazepanyl, azepinyl, oxepanyl, azocanyl, diazocanyl and the like; and
9- to 14-membered fused polycyclic (preferably bi or tricyclic) non-aromatic heterocyclic groups such as dihydrobenzofuranyl, dihydrobenzimidazolyl, dihydrobenzoxazolyl, dihydrobenzothiazolyl, dihydrobenzisothiazolyl, dihydronaphtho[2,3-b]thienyl, tetrahydroisoquinolyl, tetrahydroquinolyl, 4H-quinolizinyl, indolinyl, isoindolinyl, tetrahydrothieno[2,3-c]pyridinyl, tetrahydrobenzazepinyl, tetrahydroquinoxalinyl, tetrahydrophenanthridinyl, hexahydrophenothiazinyl, hexahydrophenoxazinyl, tetrahydrophthalazinyl, tetrahydronaphthyridinyl, tetrahydroquinazolinyl, tetrahydrocinnolinyl, tetrahydrocarbazolyl, tetrahydro-β-carbolinyl, tetrahydroacrydinyl, tetrahydrophenazinyl, tetrahydrothioxanthenyl, octahydroisoquinolyl and the like.

[0042]

In the present specification, preferable examples of the "7- to 10-membered bridged heterocyclic group" include quinuclidinyl and 7-azabicyclo[2.2.1]heptanyl.

In the present specification, examples of the "nitrogen-containing heterocyclic group" include a "heterocyclic group"

containing at least one nitrogen atom as a ring-constituting atom.

In the present specification, examples of the "optionally substituted heterocyclic group" include a heterocyclic group optionally having substituent(s) selected from the aforementioned substituent group A.

The number of the substituents in the "optionally substituted heterocyclic group" is, for example, 1 to 3. When the number of the substituents is two or more, the respective substituents may be the same or different.

[0043]

In the present specification, examples of the "acyl group" include a formyl group, a carboxy group, a carbamoyl group, a thiocarbamoyl group, a sulfino group, a sulfo group, a sulfamoyl group and a phosphono group, each optionally having "1 or 2 substituents selected from a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{3-10} cycloalkyl group, a C_{3-10} cycloalkenyl group, a C_{6-14} aryl group, a C_{7-16} aralkyl group, a 5- to 14-membered aromatic heterocyclic group and a 3- to 14-membered non-aromatic heterocyclic group, each of which optionally has 1 to 3 substituents selected from a halogen atom, an optionally halogenated C_{1-6} alkoxy group, a hydroxy group, a nitro group, a cyano group, an amino group and a carbamoyl group".

Examples of the "acyl group" also include a hydrocarbon-sulfonyl group, a heterocyclylsulfonyl group, a hydrocarbon-sulfinyl group and a heterocyclylsulfinyl group.

Here, the hydrocarbon-sulfonyl group means a hydrocarbon group-bonded sulfonyl group, the heterocyclylsulfonyl group means a heterocyclic group-bonded sulfonyl group, the hydrocarbon-sulfinyl group means a hydrocarbon group-bonded sulfinyl group and the heterocyclylsulfinyl group means a heterocyclic group-bonded sulfinyl group.

Preferable examples of the "acyl group" include a formyl group, a carboxy group, a C_{1-6} alkyl-carbonyl group, a C_{2-6}

alkenyl-carbonyl group (e.g., crotonoyl), a C_{3-10} cycloalkyl-carbonyl group (e.g., cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl), a C_{3-10} cycloalkenyl-carbonyl group (e.g., 2-cyclohexenecarbonyl), a C_{6-14} aryl-carbonyl group, a C_{7-16} aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C_{1-6} alkoxy-carbonyl group, a C_{6-14} aryloxy-carbonyl group (e.g., phenyloxycarbonyl, naphthyloxycarbonyl), a C_{7-16} aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, phenethyloxycarbonyl), a carbamoyl group, a mono- or di-C_{1-6} alkyl-carbamoyl group, a mono- or di-C_{2-6} alkenyl-carbamoyl group (e.g., diallylcarbamoyl), a mono- or di-C_{3-10} cycloalkyl-carbamoyl group (e.g., cyclopropylcarbamoyl), a mono- or di-C_{6-14} aryl-carbamoyl group (e.g., phenylcarbamoyl), a mono- or di-C_{7-16} aralkyl-carbamoyl group, a 5- to 14-membered aromatic heterocyclylcarbamoyl group (e.g., pyridylcarbamoyl), a thiocarbamoyl group, a mono- or di-C_{1-6} alkyl-thiocarbamoyl group (e.g., methylthiocarbamoyl, N-ethyl-N-methylthiocarbamoyl), a mono- or di-C_{2-6} alkenyl-thiocarbamoyl group (e.g., diallylthiocarbamoyl), a mono- or di-C_{3-10} cycloalkyl-thiocarbamoyl group (e.g., cyclopropylthiocarbamoyl, cyclohexylthiocarbamoyl), a mono- or di-C_{6-14} aryl-thiocarbamoyl group (e.g., phenylthiocarbamoyl), a mono- or di-C_{7-16} aralkyl-thiocarbamoyl group (e.g., benzylthiocarbamoyl, phenethylthiocarbamoyl), a 5- to 14-membered aromatic heterocyclylthiocarbamoyl group (e.g., pyridylthiocarbamoyl), a sulfino group, a C_{1-6} alkylsulfinyl group (e.g., methylsulfinyl, ethylsulfinyl), a sulfo group, a C_{1-6} alkylsulfonyl group, a C_{6-14} arylsulfonyl group, a phosphono group and a mono- or di-C_{1-6} alkylphosphono group (e.g., dimethylphosphono, diethylphosphono, diisopropylphosphono, dibutylphosphono).

[0044]

In the present specification, examples of the "optionally

substituted amino group" include an amino group optionally having "1 or 2 substituents selected from a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{3-10} cycloalkyl group, a C_{6-14} aryl group, a C_{7-16} aralkyl group, a C_{1-6} alkyl-carbonyl group, a C_{6-14} aryl-carbonyl group, a C_{7-16} aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C_{1-6} alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C_{1-6} alkyl-carbamoyl group, a mono- or di-C_{7-16} aralkyl-carbamoyl group, a C_{1-6} alkylsulfonyl group and a C_{6-14} arylsulfonyl group, each of which optionally has 1 to 3 substituents selected from substituent group A".

Preferable examples of the optionally substituted amino group include an amino group, a mono- or di-(optionally halogenated C_{1-6} alkyl)amino group (e.g., methylamino, trifluoromethylamino, dimethylamino, ethylamino, diethylamino, propylamino, dibutylamino), a mono- or di-C_{2-6} alkenylamino group (e.g., diallylamino), a mono- or di-C_{3-10} cycloalkylamino group (e.g., cyclopropylamino, cyclohexylamino), a mono- or di-C_{6-14} arylamino group (e.g., phenylamino), a mono- or di-C_{7-16} aralkylamino group (e.g., benzylamino, dibenzylamino), a mono- or di-(optionally halogenated C_{1-6} alkyl)-carbonylamino group (e.g., acetylamino, propionylamino), a mono- or di-C_{6-14} aryl-carbonylamino group (e.g., benzoylamino), a mono- or di-C_{7-16} aralkyl-carbonylamino group (e.g., benzylcarbonylamino), a mono- or di-5- to 14-membered aromatic heterocyclylcarbonylamino group (e.g., nicotinoylamino, isonicotinoylamino), a mono- or di-3- to 14-membered non-aromatic heterocyclylcarbonylamino group (e.g., piperidinylcarbonylamino), a mono- or di-C_{1-6} alkoxy-carbonylamino group (e.g., tert-butoxycarbonylamino), a 5- to 14-membered aromatic heterocyclylamino group (e.g., pyridylamino), a carbamoylamino group, a (mono- or di-C_{1-6} alkyl-carbamoyl)amino group (e.g., methylcarbamoylamino), a

(mono- or di-C_{7-16} aralkyl-carbamoyl)amino group (e.g., benzylcarbamoylamino), a C_{1-6} alkylsulfonylamino group (e.g., methylsulfonylamino, ethylsulfonylamino), a C_{6-14} arylsulfonylamino group (e.g., phenylsulfonylamino), a (C_{1-6} alkyl)(C_{1-6} alkyl-carbonyl)amino group (e.g., N-acetyl-N-methylamino) and a (C_{1-6} alkyl)(C_{6-14} aryl-carbonyl)amino group (e.g., N-benzoyl-N-methylamino).

[0045]

In the present specification, examples of the "optionally substituted carbamoyl group" include a carbamoyl group optionally having "1 or 2 substituents selected from a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{3-10} cycloalkyl group, a C_{6-14} aryl group, a C_{7-16} aralkyl group, a C_{1-6} alkoxy group, a C_{7-16} aralkyloxy group, a C_{1-6} alkyl-carbonyl group, a C_{6-14} aryl-carbonyl group, a C_{7-16} aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C_{1-6} alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a C_{1-6} alkylsulfonyl group, a carbamoyl group, a mono- or di-C_{1-6} alkyl-carbamoyl group and a mono- or di-C_{7-16} aralkyl-carbamoyl group, each of which optionally has 1 to 3 substituents selected from substituent group A".

Preferable examples of the optionally substituted carbamoyl group include a carbamoyl group, a mono- or di-C_{1-6} alkyl-carbamoyl group, a mono- or di-C_{2-6} alkenyl-carbamoyl group (e.g., diallylcarbamoyl), a mono- or di-C_{3-10} cycloalkyl-carbamoyl group (e.g., cyclopropylcarbamoyl, cyclohexylcarbamoyl), a mono- or di-C_{6-14} aryl-carbamoyl group (e.g., phenylcarbamoyl), a mono- or di-C_{7-16} aralkyl-carbamoyl group, a mono- or di-C_{1-6} alkyl-carbonyl-carbamoyl group (e.g., acetylcarbamoyl, propionylcarbamoyl), a mono- or di-C_{6-14} aryl-carbonyl-carbamoyl group (e.g., benzoylcarbamoyl) and a 5- to 14-membered aromatic heterocyclylcarbamoyl group (e.g., pyridylcarbamoyl).

[0046]

In the present specification, examples of the "optionally substituted thiocarbamoyl group" include a thiocarbamoyl group optionally having "1 or 2 substituents selected from a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{3-10} cycloalkyl group, a C_{6-14} aryl group, a C_{7-16} aralkyl group, a C_{1-6} alkyl-carbonyl group, a C_{6-14} aryl-carbonyl group, a C_{7-16} aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C_{1-6} alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C_{1-6} alkyl-carbamoyl group and a mono- or di-C_{7-16} aralkyl-carbamoyl group, each of which optionally has 1 to 3 substituents selected from substituent group A".

Preferable examples of the optionally substituted thiocarbamoyl group include a thiocarbamoyl group, a mono- or di-C_{1-6} alkyl-thiocarbamoyl group (e.g., methylthiocarbamoyl, ethylthiocarbamoyl, dimethylthiocarbamoyl, diethylthiocarbamoyl, N-ethyl-N-methylthiocarbamoyl), a mono- or di-C_{2-6} alkenyl-thiocarbamoyl group (e.g., diallylthiocarbamoyl), a mono- or di-C_{3-10} cycloalkyl-thiocarbamoyl group (e.g., cyclopropylthiocarbamoyl, cyclohexylthiocarbamoyl), a mono- or di-C_{6-14} aryl-thiocarbamoyl group (e.g., phenylthiocarbamoyl), a mono- or di-C_{7-16} aralkyl-thiocarbamoyl group (e.g., benzylthiocarbamoyl, phenethylthiocarbamoyl), a mono- or di-C_{1-6} alkyl-carbonyl-thiocarbamoyl group (e.g., acetylthiocarbamoyl, propionylthiocarbamoyl), a mono- or di-C_{6-14} aryl-carbonyl-thiocarbamoyl group (e.g., benzoylthiocarbamoyl) and a 5- to 14-membered aromatic heterocyclylthiocarbamoyl group (e.g., pyridylthiocarbamoyl).

[0047]

In the present specification, examples of the "optionally substituted sulfamoyl group" include a sulfamoyl group optionally having "1 or 2 substituents selected from a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{3-10} cycloalkyl group, a C_{6-}

$_{14}$ aryl group, a C_{7-16} aralkyl group, a C_{1-6} alkyl-carbonyl group, a C_{6-14} aryl-carbonyl group, a C_{7-16} aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C_{1-6} alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C_{1-6} alkyl-carbamoyl group and a mono- or di-C_{7-16} aralkyl-carbamoyl group, each of which optionally has 1 to 3 substituents selected from substituent group A".

Preferable examples of the optionally substituted sulfamoyl group include a sulfamoyl group, a mono- or di-C_{1-6} alkyl-sulfamoyl group (e.g., methylsulfamoyl, ethylsulfamoyl, dimethylsulfamoyl, diethylsulfamoyl, N-ethyl-N-methylsulfamoyl), a mono- or di-C_{2-6} alkenyl-sulfamoyl group (e.g., diallylsulfamoyl), a mono- or di-C_{3-10} cycloalkyl-sulfamoyl group (e.g., cyclopropylsulfamoyl, cyclohexylsulfamoyl), a mono- or di-C_{6-14} aryl-sulfamoyl group (e.g., phenylsulfamoyl), a mono- or di-C_{7-16} aralkyl-sulfamoyl group (e.g., benzylsulfamoyl, phenethylsulfamoyl), a mono- or di-C_{1-6} alkyl-carbonyl-sulfamoyl group (e.g., acetylsulfamoyl, propionylsulfamoyl), a mono- or di-C_{6-14} aryl-carbonyl-sulfamoyl group (e.g., benzoylsulfamoyl) and a 5- to 14-membered aromatic heterocyclylsulfamoyl group (e.g., pyridylsulfamoyl).

[0048]

In the present specification, examples of the "optionally substituted hydroxy group" include a hydroxyl group optionally having "a substituent selected from a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{3-10} cycloalkyl group, a C_{6-14} aryl group, a C_{7-16} aralkyl group, a C_{1-6} alkyl-carbonyl group, a C_{6-14} aryl-carbonyl group, a C_{7-16} aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C_{1-6} alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C_{1-6} alkyl-carbamoyl group, a mono- or di-C_{7-16} aralkyl-carbamoyl group, a C_{1-6}

alkylsulfonyl group and a C_{6-14} arylsulfonyl group, each of which optionally has 1 to 3 substituents selected from substituent group A".

Preferable examples of the optionally substituted hydroxy group include a hydroxy group, a C_{1-6} alkoxy group, a C_{2-6} alkenyloxy group (e.g., allyloxy, 2-butenyloxy, 2-pentenyloxy, 3-hexenyloxy), a C_{3-10} cycloalkyloxy group (e.g., cyclohexyloxy), a C_{6-14} aryloxy group (e.g., phenoxy, naphthyloxy), a C_{7-16} aralkyloxy group (e.g., benzyloxy, phenethyloxy), a C_{1-6} alkyl-carbonyloxy group (e.g., acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, pivaloyloxy), a C_{6-14} aryl-carbonyloxy group (e.g., benzoyloxy), a C_{7-16} aralkyl-carbonyloxy group (e.g., benzylcarbonyloxy), a 5- to 14-membered aromatic heterocyclylcarbonyloxy group (e.g., nicotinoyloxy), a 3- to 14-membered non-aromatic heterocyclylcarbonyloxy group (e.g., piperidinylcarbonyloxy), a C_{1-6} alkoxy-carbonyloxy group (e.g., tert-butoxycarbonyloxy), a 5- to 14-membered aromatic heterocyclyloxy group (e.g., pyridyloxy), a carbamoyloxy group, a C_{1-6} alkyl-carbamoyloxy group (e.g., methylcarbamoyloxy), a C_{7-16} aralkyl-carbamoyloxy group (e.g., benzylcarbamoyloxy), a C_{1-6} alkylsulfonyloxy group (e.g., methylsulfonyloxy, ethylsulfonyloxy) and a C_{6-14} arylsulfonyloxy group (e.g., phenylsulfonyloxy).

[0049]

In the present specification, examples of the "optionally substituted sulfanyl group" include a sulfanyl group optionally having "a substituent selected from a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{3-10} cycloalkyl group, a C_{6-14} aryl group, a C_{7-16} aralkyl group, a C_{1-6} alkyl-carbonyl group, a C_{6-14} aryl-carbonyl group and a 5- to 14-membered aromatic heterocyclic group, each of which optionally has 1 to 3 substituents selected from substituent group A" and a halogenated sulfanyl group.

Preferable examples of the optionally substituted sulfanyl group include a sulfanyl (-SH) group, a C_{1-6} alkylthio

group, a C_{2-6} alkenylthio group (e.g., allylthio, 2-butenylthio, 2-pentenylthio, 3-hexenylthio), a C_{3-10} cycloalkylthio group (e.g., cyclohexylthio), a C_{6-14} arylthio group (e.g., phenylthio, naphthylthio), a C_{7-16} aralkylthio group (e.g., benzylthio, phenethylthio), a C_{1-6} alkyl-carbonylthio group (e.g., acetylthio, propionylthio, butyrylthio, isobutyrylthio, pivaloylthio), a C_{6-14} aryl-carbonylthio group (e.g., benzoylthio), a 5- to 14-membered aromatic heterocyclylthio group (e.g., pyridylthio) and a halogenated thio group (e.g., pentafluorothio).

[0050]

In the present specification, examples of the "optionally substituted silyl group" include a silyl group optionally having "1 to 3 substituents selected from a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{3-10} cycloalkyl group, a C_{6-14} aryl group and a C_{7-16} aralkyl group, each of which optionally has 1 to 3 substituents selected from substituent group A".

Preferable examples of the optionally substituted silyl group include a tri-C_{1-6} alkylsilyl group (e.g., trimethylsilyl, tert-butyl(dimethyl)silyl).

[0051]

In the present specification, examples of the "hydrocarbon ring" include a C_{6-14} aromatic hydrocarbon ring, C_{3-10} cycloalkane and C_{3-10} cycloalkene.

In the present specification, examples of the "C_{6-14} aromatic hydrocarbon ring" include benzene and naphthalene.

In the present specification, examples of the "C_{3-10} cycloalkane" include cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane and cyclooctane.

In the present specification, examples of the "C_{3-10} cycloalkene" include cyclopropene, cyclobutene, cyclopentene, cyclohexene, cycloheptene and cyclooctene.

In the present specification, examples of the "heterocycle" include an aromatic heterocycle and a non-aromatic heterocycle, each containing, as a ring-constituting

atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

[0052]

In the present specification, examples of the "aromatic heterocycle" include a 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom. Preferable examples of the "aromatic heterocycle" include 5- or 6-membered monocyclic aromatic heterocycles such as thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, triazole, tetrazole, triazine and the like; and

8- to 14-membered fused polycyclic (preferably bi or tricyclic) aromatic heterocycles such as benzothiophene, benzofuran, benzimidazole, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, benzotriazole, imidazopyridine, thienopyridine, furopyridine, pyrrolopyridine, pyrazolopyridine, oxazolopyridine, thiazolopyridine, imidazopyrazine, imidazopyrimidine, thienopyrimidine, furopyrimidine, pyrrolopyrimidine, pyrazolopyrimidine, oxazolopyrimidine, thiazolopyrimidine, pyrazolopyrimidine, pyrazolotriazine, naphtho[2,3-b]thiophene, phenoxathiine, indole, isoindole, 1H-indazole, purine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, carbazole, β-carboline, phenanthridine, acridine, phenazine, phenothiazine, phenoxathiine and the like.

[0053]

In the present specification, examples of the "non-aromatic heterocycle" include a 3- to 14-membered (preferably 4- to 10-membered) non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an

oxygen atom. Preferable examples of the "non-aromatic heterocycle" include 3- to 8-membered monocyclic non-aromatic heterocycles such as aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrothiophene, tetrahydrofuran, pyrroline, pyrrolidine, imidazoline, imidazolidine, oxazoline, oxazolidine, pyrazoline, pyrazolidine, thiazoline, thiazolidine, tetrahydroisothiazole, tetrahydrooxazole, tetrahydroisoxazole, piperidine, piperazine, tetrahydropyridine, dihydropyridine, dihydrothiopyran, tetrahydropyrimidine, tetrahydropyridazine, dihydropyran, tetrahydropyran, tetrahydrothiopyran, morpholine, thiomorpholine, azepanine, diazepane, azepine, azocane, diazocane, oxepane and the like; and

9- to 14-membered fused polycyclic (preferably bi or tricyclic) non-aromatic heterocycles such as dihydrobenzofuran, dihydrobenzimidazole, dihydrobenzoxazole, dihydrobenzothiazole, dihydrobenzisothiazole, dihydronaphtho[2,3-b]thiophene, tetrahydroisoquinoline, tetrahydroquinoline, 4H-quinolizine, indoline, isoindoline, tetrahydrothieno[2,3-c]pyridine, tetrahydrobenzazepine, tetrahydroquinoxaline, tetrahydrophenanthridine, hexahydrophenothiazine, hexahydrophenoxazine, tetrahydrophthalazine, tetrahydronaphthyridine, tetrahydroquinazoline, tetrahydrocinnoline, tetrahydrocarbazole, tetrahydro-β-carboline, tetrahydroacridine, tetrahydrophenazine, tetrahydrothioxanthene, octahydroisoquinoline and the like.

In the present specification, examples of the "nitrogen-containing heterocycle" include a "heterocycle" containing at least one nitrogen atom as a ring-constituting atom.

[0054]

The definition of each symbol in the formula (I) is explained in detail in the following.

[0055]

Ring A is an optionally substituted pyridine or an optionally substituted pyridazine.

[0056]

The "pyridine" of the "optionally further substituted pyridine" for Ring A optionally has one substituent on the carbon atom adjacent to G^1, in addition to R^4. Examples of the substituent include substituents selected from the aforementioned substituent group A.

[0057]

The "pyridazine" of the "optionally further substituted pyridazine" for Ring A optionally has one substituent on the carbon atom adjacent to G^1. Examples of the substituent include substituents selected from the aforementioned substituent group A.

[0058]

Ring A is preferably an optionally further substituted pyridine.

[0059]

Ring A is more preferably pyridine optionally further having one halogen atom (e.g., a chlorine atom) on the carbon atom adjacent to G^1.

[0060]

In another embodiment, Ring A is more preferably pyridine optionally further having one substituent, on the carbon atom adjacent to G^1, selected from

(1) a halogen atom (e.g., a chlorine atom, a bromine atom),

(2) an optionally halogenated C_{1-6} alkyl group (preferably a C_{1-6} alkyl group (e.g., methyl)), and

(3) a C_{3-10} cycloalkyl group (e.g., cyclopropyl).

[0061]

G^1 is N or CR^4.

G^1 is preferably CR^4.

[0062]

R^4 is a hydrogen atom or a substituent.

R^4 is preferably a hydrogen atom.

[0063]

Ring B is an optionally substituted 6-membered aromatic

ring.

[0064]

Examples of the "6-membered aromatic ring" of the "optionally further substituted 6-membered aromatic ring" for Ring B include a benzene ring and a 6-membered aromatic heterocycle (e.g., pyridine, pyridazine, pyrimidine, triazine etc.).

[0065]

The "6-membered aromatic ring" of the "optionally substituted 6-membered aromatic ring" for Ring B optionally has 1 to 3 substituents at substitutable position(s). Examples of the substituent include substituents selected from the aforementioned substituent group A. When the number of the substituents is plural, the respective substituents may be the same or different.

[0066]

Ring B is preferably a 6-membered aromatic ring (preferably benzene, pyridine) optionally having 1 to 3 halogen atoms (e.g., a chlorine atom).

[0067]

Ring B is more preferably benzene or pyridine, each optionally having 1 to 3 halogen atoms (e.g., a chlorine atom).

[0068]

In another embodiment, Ring B is preferably a 6-membered aromatic ring (preferably benzene, pyridine) optionally having 1 to 3 substituents selected from

(1) a halogen atom (e.g., a chlorine atom, a bromine atom),

(2) an optionally halogenated C_{1-6} alkyl group (preferably a C_{1-6} alkyl group (e.g., methyl)),

(3) an optionally halogenated C_{1-6} alkoxy group (preferably a C_{1-6} alkoxy group (e.g., methoxy)), and

(4) a C_{3-10} cycloalkyl group (e.g., cyclopropyl).

[0069]

In this embodiment, Ring B is more preferably benzene or pyridine, each optionally having 1 to 3 substituents selected

from

(1) a halogen atom (e.g., a chlorine atom, a bromine atom),

(2) an optionally halogenated C_{1-6} alkyl group (preferably a C_{1-6} alkyl group (e.g., methyl)),

(3) an optionally halogenated C_{1-6} alkoxy group (preferably a C_{1-6} alkoxy group (e.g., methoxy)), and

(4) a C_{3-10} cycloalkyl group (e.g., cyclopropyl).

[0070]

R^1 and R^2 are each independently a hydrogen atom or an optionally substituted C_{1-6} alkyl group, or R^1 and R^2 are joined together to form a cycloalkane or a heterocycle, each of which is optionally substituted.

[0071]

Examples of the "cycloalkane" for R^1 and R^2 include a C_{3-10} cycloalkane.

[0072]

Examples of the "heterocycle" for R^1 and R^2 include a non-aromatic heterocycle (preferably a 3- to 8-membered monocyclic non-aromatic heterocycle, more preferably a 3- to 8-membered monocyclic saturated heterocycle).

[0073]

Preferably, R^1 and R^2 are each independently a hydrogen atom or a C_{1-6} alkyl group (e.g., methyl, ethyl), or R^1 and R^2 are joined together to form a cycloalkane (preferably a C_{3-10} cycloalkane (e.g., cyclopropane)).

[0074]

More preferably, R^1 is a hydrogen atom or a C_{1-6} alkyl group (e.g., methyl, ethyl) and R^2 is a hydrogen atom, or R^1 and R^2 are joined together to form a cycloalkane (preferably a C_{3-10} cycloalkane (e.g., cyclopropane)).

[0075]

R^3 is a hydrogen atom or a substituent.

[0076]

R^3 is preferably a hydrogen atom.

[0077]

Ring C is an optionally further substituted ring.

[0078]

Examples of the "ring" of the "optionally further substituted ring" for Ring C include a hydrocarbon ring and a heterocycle (preferably a C_{6-14} aromatic hydrocarbon ring or a 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocycle, more preferably a C_{6-14} aromatic hydrocarbon ring (preferably benzene) or a 5- or 6-membered monocyclic aromatic heterocycle (preferably pyridine, thiophene), particularly preferably benzene, pyridine or thiophene).

[0079]

The "ring" of the "optionally further substituted ring" for Ring C optionally has 1 to 5 (preferably 1 to 3) substituents at substitutable position(s). Examples of the substituent include substituents selected from the aforementioned substituent group A. When the number of the substituents is plural, the respective substituents may be the same or different.

[0080]

Ring C is preferably a C_{6-14} aromatic hydrocarbon ring (preferably benzene) further having no substituent other than R^5.

[0081]

Ring C is more preferably benzene further having no substituent other than R^5.

[0082]

In another embodiment, Ring C is preferably a C_{6-14} aromatic hydrocarbon ring (preferably benzene) or a 5- or 6-membered monocyclic aromatic heterocycle (preferably pyridine, thiophene), each optionally having 1 to 3 substituents, in addition to R^5, selected from

(1) a halogen atom (e.g., a fluorine atom, a chlorine atom), and

(2) an optionally halogenated C_{1-6} alkyl group (preferably a C_{1-6} alkyl group (e.g., methyl)).

[0083]

In this embodiment, Ring C is more preferably benzene, pyridine or thiophene, each optionally having 1 to 3 substituents, in addition to R^5, selected from

(1) a halogen atom (e.g., a fluorine atom, a chlorine atom), and

(2) an optionally halogenated C_{1-6} alkyl group (preferably a C_{1-6} alkyl group (e.g., methyl)).

[0084]

R^5 is a substituent.

[0085]

R^5 is preferably an acyl group.

R^5 is more preferably a carboxy group or a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl).

R^5 is still more preferably a carboxy group.

[0086]

In another embodiment, R^5 is preferably an acyl group (preferably a carboxy group, a C_{1-6} alkoxy-carbonyl group), a cyano group, an optionally substituted hydrocarbon group (preferably an optionally substituted C_{1-6} alkyl group), an optionally substituted carbamoyl group or an optionally substituted sulfamoyl group.

[0087]

In this embodiment, R^5 is more preferably

(1) a carboxy group,

(2) a C_{1-6} alkoxy-carbonyl group,

(3) a cyano group,

(4) a C_{1-6} alkyl group (e.g., methyl, ethyl, isopropyl) optionally having 1 to 3 substituents selected from

(a) a halogen atom (e.g., a fluorine atom),

(b) a hydroxy group, and

(c) a carboxy group,

(5) a carbamoyl group optionally having 1 or 2 substituents selected from

(a) a C_{1-6} alkyl group (e.g., methyl),

(b) a C_{1-6} alkoxy group (e.g., methoxy, ethoxy),

(c) a C_{7-16} aralkyloxy group (e.g., benzyloxy), and

(d) a C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl), or

(6) a sulfamoyl group.

[0088]

In this embodiment, R^5 is more preferably a carboxy group or a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl).

In this embodiment, R^5 is still more preferably a carboxy group.

[0089]

Ring D is an optionally substituted ring.

[0090]

Examples of the "ring" of the "optionally substituted ring" for Ring D include a hydrocarbon ring and a heterocycle (preferably a C_{6-14} aromatic hydrocarbon ring or a 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocycle, more preferably a C_{6-14} aromatic hydrocarbon ring (preferably benzene) or a 5- or 6-membered monocyclic aromatic heterocycle (preferably pyridine), particularly preferably benzene or pyridine).

[0091]

The "ring" of the "optionally substituted ring" for Ring D optionally has 1 to 5 (preferably1 to 3) substituents at substitutable position(s). Examples of the substituent include substituents selected from the aforementioned substituent group A. When the number of the substituents is plural, the respective substituents may be the same or different.

[0092]

Ring D is preferably a C_{6-14} aromatic hydrocarbon ring (preferably benzene) optionally having 1 to 3 substituents selected from

(1) a halogen atom (e.g., a fluorine atom, a chlorine atom),

(2) a cyano group,

(3) an optionally halogenated C_{1-6} alkyl group (e.g., methyl, trifluoromethyl), and

(4) an optionally halogenated C_{1-6} alkoxy group (e.g., methoxy, trifluoromethoxy).

[0093]

Ring D is more preferably benzene optionally having 1 to 3 substituents selected from

(1) a halogen atom (e.g., a fluorine atom, a chlorine atom),

(2) a cyano group,

(3) an optionally halogenated C_{1-6} alkyl group (e.g., methyl, monofluoromethyl, difluoromethyl, trifluoromethyl), and

(4) an optionally halogenated C_{1-6} alkoxy group (e.g., methoxy, monofluoromethoxy, difluoromethoxy, trifluoromethoxy).

[0094]

In another embodiment, Ring D is preferably a C_{6-14} aromatic hydrocarbon ring (preferably benzene) or a 5- or 6-membered monocyclic aromatic heterocycle (preferably pyridine), each optionally having 1 to 3 substituents selected from

(1) a halogen atom (e.g., a fluorine atom, a chlorine atom),

(2) a cyano group,

(3) an optionally halogenated C_{1-6} alkyl group (e.g., methyl, monofluoromethyl, difluoromethyl, trifluoromethyl), and

(4) an optionally halogenated C_{1-6} alkoxy group (e.g., methoxy, monofluoromethoxy, difluoromethoxy, trifluoromethoxy).

[0095]

In this embodiment, Ring D is more preferably benzene or pyridine, each optionally having 1 to 3 substituents selected from

(1) a halogen atom (e.g., a fluorine atom, a chlorine atom),

(2) a cyano group,

(3) an optionally halogenated C_{1-6} alkyl group (e.g., methyl, monofluoromethyl, difluoromethyl, trifluoromethyl), and

(4) an optionally halogenated C_{1-6} alkoxy group (e.g., methoxy, monofluoromethoxy, difluoromethoxy, trifluoromethoxy).

[0096]

W is a bond, or a spacer in which the number of atoms in the main chain is 1 to 4.

[0097]

Examples of the "spacer in which the number of atoms in the main chain is 1 to 4" for W include spacers wherein the main chain consists of 1 to 4 atoms selected from a carbon atom, a nitrogen atom, a sulfur atom (optionally oxidized) and an oxygen atom, each of which optionally has substituent(s) selected from the aforementioned substituent group A at substitutable position(s).

[0098]

Specific examples of the "spacer in which the number of atoms in the main chain is 1 to 4" for W include

(1) a bond;

(2) a C_{1-4} alkylene group (e.g., $-CH_2-$, $-(CH_2)_2-$, $-CH_2-CH(CH_3)-$, $-CH(CH_3)-CH_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$ etc.) optionally substituted by the aforementioned substituent group A (preferably an oxo group and a hydroxy group);

(3) a C_{2-4} alkenylene group (e.g., $-CH=CH-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$ etc.) optionally substituted by the aforementioned substituent group A;

(4) -X- wherein X is O, NR^6 (R^6 is a hydrogen atom or a substituent), S, S(O), S(O) or $S(O)_2$;

(5) $-(CH_2)_{m1}-X-(CH_2)_{m2}-$ wherein X is as defined above, m1 and m2 are each independently an integer of 0 to 3, and m1+m2 is an integer of 1 to 3;

(6) $-X^1-(CH_2)_m-X^2-$ wherein X^1 and X^2 are each independently O, NR^6 (R^6 is a hydrogen atom or a substituent), S, S(O), S(O) or $S(O)_2$, and m is an integer of 1 to 2;

(7) $-CO-NR^6-$ or $-NR^6-CO-$ wherein R^6 is as defined above;

(8) $-S(O)_2-NR^6-$ or $-NR^6-S(O)_2-$ wherein R^6 is as defined above;

(9) a C_{3-6} cycloalkylene (e.g., cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene etc.);

(10) a divalent non-aromatic heterocyclic group (e.g., 1,2-

aziridinediyl, 1,3-azetidinediyl, 1,3-pyrrolidinediyl, 1,3-piperidinediyl, 1,4-piperidinediyl, 1,4-morpholinediyl etc.);

(11) $-X^1-Y-X^2-$ wherein X^1 and X^2 are as defined above, and Y is a divalent non-aromatic heterocyclic group (e.g., 1,2-aziridinediyl, 1,3-azetidinediyl, 1,3-pyrrolidinediyl, 1,3-piperidinediyl etc.);

and the like.

[0099]

W is preferably -O-.

In another embodiment, W is preferably -O- or $-O-CH_2-$ (wherein the left bond is bonded to Ring B, and the right bond is bonded to Ring D).

In this embodiment, W is more preferably -O-.

[0100]

Preferable examples of compound (I) include the following compounds.

[0101]

[Compound A-1]

Compound (I) wherein

Ring A is pyridine optionally further having one halogen atom (e.g., a chlorine atom) on the carbon atom adjacent to G^1,

G^1 is CR^4,

R^4 is a hydrogen atom,

Ring B is a 6-membered aromatic ring (preferably benzene, pyridine) optionally further having 1 to 3 halogen atoms (e.g., a chlorine atom),

R^1 and R^2 are each independently a hydrogen atom or a C_{1-6} alkyl group (e.g., methyl), or R^1 and R^2 are joined together to form a cycloalkane (preferably a C_{3-10} cycloalkane (e.g., cyclopropane)),

R^3 is a hydrogen atom,

Ring C is a C_{6-14} aromatic hydrocarbon ring (preferably benzene) further having no substituent other than R^5,

R^5 is an acyl group (preferably a carboxy group or a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl)),

Ring D is a C_{6-14} aromatic hydrocarbon ring (preferably benzene) optionally having 1 to 3 substituents selected from

(1) a halogen atom (e.g., a fluorine atom, a chlorine atom),

(2) a cyano group,

(3) an optionally halogenated C_{1-6} alkyl group (e.g., methyl, monofluoromethyl, difluoromethyl, trifluoromethyl), and

(4) an optionally halogenated C_{1-6} alkoxy group (e.g., methoxy, monofluoromethoxy, difluoromethoxy, trifluoromethoxy), and

W is -O-.

[0102]

[Compound A-2]

Compound (I) wherein

Ring A is pyridine optionally further having one substituent, on the carbon atom adjacent to G^1, selected from

(1) a halogen atom (e.g., a chlorine atom, a bromine atom),

(2) an optionally halogenated C_{1-6} alkyl group (preferably a C_{1-6} alkyl group (e.g., methyl)), and

(3) a C_{3-10} cycloalkyl group (e.g., cyclopropyl),

G^1 is CR^4,

R^4 is a hydrogen atom,

Ring B is a 6-membered aromatic ring (preferably benzene, pyridine) optionally having 1 to 3 substituents selected from

(1) a halogen atom (e.g., a chlorine atom, a bromine atom),

(2) an optionally halogenated C_{1-6} alkyl group (preferably a C_{1-6} alkyl group (e.g., methyl)),

(3) an optionally halogenated C_{1-6} alkoxy group (preferably a C_{1-6} alkoxy group (e.g., methoxy)), and

(4) a C_{3-10} cycloalkyl group (e.g., cyclopropyl),

R^1 and R^2 are each independently a hydrogen atom or a C_{1-6} alkyl group (e.g., methyl, ethyl), or R^1 and R^2 are joined together to form a cycloalkane (preferably a C_{3-10} cycloalkane (e.g., cyclopropane)),

R^3 is a hydrogen atom,

Ring C is a C_{6-14} aromatic hydrocarbon ring (preferably benzene) or a 5- or 6-membered monocyclic aromatic heterocycle

(preferably pyridine, thiophene), each optionally having 1 to 3 substituents, in addition to R^5, selected from

(1) a halogen atom (e.g., a fluorine atom, a chlorine atom), and

(2) an optionally halogenated C_{1-6} alkyl group (preferably a C_{1-6} alkyl group (e.g., methyl)),

R^5 is

(1) a carboxy group,

(2) a C_{1-6} alkoxy-carbonyl group,

(3) a cyano group,

(4) a C_{1-6} alkyl group (e.g., methyl, ethyl, isopropyl) optionally having 1 to 3 substituents selected from

(a) a halogen atom (e.g., a fluorine atom),

(b) a hydroxy group, and

(c) a carboxy group,

(5) a carbamoyl group optionally having 1 or 2 substituents selected from

(a) a C_{1-6} alkyl group (e.g., methyl),

(b) a C_{1-6} alkoxy group (e.g., methoxy, ethoxy),

(c) a C_{7-16} aralkyloxy group (e.g., benzyloxy), and

(d) a C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl), or

(6) a sulfamoyl group,

Ring D is a C_{6-14} aromatic hydrocarbon ring (preferably benzene) or a 5- or 6-membered monocyclic aromatic heterocycle (preferably pyridine), each optionally having 1 to 3 substituents selected from

(1) a halogen atom (e.g., a fluorine atom, a chlorine atom),

(2) a cyano group,

(3) an optionally halogenated C_{1-6} alkyl group (e.g., methyl, monofluoromethyl, difluoromethyl, trifluoromethyl), and

(4) an optionally halogenated C_{1-6} alkoxy group (e.g., methoxy, monofluoromethoxy, difluoromethoxy, trifluoromethoxy), and

W is -O- or $-O-CH_2-$ (wherein the left bond is bonded to Ring B, and the right bond is bonded to Ring D).

[0103]

[Compound B-2]

Compound (I) wherein

Ring A is pyridine optionally further having one substituent, on the carbon atom adjacent to G^1, selected from

(1) a halogen atom (e.g., a chlorine atom, a bromine atom),

(2) an optionally halogenated C_{1-6} alkyl group (preferably a C_{1-6} alkyl group (e.g., methyl)), and

(3) a C_{3-10} cycloalkyl group (e.g., cyclopropyl),

G^1 is CR^4,

R^4 is a hydrogen atom,

Ring B is benzene or pyridine, each optionally having 1 to 3 substituents selected from

(1) a halogen atom (e.g., a chlorine atom, a bromine atom),

(2) an optionally halogenated C_{1-6} alkyl group (preferably a C_{1-6} alkyl group (e.g., methyl)),

(3) an optionally halogenated C_{1-6} alkoxy group (preferably a C_{1-6} alkoxy group (e.g., methoxy)), and

(4) a C_{3-10} cycloalkyl group (e.g., cyclopropyl),

R^1 is a hydrogen atom or a C_{1-6} alkyl group (e.g., methyl, ethyl),

R^2 is a hydrogen atom, or

R^1 and R^2 are joined together to form a cycloalkane (preferably a C_{3-10} cycloalkane (e.g., cyclopropane)),

R^3 is a hydrogen atom,

Ring C is benzene, pyridine or thiophene, each optionally having 1 to 3 substituents, in addition to R^5, selected from

(1) a halogen atom (e.g., a fluorine atom, a chlorine atom), and

(2) an optionally halogenated C_{1-6} alkyl group (preferably a C_{1-6} alkyl group (e.g., methyl)),

R^5 is

(1) a carboxy group,

(2) a C_{1-6} alkoxy-carbonyl group,

(3) a cyano group,

(4) a C_{1-6} alkyl group (e.g., methyl, ethyl, isopropyl) optionally having 1 to 3 substituents selected from

(a) a halogen atom (e.g., a fluorine atom),

(b) a hydroxy group, and

(c) a carboxy group,

(5) a carbamoyl group optionally having 1 or 2 substituents selected from

(a) a C_{1-6} alkyl group (e.g., methyl),

(b) a C_{1-6} alkoxy group (e.g., methoxy, ethoxy),

(c) a C_{7-16} aralkyloxy group (e.g., benzyloxy), and

(d) a C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl), or

(6) a sulfamoyl group,

Ring D is benzene or pyridine, each optionally having 1 to 3 substituents selected from

(1) a halogen atom (e.g., a fluorine atom, a chlorine atom),

(2) a cyano group,

(3) an optionally halogenated C_{1-6} alkyl group (e.g., methyl, monofluoromethyl, difluoromethyl, trifluoromethyl), and

(4) an optionally halogenated C_{1-6} alkoxy group (e.g., methoxy, monofluoromethoxy, difluoromethoxy, trifluoromethoxy), and

W is -O- or $-O-CH_2-$ (wherein the left bond is bonded to Ring B, and the right bond is bonded to Ring D).

[0104]

[Compound C-2]

Compound (I) wherein

Ring A is pyridine optionally further having one substituent, on the carbon atom adjacent to G^1, selected from

(1) a halogen atom (e.g., a chlorine atom, a bromine atom),

(2) an optionally halogenated C_{1-6} alkyl group (preferably a C_{1-6} alkyl group (e.g., methyl)), and

(3) a C_{3-10} cycloalkyl group (e.g., cyclopropyl),

G^1 is CR^4,

R^4 is a hydrogen atom,

Ring B is benzene or pyridine, each optionally having 1

to 3 substituents selected from

(1) a halogen atom (e.g., a chlorine atom, a bromine atom),

(2) an optionally halogenated C_{1-6} alkyl group (preferably a C_{1-6} alkyl group (e.g., methyl)),

(3) an optionally halogenated C_{1-6} alkoxy group (preferably a C_{1-6} alkoxy group (e.g., methoxy)), and

(4) a C_{3-10} cycloalkyl group (e.g., cyclopropyl),

R^1 is a hydrogen atom or a C_{1-6} alkyl group (e.g., methyl, ethyl),

R^2 is a hydrogen atom, or

R^1 and R^2 are joined together to form a cycloalkane (preferably a C_{3-10} cycloalkane (e.g., cyclopropane)),

R^3 is a hydrogen atom,

Ring C is benzene, pyridine or thiophene, each optionally having 1 to 3 substituents, in addition to R^5, selected from

(1) a halogen atom (e.g., a fluorine atom, a chlorine atom), and

(2) an optionally halogenated C_{1-6} alkyl group (preferably a C_{1-6} alkyl group (e.g., methyl)),

R^5 is a carboxy group,

Ring D is benzene or pyridine, each optionally having 1 to 3 substituents selected from

(1) a halogen atom (e.g., a fluorine atom, a chlorine atom),

(2) a cyano group,

(3) an optionally halogenated C_{1-6} alkyl group (e.g., methyl, monofluoromethyl, difluoromethyl, trifluoromethyl), and

(4) an optionally halogenated C_{1-6} alkoxy group (e.g., methoxy, monofluoromethoxy, difluoromethoxy, trifluoromethoxy), and

W is -O-.

[0105]

When compound (I) is in a form of a salt, examples thereof include metal salts, an ammonium salt, salts with organic base, salts with inorganic acid, salts with organic acid, salts with basic or acidic amino acid, and the like.

Preferable examples of the metal salt include alkali metal salts such as sodium salt, potassium salt and the like; alkaline earth metal salts such as calcium salt, magnesium salt, barium salt and the like; an aluminum salt, and the like. Preferable examples of the salt with organic base include salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like. Preferable examples of the salt with inorganic acid include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like. Preferable examples of the salt with organic acid include salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like. Preferable examples of the salt with basic amino acid include salts with arginine, lysine, ornithine and the like. Preferable examples of the salt with acidic amino acid include salts with aspartic acid, glutamic acid and the like.

Among them, a pharmaceutically acceptable salt is preferable. For example, when a compound has an acidic functional group, examples thereof include inorganic salts such as alkali metal salts (e.g., sodium salt, potassium salt etc.), alkaline earth metal salts (e.g., calcium salt, magnesium salt etc.) and the like, ammonium salt etc., and when a compound has a basic functional group, examples thereof include salts with inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like, and salts with organic acid such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

[0106]

Compound (I) may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes are provided as one embodiment of the invention, and are illustrated by the following representative process. Necessary starting materials may be obtained by standard procedure of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process and within the following examples. Alternatively, necessary starting materials are obtained by a method known per se or a method analogous thereto.

[0107]

The starting material and/or the production intermediate for the compound (I) may form a salt. While the salt is not particularly limited as long as the reaction can be performed, examples thereof include those similar to the salts of compound (I) and the like.

[0108]

When the starting material has an amino group, a carboxyl group, a hydroxy group or a heterocyclic group, these groups may be protected by a protecting group generally used in peptide chemistry and the like. By removing the protecting group as necessary after the reaction, the objective compound can be obtained. The protection and deprotection can be performed according to a method known per se, for example, the method described in "Protective Groups in Organic Synthesis, 3rd Ed", John Wiley and Sons, Inc. (1999) (Theodora W. Greene, Peter G. M. Wuts). Preferable examples of the protecting group include a tert-butylcarbamate group, a benzylcarbamate group, a benzyl group, a methyl group, an ethyl group, a tert-butyl and the like.

[0109]

The compound obtained in each step can be used directly as the reaction mixture or as a crude product for the next reaction. It can also be isolated from a reaction mixture by a

conventional method, and can be easily purified by a separation means such as recrystallization, distillation, chromatography and the like. When the compound in the formula is commercially available, a commercially available product can also be used directly.

[0110]

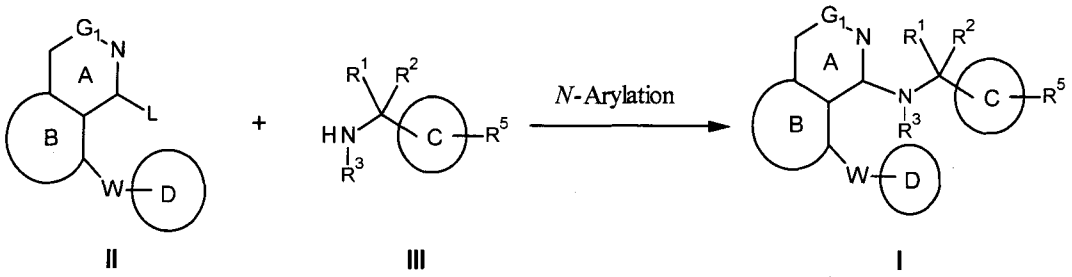
Unless otherwise specified, each symbol in the general formulas in the schemes is as defined above.

[0111]

Compound (I) is prepared as outlined in Schemes below:

Scheme 1: Synthesis of compound (I)

[0112]



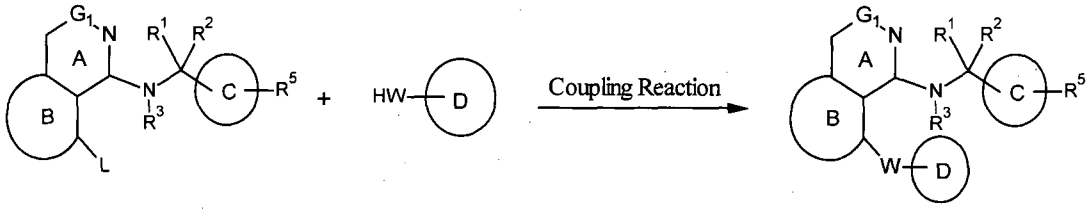
[0113]

Compound (I) may be prepared by reacting compound (II) wherein L is a leaving group such as a halogen atom, a C_{1-6} alkoxy group, a C_{6-14} aryloxy group, a sulfanyl group, a C_{1-6} alkylthio group, a C_{6-14} arylthio group, a C_{1-6} alkylsulfinyl group, a C_{6-14} arylsulfinyl group, a C_{1-6} alkylsulfonyl group, a C_{6-14} arylsulfonyl group and a boronic acid group, with an amine of compound (III) (*N*-arylation reaction) as shown in Scheme 1. Functional groups in compound (II) or (III) may be protected if necessary, and after the *N*-arylation reaction, it can be removed by conventional means. Compound (I) having an ester moiety may be further hydrolyzed to obtain the corresponding carboxylic acid, which may be further derivatized.

[0114]

Scheme 2: Synthesis of compound (I) wherein W is not a bond

[0115]



IV V I

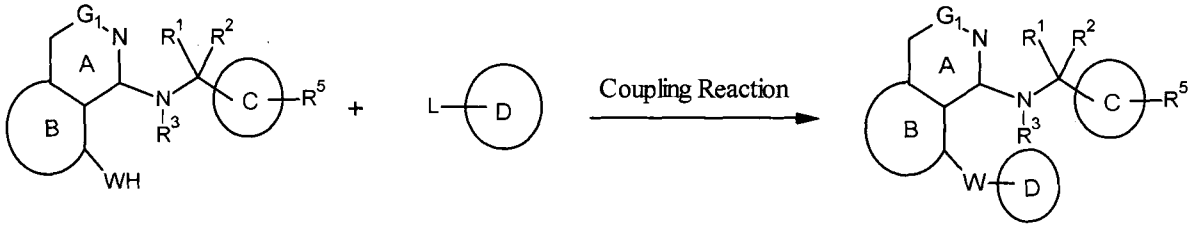
[0116]

As shown in Scheme 2, compound (I) may be prepared by coupling compound (IV) wherein L is a leaving group, with compound (V) wherein W is a spacer in which the number of atoms in the main chain is 1 to 4.

[0117]

Scheme 3: Synthesis of compound (I)

[0118]



VI VII I

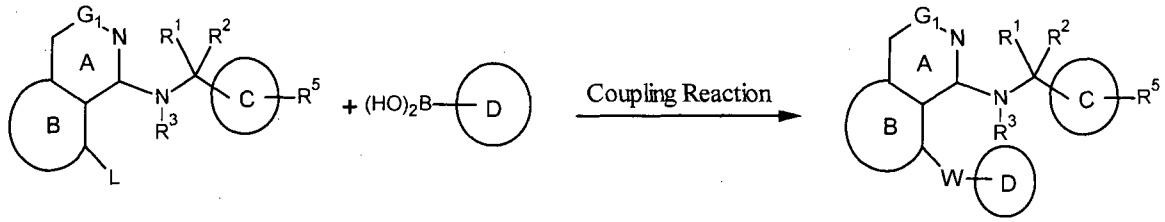
[0119]

As shown in Scheme 3, compound (I) may be prepared by coupling compound (VI) with compound (VII) wherein L is a leaving group.

[0120]

Scheme 4: Synthesis of compound (I) wherein W is a bond

[0121]



IV VIII I

[0122]

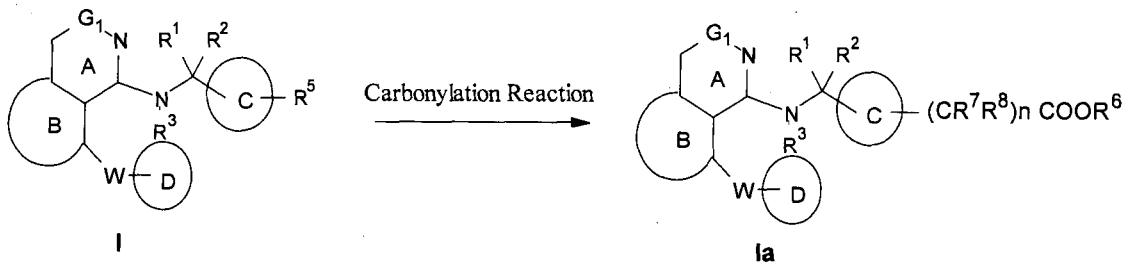
As shown in Scheme 4, compound (I) may be prepared by the coupling compound (IV) wherein L is leaving group, with

compound (VIII).

[0123]

Scheme 5: Synthesis of compound (Ia), which is compound (I) wherein R^5 is $-(CR^7R^8)n(CO)OR^6$ wherein R^7 and R^8 are each independently a hydrogen atom or a C_{1-6} alkyl group, R^6 is a C_{1-6} alkyl group, and n is 0-1

[0124]



I Ia

[0125]

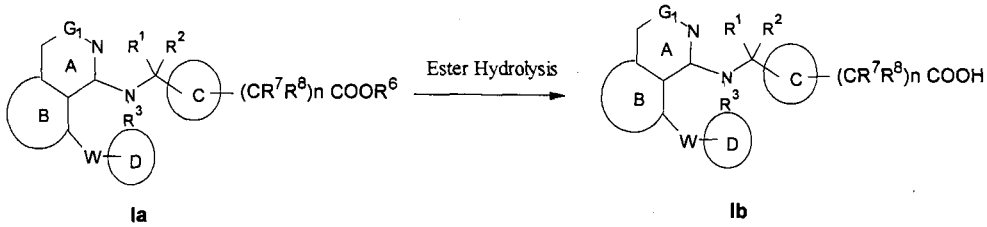
As shown in Scheme 5, compound (Ia) may be prepared by carbonylation of compound (I) wherein R^5 is a halogen atom, preferably a bromine atom. Functional groups in compound (I) may be protected if necessary, and after the carbonylation, it can be removed by conventional means.

[0126]

[0127]

Scheme 6: Synthesis of compound (Ib), which is compound (I) wherein R^5 is $-(CR^7R^8)n(CO)OH$ wherein R^7 and R^8 are each independently a hydrogen atom or a C_{1-6} alkyl group, and n is 0-1

[0128]



Ia Ib

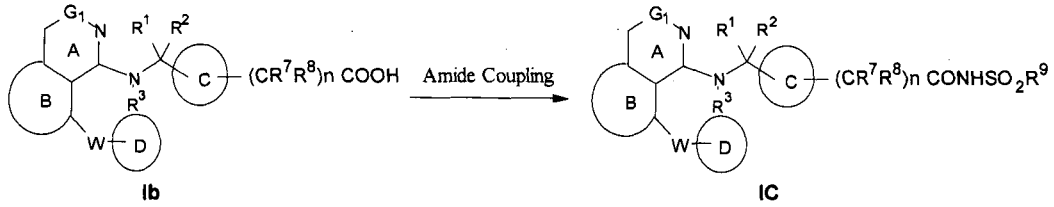
[0129]

As shown in Scheme 6, compound (Ib) may be prepared by ester hydrolysis of compound (Ia).

[0130]

Scheme 7: Synthesis of compound (Ic), which is compound (I) wherein R^5 is $-(CR^7R^8)n(CO)NHS(O)_2R^9$ wherein R^7 and R^8 are each independently a hydrogen atom or a C_{1-6} alkyl group, R^9 is a C_{1-6} alkyl group, a C_{3-10} cycloalkyl group, a C_{6-14} aryl group or a heteroaromatic group, and n is 0-1

[0131]



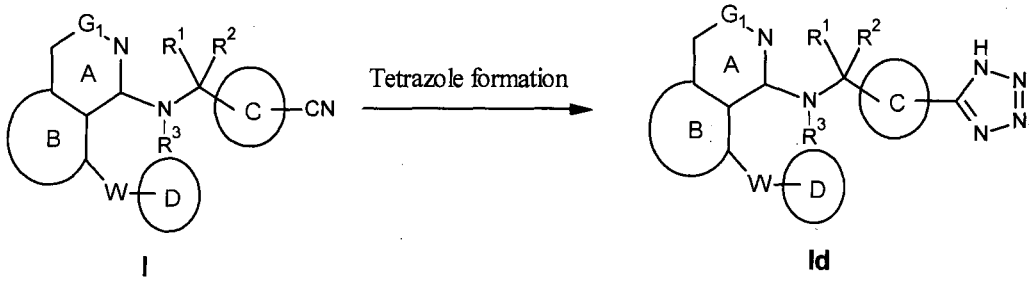
[0132]

As shown in Scheme 7, compound (Ic) may be prepared by amide coupling of compound (Ib) with the corresponding sulfonamide.

[0133]

Scheme 8: Synthesis of compound (Id), which is compound (I) wherein R^5 is 5-tetrazolyl

[0134]



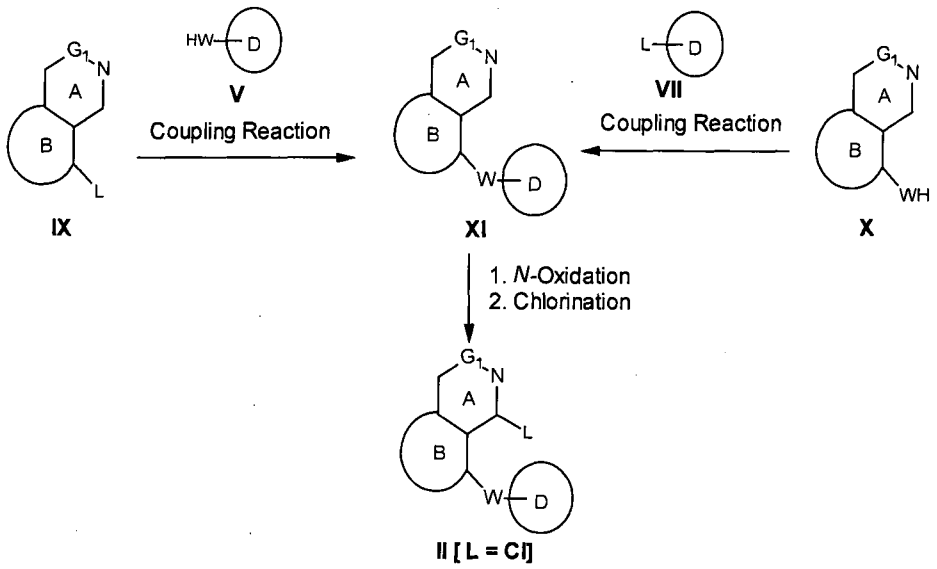
[0135]

As shown in Scheme 8, compound (Id) may be prepared from compound (I) wherein R^5 is a cyano group, by conversion of the nitrile group to tetrazole (Tetrazole formation).

[0136]

Scheme 9: Synthesis of compound (II) wherein G_1 is CR^4 and L is a leaving group, preferably a chlorine atom

[0137]



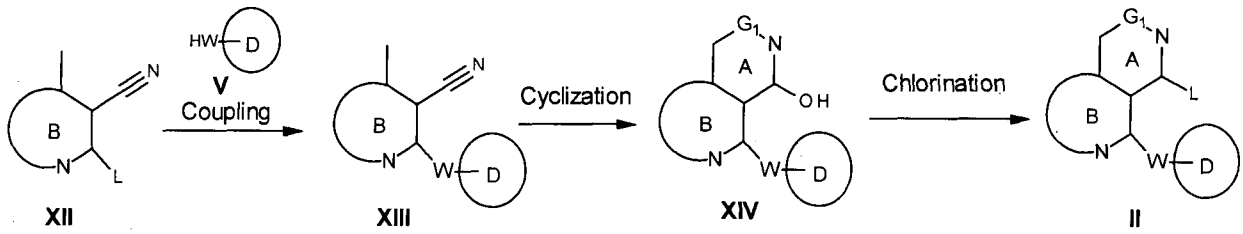
[0138]

As shown in Scheme 9, compound (II) may be prepared by coupling compound (IX) with compound (V) to obtain compound (XI), followed by *N*-oxidation and subsequent chlorination. Alternatively, compound (XI) may be obtained by coupling compound (X) with compound (VII).

[0139]

Scheme 10: Synthesis of compound (II) wherein G_1 is CR^4, L is a leaving group, preferably a chlorine atom or a bromine atom, and ring B is a nitrogen-containing 6-membered heteroaromatic ring such as pyridine, pyrimidine or pyridazine

[0140]



[0141]

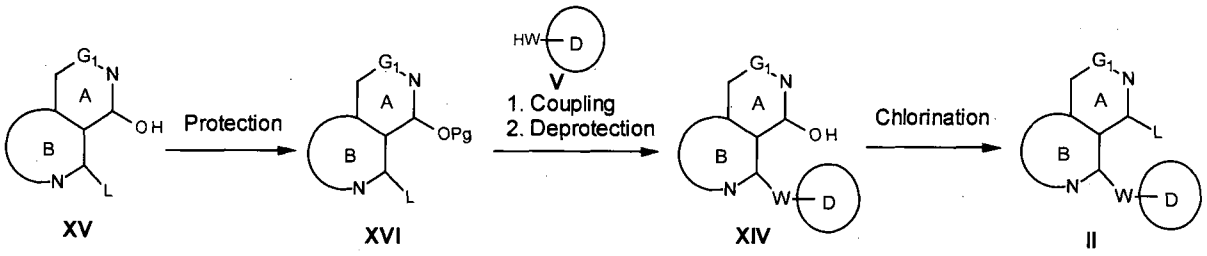
As shown in Scheme 10, compound (II) may be prepared by coupling compound (XII) with compound (V), subjecting the resulting compound (XIII) to cyclization, and subjecting the resulting compound (XIV) to chlorination.

[0142]

Scheme 11: Synthesis of compound (II) wherein L is a leaving

group and ring B is a nitrogen-containing 6-membered heteroaromatic ring such as pyridine, pyrimidine or pyridazine

[0143]



[0144]

As shown in Scheme 11, compound (II) may be prepared by subjecting compound (XV) to O-protection, subjecting the resulting compound (XVI) to coupling followed by deprotection, and subjecting the resulting compound (XIV) to chlorination.

[0145]

N-Arylation:

Aromatic compound having a suitable leaving group, for example, a halogen atom, a C_{1-6} alkoxy group, a C_{6-14} aryloxy group, a sulfanyl group, a C_{1-6} alkylthio group, a C_{6-14} arylthio group, a C_{1-6} alkylsulfinyl group, a C_{6-14} arylsulfinyl group, a C_{1-6} alkylsulfonyl group, a C_{6-14} arylsulfonyl group and a boronic acid group, may be reacted with a primary or secondary amine. The reaction may be carried out in the absence or presence of a base, in an appropriate solvent or without solvent.

Preferred base is selected from organic non-nucleophilic bases such as triethylamine, di-isopropylethylamine (Hünig's base), pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyrimidine, *N*-methylpyrrolidine and diazabicyclo[5.4.0]undec-7ene (DBU); alkali or alkaline earth metal carbonates such as sodium carbonate and potassium carbonate; alkali metal hydrides such as sodium hydride; and phosphazene bases such as 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP). Preferred polar solvent inert to the reaction includes alcohols (e.g., methanol, ethanol, propanol, n-butanol etc.), ethers (e.g.,

tetrahydrofuran (THF), dioxane, dimethoxyethane (DME) etc.), and amides (e.g., N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), *N*-methylpyrrolidine (NMP) etc.). Alternatively, the reaction may be carried out in a melt without addition of a solvent. The reaction is carried out at elevated temperatures, preferably from approximately 60°C to reflux temperature. When L is a boronic acid group, the reaction may be carried out in the presence of a suitable catalyst.

[0146]

Coupling Reaction:

The coupling reaction may be carried out in the absence or presence of a base, in an inert solvent or without solvent. Preferred base is selected from an alkali or alkaline earth metal hydroxides, alkoxides, carbonates and hydrides such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, potassium *tert*-butoxide, sodium carbonate, cesium carbonate, potassium carbonate, BEMP, cesium fluoride (CSF), sodium hydride and potassium hydride. Preferred inert solvents for the reaction include acetone, benzene, toluene, xylene, nitrobenzene, nitromethane, pyridine, dichloromethane, dichloroethane, THF, DME, DMF, DMA, dioxane, dimethylsulfoxide (DMSO) and NMP. The reaction temperature is generally in the range of 0°C to 200°C. The reaction may be carried out in presence of a metal catalyst such as copper (e.g. cuprous iodide or copper bronze) and palladium.

The coupling reaction may be a Suzuki-cross coupling of an aryl halide with an organoboronic acid. Preferred solvents for the reaction may be aromatic hydrocarbons (e.g., benzene, toluene, xylene, nitrobenzene, pyridine etc.); halogenated hydrocarbons (e.g., methylene chloride (DCM), chloroform ($CHCl_3$), carbon tetrachloride (CCl_4), ethylene dichloride (EDC) etc.); ethers (e.g., diethyl ether, diisopropyl ether, DME, THF, dioxane etc.); alcohols (e.g., methanol, ethanol etc.); ethyl acetate, acetonitrile, DMF, DMSO, water and mixture

thereof. The reaction may be carried out at 0°C to reflux temperature. The reaction may be carried out in presence of a suitable catalyst such as tetrakis(triphenylphosphine)palladium(0), bis(tricyclohexylphosphine)palladium(0), bis(triphenylphosphine)palladium(II) chloride, bis(triphenylphosphine)palladium(II) acetate, trifluoromethanesulfonate palladium(II) acetate and palladium(II) chloride. The reaction may be carried out in presence of a suitable additive agent (e.g., triphenylphosphine, tricyclohexylphosphine, tri-*tert*-butylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, tri-2-furylphophine, 2-(dicyclohexylphosphino)biphenyl, 2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl etc.). The reaction may be carried out in presence or absence of a base. Preferred base is selected from lithium hydroxide, sodium hydroxide, potassium hydroxide, barium hydroxide, potassium carbonate, cesium carbonate, sodium ethoxide, potassium *tert*-butoxide, cesium fluoride, tetrabutylammonium fluoride, pyridine, 1,8-diazabicyclo[5,4.0]undecane, triethylamine and *N*-methylmorpholine. The reaction may be carried out in presence or absence of a dehydrating agent (e.g., molecular sieves etc.).

[0147]

Carbonylation Reaction:

The carbonylation reaction may be carried out by reacting an aryl halide with carbon monoxide in presence of a catalyst and /or a base in an inert solvent. The suitable catalyst include palladium reagents such as palladium acetate and palladium dibenzylacetone; and nickel catalysts. Preferred base is selected from *N,N*-diisopropylethylamine, *N*-methylmorpholine, triethylamine etc. If required, this reaction may be carried out in the presence or absence of an additive such as 1,1'-bis(diphenylphosphino)ferrocene, triphenylphosphine and 1,3-bis-(diphenylphosphine)propane. The

reaction may be carried out in a suitable solvent such as acetone, nitromethane, DMF, DMSO, NMP, acetonitrile, DCM, EDC, THF, methanol, ethanol and dioxane. While the reaction temperature varies depending on the kind of the solvent and reagent used for the reaction, it is generally -20°C to 150°C, preferably 50°C to 80°C.

[0148]

Ester Hydrolysis:

Ester hydrolysis may be carried out under general saponification conditions employing an inorganic base such as alkali and alkaline earth metal hydroxides, carbonates and bicarbonates (e.g., lithium hydroxide, sodium hydride, sodium carbonate, potassium carbonate, cesium carbonate etc.) in the presence of a solvent such as water, methanol, ethanol, diethyl ether, THF, DME, DMF and DMSO or mixtures thereof. These reactions may be carried out at 0°C to refluxing temperature.

Alternatively, ester hydrolysis may be carried out under acidic condition, for example, in presence of a hydrogen halide (e.g., hydrochloric acid, hydrobromic acid etc.), a sulfonic acid (e.g., p-toluenesulfonic acid, benzenesulfonic acid, pyridium p-toluenesulfonate etc.) or a carboxylic acid (e.g., acetic acid, trifluoroacetic acid etc.). The suitable solvent includes alcohols (e.g., methanol, ethanol, propanol, butanol, 2-methoxyethanol, ethylene glycol etc.); ethers (e.g., diethyl ether, THF, dioxane, DME etc.); halogenated solvents (e.g., DCM, EDC, chloroform etc.); hexanmethylphophoramide and DMSO. The reaction may be carried out at temperature in the range from -20°C to 100°C, preferably from 20°C to 35°C.

[0149]

Amide Coupling:

Condition-I:

Amide coupling may be carried out using any suitable amide coupling regents such as oxalyl chloride, thionyl chloride, BOP-Cl, DCC, HOBt, HOAt, HATU, EDCI,

propylphosphonic anhydride (T3P), alkyl chloroformate and the like. Preferred base is selected from organic non-nucleophillic bases such as triethylamine, di-isopropylethyl amine, pyridine, *N*-methyl pyrrolidine, *N,N*-dimethylaminopyridine, DBU, other hindered amines and pyridines. The amide coupling may be carried out in the presence of a solvent such as dichloromethane, dichloroethane, DMF, N,N-dimethylacetamide, THF, acetonitrile or mixture of solvent. The reaction may be carried out at a temperature ranging from -20°C to 150°C, preferably from about 0°C to 100°C. The reaction may be carried out optionally in presence of a catalytic amount of DMF.

Condition-II:

When R is not H, the amide coupling may be carried out by heating ester and amine either in the absence of a solvent or in presence of a high boiling solvent such as toluene, xylene and DMSO. Amide coupling may be carried out in presence of a trialkyl aluminium (Chem. Commun., 2008, 1100-1102).

[0150]

Tetrazole formation:

Aryl tetrazole (5H-substituted tetrazole) may be prepared by converting a cyano group into a tetrazole group in an inert solvent such as acetone, DMF, DMSO, NMP and water. Suitable tetrazole forming reagent includes sodium azide, lithium azide, trialkyltin azide and trimethylsilylazide. This reaction may be carried out in presence or absence of a catalyst such as dialkyltin oxide (alkyl is methyl or butyl), alkylamino hydrochloride or hydrobromide, lithium chloride and copper sulphate. The reaction may be carried out in the presence or absence of an acid or a base. Examples of the suitable base include trimethylamine, triethylamine and *N,N*-diisopropyl ethyl amine, and examples of the suitable acid include ammonium chloride, hydrogen chloride, aluminium chloride and zinc bromide. The reaction may be carried out at temperature 50°C to 200°C.

[0151]

N-Oxidation:

N-Oxidation may be carried out using a suitable reagent such as H_2O_2/AcOH, H_2O_2/manganese tetrakis(2,6-dichlorophenyl)porphyrin, H_2O_2/methyltrioxorhenium (MTO), dimethyldioxirane (DMD), bis(trimethylsilyl)peroxide (BTSP), Caro's acid, m-chloroperoxybenzoic acid and oxaziridines. The reaction may be carried out in a suitable inert solvent such as acetonitrile, DCM and DCE. The reaction may be carried out at a temperature ranging from -20°C to 100°C, preferably from about 0°C to 100°C.

[0152]

Chlorination:

Chlorination may be carried out using a suitable reagent such as $POCl_3$, $SOCl_2$, $(CO)_2Cl_2$, *N*-chloro succinimide and CBr_4/triphenylphosphine. The reaction may be carried out in presence or absence of an additive (e.g., ammonium chloride, DBU, PCl_5, triethylamine, diisopropylethyl amine, pyridine, etc.). The reaction may be carried out in a suitable inert solvent such as acetonitrile, toluene, chlorobenzene and DCE. The reaction may be carried out at a temperature ranging from -20°C to reflux temperature, preferably at 0°C to 100°C. The reaction may be carried out in presence or absence of an additive and a solvent.

[0153]

Compound (I) contains a stereoisomer depending to the kind of a substituent, and each stereoisomer and a mixture thereof are encompassed in the present invention.

Compound (I) may be a hydrate or a non-hydrate.

When desired, compound (I) can be synthesized by performing deprotection reaction, acylation reaction, alkylation reaction, hydrogenation reaction, oxidation reaction, reduction reaction, reaction of carbon chain extension, substituent exchange reaction singly or two or more thereof in combination.

When the objective product is obtained as a free form by the above-mentioned reaction, it can be converted to a salt according to a conventional method, or when the objective product is obtained as a salt, it can be converted to a free form or other salt according to a conventional method. The thus-obtained compound (I) can also be isolated and purified from a reaction mixture according to a known method such as phase transfer, concentration, solvent extraction, distillation, crystallization, recrystallization, chromatography and the like.

When compound (I) contains a configurational isomer, a diastereomer, a conformer and the like, each can be isolated according to the above-mentioned separation and purification methods, if desired. In addition, when compound (I) is racemic, d-form and l-form can be isolated according to a conventional optical resolution.

[0154]

In each of the above-mentioned reactions, when the compound has a functional group such as an amino group, a hydroxy group or a carboxyl group, the reaction can be carried out after a protecting group generally used in peptide chemistry and the like is introduced into these groups. By removing the protecting group as necessary after the reaction, the objective compound can be obtained.

Examples of the protecting group include formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl etc.), phenylcarbonyl, C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl etc.), phenyloxycarbonyl, C_{7-10} aralkyloxy-carbonyl (e.g., benzyloxycarbonyl etc.), trityl, phthaloyl and the like, each of which is optionally substituted. Examples of the substituent include a halogen atom (e.g., fluorine, chlorine, bromine, iodine etc.), C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, valeryl etc.), nitro and the like. The number of substituents is, for example, 1 to 3.

The removal method of the protecting group can be carried

out according to a method known per se, and for example, a method using acid, base, ultraviolet rays, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate and the like, a reduction method, and the like can be employed.

[0155]

The thus-obtained compound (I), other reaction intermediate therefor and starting materials thereof can be isolated and purified from a reaction mixture according to a method known per se, for example, extraction, concentration, neutralization, filtration, distillation, recrystallization, column chromatography, thin layer chromatography, preparative high performance liquid chromatography (preparative HPLC), moderate-pressure preparative liquid chromatography (moderate-pressure preparative LC) and the like.

[0156]

A salt of compound (I) can be produced according to a method known *per se*. For example, when compound (I) is a basic compound, it can be produced by adding an inorganic acid or organic acid, or when compound (I) is an acidic compound, by adding an organic base or an inorganic base.

When compound (I) contains an optical isomer, each optical isomer and a mixture thereof are encompassed in the scope of the present invention, and these isomers can be subjected to optical resolution or can be produced respectively, according to a method known per se, if desired.

When compound (I) contains a configurational isomer, a diastereomer, a conformer and the like, each can be isolated according to the above-mentioned separation and purification methods, if desired. In addition, when compound (I) is racemic, S-form and R-form can be isolated according to a conventional optical resolution.

When compound (I) contains a stereoisomer, each isomer and a mixture thereof are encompassed in the present invention.

[0157]

Compound (I) may be a prodrug, and the prodrug of compound (I) refers to a compound which is converted to compound (I) as a result of a reaction with an enzyme, gastric acid, etc. under physiological conditions *in vivo*, thus a compound that undergoes enzymatic oxidation, reduction, hydrolysis etc. to convert to compound (I) and a compound that undergoes hydrolysis and the like by gastric acid, etc. to convert to compound (I).

[0158]

Examples of the prodrug for compound (I) include (1) a compound obtained by subjecting an amino group in compound (I) to acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting an amino group in compound (I) to eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofurylation, pyrrolidylmethylation, pivaloyloxymethylation, tert-butylation, ethoxycarbonylation, tert-butoxycarbonylation, acetylation, cyclopropylcarbonylation and the like);
(2) a compound obtained by subjecting a hydroxy group in compound (I) to acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting a hydroxy group in compound (I) to acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation or dimethylaminomethylcarbonylation and the like);
(3) a compound obtained by subjecting a carboxyl group in compound (I) to esterification or amidation (e.g., a compound obtained by subjecting a carboxyl group in compound (I) to ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification or methylamidation and the like) and the like. Any of these compounds can be

produced from compound (I) according to a method known *per se*.

[0159]

A prodrug of compound (I) may also be one which is converted to compound (I) under physiological conditions as described in "IYAKUHIN no KAIHATSU (Development of Pharmaceuticals)", Vol. 7, Design of Molecules, p. 163-198, Published by HIROKAWA SHOTEN (1990).

[0160]

In the present specification, compound (I) and a prodrug thereof are sometimes collectively abbreviated as "the compound of the present invention".

[0161]

When compound (I) has isomers such as optical isomer, stereoisomer, positional isomer, rotamer and the like, such isomers and a mixture thereof are also encompassed in compound (I). For example, when compound (I) has optical isomers, an optical isomer resolved from this compound is also encompassed in compound (I). These isomers can be obtained as a single product according to synthesis methods or separation methods known *per se* (e.g., concentration, solvent extraction, column chromatography, recrystallization, etc.).

[0162]

Compound (I) may be a crystal, and a single crystal form and a mixture of crystal forms are both encompassed in compound (I). The crystal can be produced by crystallizing according to a crystallization method known *per se*.

Compound (I) may be a hydrate, a non-hydrate, a solvate or a non-solvate.

Compound (I) may be labeled with an isotope (e.g., ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{35}S, ^{125}I etc.) and the like.

Compound (I) also encompasses a deuterium conversion form wherein ^{1}H is converted to $^{2}H(D)$.

Compound (I) may be a pharmaceutically acceptable cocrystal or a salt thereof. The cocrystal or a salt thereof means a crystalline substance constituted with two or more

special solids at room temperature, each having different physical properties (e.g., structure, melting point, melting heat, hygroscopicity, solubility and stability etc.). The cocrystal or a salt thereof can be produced according to a cocrystallization a method known *per se*.

Compound (I) may also be used as a PET tracer.

[0163]

The compound of the present invention has low toxicity, and can be used as it is or in the form of a pharmaceutical composition by mixing with a pharmacologically acceptable carrier etc. to mammals (e.g., human, mouse, rat, rabbit, dog, cat, bovine, horse, swine, monkey) as an agent for the prophylaxis or treatment of various diseases mentioned below.

[0164]

As pharmacologically acceptable carriers, various organic or inorganic carrier substances conventionally used as preparation materials can be used. These are incorporated as excipient, lubricant, binder and disintegrant for solid preparations, or solvent, solubilizing agent, suspending agent, isotonicity agent, buffer and soothing agent for liquid preparations, and the like, and preparation additives such as preservative, antioxidant, colorant, sweetening agent and the like can be added as necessary.

[0165]

Preferable examples of the excipient include lactose, sucrose, D-mannitol, D-sorbitol, starch, gelatinated starch, dextrin, crystalline cellulose, low-substituted hydroxypropylcellulose, sodium carboxymethylcellulose, gum arabic, pullulan, light anhydrous silicic acid, synthesis aluminum silicate and magnesium alumino metasilicate.

[0166]

Preferable examples of the lubricant include magnesium stearate, calcium stearate, talc and colloidal silica.

[0167]

Preferable examples of the binder include gelatinated

starch, sucrose, gelatin, gum arabic, methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, crystalline cellulose, sucrose, D-mannitol, trehalose, dextrin, pullulan, hydroxypropylcellulose, hydroxypropylmethylcellulose and polyvinylpyrrolidone.

[0168]

Preferable examples of the disintegrant include lactose, sucrose, starch, carboxymethylcellulose, calcium carboxymethylcellulose, croscarmellose sodium, sodium carboxymethyl starch, light anhydrous silicic acid and low-substituted hydroxypropylcellulose.

[0169]

Preferable examples of the solvent include water for injection, physiological brine, Ringer's solution, alcohol, propylene glycol, polyethylene glycol, sesame oil, corn oil, olive oil and cottonseed oil.

[0170]

Preferable examples of the solubilizing agents include polyethylene glycol, propylene glycol, D-mannitol, trehalose, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, sodium salicylate and sodium acetate.

[0171]

Preferable examples of the suspending agent include surfactants such as stearyltriethanolamine, sodium lauryl sulfate, lauryl aminopropionate, lecithin, benzalkonium chloride, benzethonium chloride, glycerol monostearate and the like; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, sodium carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and the like; polysorbates, and polyoxyethylene hydrogenated castor oil.

[0172]

Preferable examples of the isotonicity agent include sodium chloride, glycerol, D-mannitol, D-sorbitol and glucose.

[0173]

Preferable examples of the buffer include buffers such as phosphate, acetate, carbonate, citrate and the like.

Preferable examples of the soothing agent include benzyl alcohol.

[0174]

Preferable examples of the preservative include p-oxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

Preferable examples of the antioxidant include sulfite and ascorbate.

[0175]

Preferable examples of the colorant include aqueous water-soluble food tar colors (e.g., food colors such as Food Color Red Nos. 2 and 3, Food Color Yellow Nos. 4 and 5, Food Color Blue Nos. 1 and 2 and the like), water insoluble lake dyes (e.g., aluminum salt of the above-mentioned water-soluble food tar color) and natural dyes (e.g., β-carotene, chlorophyll, ferric oxide red).

[0176]

Preferable examples of the sweetening agent include saccharin sodium, dipotassium glycyrrhizinate, aspartame and stevia.

[0177]

Examples of the dosage form of the pharmaceutical composition include oral preparations such as tablet (including sugar-coated tablet, film-coated tablet, sublingual tablet, orally disintegrating tablet), capsules (including soft capsule, microcapsule), granule, powder, troche, syrup, emulsion, suspension, films (e.g., orally disintegrable films) and the like; and parenteral agents such as injection (e.g., subcutaneous injection, intravenous injection, intramuscular injection, intraperitoneal injection, drip infusion), external preparations (e.g., dermal preparation, ointment), suppository (e.g., rectal suppository, vaginal suppository), pellet, nasal

preparation, pulmonary preparation (inhalant), eye drop and the like.

These can be respectively safely administered orally or parenterally (e.g., topically, rectally, intravenously administered).

[0178]

These preparations may be a release control preparation (e.g., sustained-release microcapsule) such as an immediate-release preparation, a sustained-release preparation and the like.

[0179]

The pharmaceutical composition can be produced according to a method conventionally used in the field of pharmaceutical formulation, for example, the method described in the Japanese Pharmacopoeia, and the like.

[0180]

While the content of the compound of the present invention in the pharmaceutical composition varies depending on the dosage form, dose of the compound of the present invention and the like, it is for example, about 0.1 to 100 wt%.

[0181]

During production of an oral preparation, coating may be applied as necessary for the purpose of masking of taste, enteric property or durability.

[0182]

Examples of the coating base to be used for coating include sugar coating base, water-soluble film coating base, enteric film coating base and sustained-release film coating base.

[0183]

As the sugar coating base, sucrose is used. Moreover, one or more kinds selected from talc, precipitated calcium carbonate, gelatin, gum arabic, pullulan, carnauba wax and the like may be used in combination.

[0184]

Examples of the water-soluble film coating base include cellulose polymers such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, methylhydroxyethyl cellulose etc.; synthetic polymers such as polyvinylacetal diethylaminoacetate, aminoalkyl methacrylate copolymer E [Eudragit E (trade name)], polyvinylpyrrolidone etc.; and polysaccharides such as pullulan etc.

[0185]

Examples of the enteric film coating base include cellulose polymers such as hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, carboxymethylethyl cellulose, cellulose acetate phthalate etc.; acrylic polymers such as methacrylic acid copolymer L [Eudragit L (trade name)], methacrylic acid copolymer LD [Eudragit L-30D55 (trade name)], methacrylic acid copolymer S [Eudragit S (trade name)] etc.; and naturally occurring substances such as shellac etc.

[0186]

Examples of the sustained-release film coating base include cellulose polymers such as ethyl cellulose etc.; and acrylic polymers such as aminoalkyl methacrylate copolymer RS [Eudragit RS (trade name)], ethyl acrylate-methyl methacrylate copolymer suspension [Eudragit NE (trade name)] etc.

[0187]

The above-mentioned coating bases may be used after mixing with two or more kinds thereof at appropriate ratios. For coating, for example, a light shielding agent such as titanium oxide, red ferric oxide and the like can be used.

[0188]

The compound of the present invention shows low toxicity (e.g., acute toxicity, chronic toxicity, genetic toxicity, reproductive toxicity, cardiotoxicity, carcinogenicity) and a few side effects. Therefore, it can be used as an agent for the prophylaxis or treatment or a diagnostic of various

diseases in a mammal (e.g., human, bovine, horse, dog, cat, monkey, mouse, rat).

[0189]

Since the compound of the present invention have superior EP4 receptor antagonistic action, they are also useful as safe medicaments based on such action.

For example, the medicament of the present invention containing the compound of the present invention can be used for a mammal (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey, human etc.) as an agent for the prophylaxis or treatment of EP4 receptor associated diseases, specifically, the diseases described in (1) - (7) below.

[0190]

(1) inflammatory diseases (e.g., acute pancreatitis, chronic pancreatitis, asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease (COPD), inflammatory bone disease, inflammatory pulmonary disease, inflammatory bowel disease, celiac disease, hepatitis, systemic inflammatory response syndrome (SIRS), postoperative or posttraumatic inflammation, pneumonia, nephritis, meningitis, cystitis, pharyngolaryngitis, gastric mucosal injury, meningitis, spondylitis, arthritis, dermatitis, chronic pneumonia, bronchitis, pulmonary infarction, silicosis, pulmonary sarcoidosis etc.),

(2) autoimmune diseases (e.g., psoriasis, rheumatoid arthritis, inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis etc.), Sjogren's syndrome, Behcet's disease, multiple sclerosis, systemic lupus erythematosus, ankylopoietic spondylarthritis, polymyositis, dermatomyositis (DM), polyarteritis nodosa (PN), mixed connective tissue disease (MCTD), scleroderma, profundus lupus erythematosus, chronic thyroiditis, Graves' disease, autoimmune gastritis, type I and type II diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, graft versus host disease,

Addison's disease, abnormal immunoresponse, arthritis, dermatitis, radiodermatitis etc.)(especially, psoriasis, rheumatoid arthritis, inflammatory bowel disease, Sjogren's syndrome, Behcet's disease, multiple sclerosis and systemic lupus erythematosus),

(3) osteoarticular degenerative disease (e.g., rheumatoid arthritis, osteoporosis, osteoarthritis etc.),

(4) neoplastic diseases [e.g., malignant tumor, angiogenesis glaucoma, infantile hemangioma, multiple myeloma, acute myeloblastic leukemia, chronic sarcoma, multiple myeloma, chronic myelogenous leukemia, metastasis melanoma, Kaposi's sacroma, vascular proliferation, cachexia, metastasis of the breast cancer, cancer (e.g., colorectal cancer (e.g., familial colorectal cancer, hereditary nonpolyposis colorectal cancer, gastrointestinal stromal tumor etc.), lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, malignant mesothelioma etc.), mesothelioma, pancreatic cancer (e.g., pancreatic duct cancer etc.), gastric cancer (e.g., mucinous adenocarcinoma, adenosquamous carcinoma etc.), papillary adenocarcinoma, breast cancer (e.g., invasive ductal carcinoma, ductal carcinoma in situ, inflammatory breast cancer etc.), ovarian cancer (e.g., ovarian epithelial carcinoma, extragonadal germ cell tumor, ovarian germ cell tumor, ovarian low malignant potential tumor etc.), prostate cancer (e.g., hormone-dependent prostate cancer, non-hormone dependent prostate cancer etc.), liver cancer (e.g., primary liver cancer, extrahepatic bile duct cancer etc.), thyroid cancer (e.g., medullary thyroid carcinoma etc.), kidney cancer (e.g., renal cell carcinoma, transitional cell carcinoma in kidney and urinary duct etc.), uterine cancer, brain tumor (e.g., pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma etc.), melanoma, sarcoma, urinary bladder cancer, hematologic cancer and the like including multiple myeloma, hypophyseal adenoma, glioma, acoustic neurinoma, retinoblastoma, pharyngeal cancer, laryngeal cancer,

cancer of the tongue, thymoma, esophagus cancer, duodenal cancer, colorectal cancer, rectal cancer, hepatoma, pancreatic endocrine tumor, bile duct cancer, gallbladder cancer, penile cancer, urinary duct cancer, testis tumor, vulvar cancer, cervix cancer, endometrial cancer, uterus sarcoma, cholionic disease, vaginal cancer, skin cancer, fungoid mycosis, basal cell tumor, soft tissue sarcoma, malignant lymphoma, Hodgkin's disease, myelodysplastic syndrome, acute lymphocytic leukemia, chronic lymphocytic leukemia, adult T cell leukemia, chronic bone marrow proliferative disease, pancreatic endocrine tumor, fibrous histiocytoma, leiomyosarcoma, rhabdomyosarcoma, cancer of unknown primary),

(5) cardiovascular disease (e.g., heart disease (e.g., cardiac hypertrophy, acute heart failure and chronic heart failure including congestive, cardiomyopathy, angina pectoris, myocarditis, arrhythmia, tachycardia, myocardial infarction), myocardial ischemia, venous insufficiency, heart failure after myocardial infarction, hypertension, cor pulmonale, arteriosclerosis including atherosclerosis (e.g., aortic aneurysm (e.g., abdominal aortic aneurysm, thoracic aortic aneurysm, thoracoabdominal aortic aneurysm), coronary atherosclerosis, cerebral atherosclerosis, peripheral arterial disease, arteriosclerosis obliterans, chronic arterial occlusion), intervention (e.g., percutaneous transluminal coronary angioplasty, stent placement, coronary angioscopy, intravascular ultrasound, thrombolysis therapy), vascular hypertrophy or vascular occluson and organ dysfunction after heart transplant, vascular reocclusion and restenosis after bypass surgery),

(6) hormone-dependent diseases (sex hormone-dependent cancers (e.g., prostate cancer, uterine cancer, breast cancer, pituitary tumor), prostatic hyperplasia, endometriosis, uterine fibroid, precocious puberty, dysmenorrhea, amenorrhea, premenstrual syndrome, polycystic ovary syndrome),

(7) acute and chronic pain (e.g., neuropathic pain (e.g.,

peripheral neuropathy, diabetic neuropathy, post herpetic neuralgia, trigeminal neuralgia, back pain, cancer neuropathy, HIV neuropathy, phantom limb pain, carpal tunnel syndrome, central post-stroke pain, and pain associated with chronic alcoholism, hypothyroidism, uremia, multiple sclerosis, spinal cord injury, Parkinson's disease, epilepsy and vitamin deficiency), inflammatory pain (e.g., osteoarthritis, ankylosing spondylitis), visceral pain (e.g., pain associated with gastrointestinal disorders (gastro-esophageal reflux, dyspepsia, irritable bowel syndrome (IBS), functional abdominal pain syndrome (FAPS), inflammatory bowel disease (IBD), Crohn's disease, ileitis, ulcerative colitis)), pain from central nervous system trauma, strains/sprains, burns, myocardial infarction and acute pancreatitis, postoperative pain, renal colic, posttraumatic pain, back pain, cancer pain (e.g., tumor related pain (e.g., bone pain, headache, facial pain or visceral pain), pain associated with cancer therapy (e.g., pain associated with postchemotherapy syndrome, chronic postsurgical pain syndrome, post radiation syndrome), chemotherapy, immunotherapy, hormonal therapy or radiotherapy), pain resulting from musculo-skeletal disorders (e.g., myalgia, fibromyalgia, spondylitis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, dystrophinopathy, glycogenosis, polymyositis and pyomyositis), heart and vascular pain (e.g., pain caused by angina, myocardical infarction, mitral stenosis, pericarditis, Raynaud's phenomenon, scleroderma and skeletal muscle ischemia), head pain (e.g., migraine (including migraine with aura and migraine without aura), cluster headache, tension-type headache, mixed headache and headache associated with vascular disorders), orofacial pain (e.g., dental pain, otic pain, burning mouth syndrome and temporomandibular myofascial pain)).

[0191]

The medicament of the present invention can be preferably used as an agent for the prophylaxis or treatment of

rheumatoid arthritis, thoracic and abdominal aortic aneurysm, endometriosis or ankylosing spondylitis.

[0192]

Here, the above-mentioned "prophylaxis" of a disease means, for example, administration of a medicament containing the compound of the present invention to patients who are expected to have a high risk of the onset due to some factor relating to the disease but have not developed the disease or patients who have developed the disease but do not have a subjective symptom, or administration of a medicament containing the compound of the present invention to patients who are feared to show recurrence of the disease after treatment of the disease.

and the like.

[0193]

The dose of the compound of the present invention varies depending on the administration subject, route of administration, target disease, symptoms, etc. For example, when it is administered orally to an adult patient (body weight 60 kg), its dose is about 0.01 to 100 mg/kg body weight per dose, preferably 0.05 to 30 mg/kg body weight per dose, more preferably 0.1 to 10 mg/kg body weight per dose and this amount is desirably administered in 1 to 3 portions daily.

[0194]

The compound of the present invention can also be used together with other medicaments.

Hereinafter, a medicament to be used in combination with the compound of the present invention is referred to as "concomitant drug", and a combination of the compound of the present invention and concomitant drug is referred to as "the combination agent of the present invention".

For example, when the compound of the present invention is used as a prophylactic or therapeutic agent for EP4 receptor associated disease, it can be used in combination with the following drugs.

(1) non-steroidal anti-inflammatory drug (NSAIDs)

(i) Classical NSAIDs

alcofenac, aceclofenac, sulindac, tolmetin, etodolac, fenoprofen, thiaprofenic acid, meclofenamic acid, meloxicam, tenoxicam, lornoxicam, nabumeton, acetaminophen, phenacetin, ethenzamide, sulpyrine, antipyrine, migrenin, aspirin, mefenamic acid, flufenamic acid, diclofenac sodium, loxoprofen sodium, phenylbutazone, indomethacin, ibuprofen, ketoprofen, naproxen, oxaprozin, flurbiprofen, fenbufen, pranoprofen, floctafenine, piroxicam, epirizole, tiaramide hydrochloride, zaltoprofen, gabexate mesylate, camostat mesylate, ulinastatin, colchicine, probenecid, sulfinpyrazone, benzbromarone, allopurinol, sodium aurothiomalate, hyaluronate sodium, sodium salicylate, morphine hydrochloride, salicylic acid, atropine, scopolamine, morphine, pethidine, levorphanol, oxymorphone or a salt thereof and the like.

(ii) cyclooxygenase inhibitor (COX-1 selective inhibitor, COX-2 selective inhibitor etc.)

salicylic acid derivatives (e.g., celecoxib, aspirin), etoricoxib, valdecoxib, diclofenac, indomethacin, loxoprofen and the like.

(iii) nitric oxide-releasing NSAIDs.

(iv) JAK inhibitor

tofacitinib, ruxolitinib and the like.

[0195]

(2) disease-modifying anti-rheumatic drugs (DMARDs)

(i) Gold preparation

auranofin and the like.

(ii) penicillamine

D-penicillamine and the like.

(iii) aminosalicylic acid preparation

sulfasalazine, mesalazine, olsalazine, balsalazide and the like.

(iv) antimalarial drug

chloroquine and the like.

(v) pyrimidine synthesis inhibitor

leflunomide and the like.

(vi) prograf

[0196]

(3) anti-cytokine drug

(I) protein drug

(i) TNF inhibitor

etanercept, infliximab, adalimumab, certolizumab pegol, golimumab, PASSTNF-α, soluble TNF-α receptor, TNF-α binding protein, anti-TNF-α antibody and the like.

(ii) interleukin-1 inhibitor

anakinra (interleukin-1 receptor antagonist), soluble interleukin-1 receptor and the like.

(iii) interleukin-6 inhibitor

tocilizumab (anti-interleukin-6 receptor antibody), anti-interleukin-6 antibody and the like.

(iv) interleukin-10 drug

interleukin-10 and the like.

(v) interleukin-12/23 inhibitor

ustekinumab, briakinumab (anti-interleukin-12/23 antibody) and the like.

(II) non-protein drug

(i) MAPK inhibitor

BMS-582949 and the like.

(ii) gene modulator

inhibitor of molecule involved in signal transduction, such as NF-κ, NF-κB, IKK-1, IKK-2, AP-1 and the like, and the like.

(iii) cytokine production inhibitor

iguratimod, tetomilast and the like.

(iv) TNF-α converting enzyme inhibitor

(v) interleukin-1β converting enzyme inhibitor

VX-765 and the like.

(vi) interleukin-6 antagonist

HMPL-004 and the like.

(vii) interleukin-8 inhibitor

IL-8 antagonist, CXCR1 & CXCR2 antagonist, reparixin and the like.

(viii) chemokine antagonist

CCR9 antagonist (CCX-282, CCX-025), MCP-1 antagonist and the like.

(ix) interleukin-2 receptor antagonist

denileukin, diftitox and the like.

(x) therapeutic vaccines

TNF-α vaccine and the like.

(xi) gene therapy drug

gene therapy drugs aiming at promoting the expression of gene having an anti-inflammatory action such as interleukin-4, interleukin-10, soluble interleukin-1 receptor, soluble TNF-α receptor and the like.

(xii) antisense compound

ISIS 104838 and the like.

[0197]

(4) integrin inhibitor

natalizumab, vedolizumab, AJM300, TRK-170, E-6007 and the like.

(5) immunomodulator (immunosuppressant)

methotrexate, cyclophosphamide, MX-68, atiprimod dihydrochloride, BMS-188667, CKD-461, rimexolone, cyclosporine, tacrolimus, gusperimus, azathiopurine, antilymphocyte serum, freeze-dried sulfonated normal immunoglobulin, erythropoietin, colony stimulating factor, interleukin, interferon and the like.

(6) steroid

dexamethasone, hexestrol, methimazole, betamethasone, triamcinolone, triamcinolone acetonide, fluocinonide, fluocinolone acetonide, predonisolone, methylpredonisolone, cortisone acetate, hydrocortisone, fluorometholone, beclomethasone dipropionate, estriol and the like.

(7) angiotensin converting enzyme inhibitor

enalapril, captopril, ramipril, lisinopril, cilazapril, perindopril and the like.

[0198]

(8) angiotensin II receptor antagonist

candesartan, candesartan cilexetil, azilsartan, azilsartan medoxomil, valsartan, irbesartan, olmesartan, eprosartan and the like.

(9) diuretic drug

hydrochlorothiazide, spironolactone, furosemide, indapamide, bendrofluazide, cyclopenthiazide and the like.

(10) cardiotonic drug

digoxin, dobutamine and the like.

(11) β receptor antagonist

carvedilol, metoprolol, atenolol and the like.

(12) Ca sensitizer

MCC-135 and the like.

(13) Ca channel antagonist

nifedipine, diltiazem, verapamil and the like.

(14) anti-platelet drug, anticoagulator

heparin, aspirin, warfarin and the like.

(15) HMG-CoA reductase inhibitor

atorvastatin, simvastatin and the like.

[0199]

(16) contraceptive

(i) sex hormone or derivatives thereof

gestagen or a derivative thereof (progesterone, 17α-hydroxy progesterone, medroxyprogesterone, medroxyprogesterone acetate, norethisterone, norethisterone enanthate, norethindrone, norethindrone acetate, norethynodrel, levonorgestrel, norgestrel, ethynodiol diacetate, desogestrel, norgestimate, gestodene, progestin, etonogestrel, drospirenone, dienogest, trimegestone, nestorone, chlormadinone acetate, mifepristone, nomegestrol acetate, Org-30659, TX-525, EMM-310525) or a combination agent of a gestagen or a derivative thereof and an estrogen or a derivative thereof (estradiol,

estradiol benzoate, estradiol cypionate, estradiol dipropionate, estradiol enanthate, estradiol hexahydrobenzoate, estradiol phenylpropionate, estradiol undecanoate, estradiol valerate, estrone, ethinylestradiol, mestranol) and the like.

(ii) antiestrogen

ormeloxifene, mifepristone, Org-33628 and the like.

(iii) spermatocide

ushercell and the like.

[0200]

(17) others

(i) T cell inhibitors

(ii) inosine monophosphate dehydrogenase (IMPDH) inhibitor

mycophenolate mofetil and the like.

(iii) adhesion molecule inhibitor

ISIS-2302, selectin inhibitor, ELAM-1, VCAM-1, ICAM-1 and the like.

(iv) thalidomide

(v) cathepsin inhibitor

(vi) matrix metalloprotease (MMPs) inhibitor

V-85546 and the like.

(vii) glucose-6-phosphate dehydrogenase inhibitor

(viii) Dihydroorotate dehydrogenase (DHODH) inhibitor

(ix) phosphodiesterase IV(PDE IV) inhibitor

roflumilast, CG-1088 and the like.

(x) phospholipase A_2 inhibitor

(xi) iNOS inhibitor

VAS-203 and the like.

(xii) microtubule stimulating drug

paclitaxel and the like.

(xiii) microtuble inhibitor

reumacon and the like.

(xiv) MHC class II antagonist

(xv) prostacyclin agonist

iloprost and the like.

(xvi) CD4 antagonist

zanolimumab and the like.

(xvii) CD23 antagonist

(xviii) LTB4 receptor antagonist

DW-1305 and the like.

(xix) 5-lipoxygenase inhibitor

zileuton and the like.

(xx) cholinesterase inhibitor

galanthamine and the like.

(xxi) tyrosine kinase inhibitor

Tyk2 inhibitor (the compound described in WO 2010/142752) and the like.

(xxii) cathepsin B inhibitor

(xxiii) adenosine deaminase inhibitor

pentostatin and the like.

(xxiv) osteogenesis stimulator

(xxv) dipeptidylpeptidase inhibitor

(xxvi) collagen agonist

(xxvii) capsaicin cream

(xxviii) hyaluronic acid derivative

synvisc (hylan G-F 20), orthovisc and the like.

(xxix) glucosamine sulfate

(xxx) amiprilose

(xxxi) CD-20 inhibitor

rituximab, ibritumomab, tositumomab, ofatumumab and the like.

(xxxii) BAFF inhibitor

belimumab, tabalumab, atacicept, A-623 and the like.

(xxxiii) CD52 inhibitor

alemtuzumab and the like.

(xxxiv) IL-17 inhibitor

secukinumab (AIN-457), LY-2439821, AMG827 and the like

[0201]

Other concomitant drugs besides the above-mentioned include, for example, antibacterial agent, antifungal agent, antiprotozoal agent, antibiotic, antitussive and expectorant

drug, sedative, anesthetic, antiulcer drug, antiarrhythmic agent, hypotensive diuretic drug, anticoagulant, tranquilizer, antipsychotic, antitumor drug, hypolipidemic drug, muscle relaxant, antiepileptic drug, antidepressant, antiallergic drug, cardiac stimulants, therapeutic drug for arrhythmia, vasodilator, vasoconstrictor, therapeutic drug for diabetes, antinarcotic, vitamin, vitamin derivative, antiasthmatic, therapeutic agent for pollakisuria/anischuria, antipruritic drug, therapeutic agent for atopic dermatitis, therapeutic agent for allergic rhinitis, hypertensor, endotoxin-antagonist or -antibody, signal transduction inhibitor, inhibitor of inflammatory mediator activity, antibody to inhibit inflammatory mediator activity, inhibitor of anti-inflammatory mediator activity, antibody to inhibit anti-inflammatory mediator activity and the like. Specific examples thereof include the following.

[0202]

(1) antibacterial agent

(i) sulfa drug

sulfamethizole, sulfisoxazole, sulfamonomethoxine, sulfamethizole, salazosulfapyridine, silver sulfadiazine and the like.

(ii) quinolone antibacterial agent

nalidixic acid, pipemidic acid trihydrate, enoxacin, norfloxacin, ofloxacin, tosufloxacin tosylate, ciprofloxacin hydrochloride, lomefloxacin hydrochloride, sparfloxacin, fleroxacin and the like.

(iii) antiphthisic

isoniazid, ethambutol (ethambutol hydrochloride), p-aminosalicylic acid (calcium p-aminosalicylate), pyrazinamide, ethionamide, protionamide, rifampicin, streptomycin sulfate, kanamycin sulfate, cycloserine and the like.

(iv) antiacidfast bacterium drug

diaphenylsulfone, rifampicin and the like.

(v) antiviral drug

idoxuridine, acyclovir, vidarabine, gancyclovir and the like.

[0203]

(vi) anti-HIV agent

zidovudine, didanosine, zalcitabine, indinavir sulfate ethanolate, ritonavir and the like.

(vii) antispirochetele

(viii) antibiotic

tetracycline hydrochloride, ampicillin, piperacillin, gentamicin, dibekacin, kanendomycin, lividomycin, tobramycin, amikacin, fradiomycin, sisomicin, tetracycline, oxytetracycline, rolitetracycline, doxycycline, ampicillin, piperacillin, ticarcillin, cephalothin, cephapirin, cephaloridine, cefaclor, cephalexin, cefroxadine, cefadroxil, cefamandole, cefotoam, cefuroxime, cefotiam, cefotiam hexetil, cefuroxime axetil, cefdinir, cefditoren pivoxil, ceftazidime, cefpiramide, cefsulodin, cefmenoxime, cefpodoxime proxetil, cefpirome, cefozopran, cefepime, cefsulodin, cefmenoxime, cefmetazole, cefminox, cefoxitin, cefbuperazone, latamoxef, flomoxef, cefazolin, cefotaxime, cefoperazone, ceftizoxime, moxalactam, thienamycin, sulfazecin, aztreonam or a salt a salt thereof, griseofulvin, lankacidin-group [Journal of Antibiotics (J. Antibiotics), 38, 877-885(1985)], azole compound [2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3(2H,4H)-1,2,4-triazolone, fluconazole, itraconazole and the like] and the like.

[0204]

(2) antifungal agent

(i) polyethylene antibiotic (e.g., amphotericin B, nystatin, trichomycin)

(ii) griseofulvin, pyrrolnitrin and the like

(iii) cytosine metabolism antagonist (e.g., flucytosine)

(iv) imidazole derivative (e.g., econazole, clotrimazole, miconazole nitrate, bifonazole, croconazole)

(v) triazole derivative (e.g., fluconazole, itraconazole)

(vi) thiocarbamic acid derivative (e.g., trinaphthol) and the like.

(3) antiprotozoal agent

metronidazole, tinidazole, diethylcarbamazine citrate, quinine hydrochloride, quinine sulfate and the like.

[0205]

(4) antitussive and expectorant drug

ephedrine hydrochloride, noscapine hydrochloride, codeine phosphate, dihydrocodeine phosphate, isoproterenol hydrochloride, ephedrine hydrochloride, methylephedrine hydrochloride, noscapine hydrochloride, alloclamide, chlophedianol, picoperidamine, cloperastine, protokylol, isoproterenol, salbutamol, terbutaline, oxymetebanol, morphine hydrochloride, dextromethorfan hydrobromide, oxycodone hydrochloride, dimemorphan phosphate, tipepidine hibenzate, pentoxyverine citrate, clofedanol hydrochloride, benzonatate, guaifenesin, bromhexine hydrochloride, ambroxol hydrochloride, acetylcysteine, ethyl cysteine hydrochloride, carbocysteine and the like.

(5) sedative

chlorpromazine hydrochloride, atropine sulfate, phenobarbital, barbital, amobarbital, pentobarbital, thiopental sodium, thiamylal sodium, nitrazepam, estazolam, flurazepam, haloxazolam, triazolam, flunitrazepam, bromovalerylurea, chloral hydrate, triclofos sodium and the like.

[0206]

(6) anesthetic

(6-1) local anesthetic

cocaine hydrochloride, procaine hydrochloride, lidocaine, dibucaine hydrochloride, tetracaine hydrochloride, mepivacaine hydrochloride, bupivacaine hydrochloride, oxybuprocaine hydrochloride, ethyl aminobenzoate, oxethazaine and the like.

(6-2) general anesthetic

(i) inhalation anesthetic (e.g., ether, halothane, nitrous oxide, isoflurane, enflurane),
(ii) intravenous anesthetic (e.g., ketamine hydrochloride, droperidol, thiopental sodium, thiamylal sodium, pentobarbital) and the like.

(7) antiulcer drug

histidine hydrochloride, lansoprazole, metoclopramide, pirenzepine, cimetidine, ranitidine, famotidine, urogastrone, oxethazaine, proglumide, omeprazole, sucralfate, sulpiride, cetraxate, gefarnate, aldioxa, teprenone, prostaglandin and the like.

(8) antiarrhythmic agent

(i) sodium channel blocker (e.g., quinidine, procainamide, disopyramide, ajmaline, lidocaine, mexiletine, phenytoin),
(ii) β-blocker (e.g., propranolol, alprenolol, bufetolol hydrochloride, oxprenolol, atenolol, acebutolol, metoprolol, bisoprolol, pindolol, carteolol, arotinolol hydrochloride),
(iii) potassium channel blocker (e.g., amiodarone),
(iv) calcium channel blocker (e.g., verapamil, diltiazem) and the like.

[0207]

(9) hypotensive diuretic drug

hexamethonium bromide, clonidine hydrochloride, hydrochlorothiazide, trichlormethiazide, furosemide, ethacrynic acid, bumetanide, mefruside, azosemide, spironolactone, potassium canrenoate, triamterene, amiloride, acetazolamide, D-mannitol, isosorbide, aminophylline and the like.

(10) anticoagulant

heparin sodium, sodium citrate, activated protein C, tissue factor pathway inhibitor, antithrombin III, dalteparin sodium, warfarin potassium, argatroban, gabexate, sodium citrate, ozagrel sodium, ethyl icosapentate, beraprost sodium, alprostadil, ticlopidine hydrochloride, pentoxifylline, dipyridamole, tisokinase, urokinase, streptokinase and the

like.

(11) tranquilizer

diazepam, lorazepam, oxazepam, chlordiazepoxide, medazepam, oxazolam, cloxazolam, clotiazepam, bromazepam, etizolam, fludiazepam, hydroxyzine and the like.

(12) antipsychotic

chlorpromazine hydrochloride, prochlorperazine, trifluoperazine, thioridazine hydrochloride, perphenazine maleate, fluphenazine enanthate, prochlorperazine maleate, levomepromazine maleate, promethazine hydrochloride, haloperidol, bromperidol, spiperone, reserpine, clocapramine hydrochloride, sulpiride, zotepine and the like.

[0208]

(13) antitumor drug

6-O-(N-chloroacetylcarbamoyl)fumagillol, bleomycin, methotrexate, actinomycin D, mitomycin C, daunorubicin, adriamycin, neocarzinostatin, cytosine arabinoside, fluorouracil, tetrahydrofuryl-5-fluorouracil, picibanil, lentinan, levamisole, bestatin, azimexon, glycyrrhizin, doxorubicin hydrochloride, aclarubicin hydrochloride, bleomycin hydrochloride, peplomycin sulfate, vincristine sulfate, vinblastine sulfate, irinotecan hydrochloride, cyclophosphamide, melphalan, busulfan, thiotepa, procarbazine hydrochloride, cisplatin, azathioprine, mercaptopurine, tegafur, carmofur, cytarabine, methyltestosterone, testosterone propionate, testosterone enanthate, mepitiostane, fosfestrol, chlormadinone acetate, leuprorelin acetate, buserelin acetate and the like.

(14) hypolipidemic drug

clofibrate, ethyl 2-chloro-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionate [Chemical and Pharmaceutical Bulletin (Chem. Pharm. Bull), 38, 2792-2796 (1990)], pravastatin, simvastatin, probucol, bezafibrate, clinofibrate, nicomol, cholestyramine, dextran sulfate sodium and the like.

(15) muscle relaxant

pridinol, tubocurarine, pancuronium, tolperisone hydrochloride, chlorphenesin carbamate, baclofen, chlormezanone, mephenesin, chlorzoxazone, eperisone, tizanidine and the like.

(16) antiepileptic drug

phenytoin, ethosuximide, acetazolamide, chlordiazepoxide, trimethadione, carbamazepine, phenobarbital, primidone, sulthiame, sodium valproate, clonazepam, diazepam, nitrazepam and the like.

[0209]

(17) antidepressant

imipramine, clomipramine, noxiptiline, phenelzine, amitriptyline hydrochloride, nortriptyline hydrochloride, amoxapine, mianserin hydrochloride, maprotiline hydrochloride, sulpiride, fluvoxamine maleate, trazodone hydrochloride and the like.

(18) antiallergic drug

diphenhydramine, chlorpheniramine, tripelennamine, metodilamine, clemizole, diphenylpyraline, methoxyphenamine, sodium cromoglicate, tranilast, repirinast, amlexanox, ibudilast, ketotifen, terfenadine, mequitazine, azelastine hydrochloride, epinastine, ozagrel hydrochloride, pranlukast hydrate, seratrodast and the like.

(19) cardiac stimulants

trans-π-oxocamphor, terephyllol, aminophylline, etilefrine, dopamine, dobutamine, denopamine, aminophylline, vesnarinone, amrinone, pimobendan, ubidecarenone, digitoxin, digoxin, methyldigoxin, lanatoside C, G-strophanthin and the like.

(20) vasodilator

oxyfedrine, diltiazem, tolazoline, hexobendine, bamethan, clonidine, methyldopa, guanabenz and the like.

(21) vasoconstrictor

dopamine, dobutamine denopamine and the like.

(22) hypotensive diuretic

hexamethonium bromide, pentolinium, mecamylamine, ecarazine, clonidine, diltiazem, nifedipine and the like.

(23) therapeutic drug for diabetes

tolbutamide, chlorpropamide, acetohexamide, glibenclamide, tolazamide, acarbose, epalrestat, troglitazone, glucagon, glymidine, glipizide, phenformin, buformin, metformin and the like.

[0210]

(24) antinarcotic

levallorphan, nalorphine, naloxone or a salt thereof and the like.

(25) liposoluble vitamins

(i) vitamin A: vitamin A_1, vitamin A_2 and retinol palmitate

(ii) vitamin D: vitamin D_1, D_2, D_3, $D_4$and D_5

(iii) vitamin E: α-tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, dl-α-tocopherol nicotinate

(iv) vitamin K: vitamin K_1, K_2, $K_3$and K_4

(v) folic acid (vitamin M) and the like.

(26) vitamin derivative

various derivatives of vitamins, for example, vitamin D_3 derivatives such as 5,6-trans-cholecalciferol, 2,5-hydroxycholecalciferol, 1-α-hydroxycholecalciferol and the like, vitamin D_2 derivatives such as 5,6-trans-ergocalciferol and the like, and the like.

(27) antiasthmatic

isoprenaline hydrochloride, salbutamol sulfate, procaterol hydrochloride, terbutaline sulfate, trimetoquinol hydrochloride, tulobuterol hydrochloride, orciprenaline sulfate, fenoterol hydrobromide, ephedrine hydrochloride, ipratropium bromide, oxitropium bromide, flutropium bromide, theophylline, aminophylline, sodium cromoglicate, tranilast, repirinast, amlexanox, ibudilast, ketotifen, terfenadine, mequitazine, azelastine, epinastine, ozagrel hydrochloride, pranlkast hydrate, seratrodast, dexamethasone, prednisolone, hydrocortisone, hydrocortisone sodium succinate, beclometasone

dipropionate and the like.

(28) therapeutic agent for pollakisuria/anischuria

flavoxate hydrochloride and the like.

(29) therapeutic agent for atopic dermatitis

sodium cromoglicate and the like.

[0211]

(30) therapeutic agent for allergic rhinitis

sodium cromoglicate, chlorpheniramine maleate, alimemazine tartrate, clemastine fumarate, homochlorcyclizine hydrochloride, fexofenadine, mequitazine and the like.

(31) hypertensor

dopamine, dobutamine, denopamine, digitoxin, digoxin, methyldigoxin, lanatoside C, G-strophanthin and the like.

(32) others

hydroxycam, diacerein, megestrol acetate, nicergoline, prostaglandins and the like.

[0212]

In another embodiment, when the compound of the present invention is used as an agent for the prophylaxis or treatment of chronic or acute pain, from among EP4 receptor associated disease, it can be used in combination with the following drugs.

(1) opioid analgesic, for example, morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine or pentazocine;

(2) non-steroidal antiinflammatory drug (NSAID), for example, aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin or zomepirac; cyclooxygenase-2 (COX-2) inhibitors, for example, celecoxib, rofecoxib, meloxicam, 4-

(4-cyclohexyl-2-methyl-1,3-oxazol-5-yl)-2-fluorobenzenesulfonamide, L-745, L-337, N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide, N-(2-cyclohexyloxy-4-nitrophenyl)methanesulfonamide or N-(methylsulfonyl)-2-(cyclohexyloxy)-4-nitroaniline; or a pharmaceutically acceptable salt thereof;

(3) barbiturate sedative, for example, amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobartital, secobarbital, talbutal, theamylal or thiopental or a pharmaceutically acceptable salt thereof;

(4) benzodiazepine having a sedative action, for example, chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam or a pharmaceutically acceptable salt thereof;

(5) H1 antagonist having a sedative action, for example, diphenhydramine, pyhlamine, promethazine, chlorpheniramine or chlorcyclizine or a pharmaceutically acceptable salt thereof;

(6) sedative, for example, loxoprofen sodium, acetaminophen, acetylsalicylic acid, glutethimide, meprobamate, methaqualone or dichloralphenazone or a pharmaceutically acceptable salt thereof;

(7) skeletal muscle relaxant, for example, baclofen, cahsoprodol, chlorzoxazone, cyclobenzaphne, methocarbamol or orphrenadine or a pharmaceutically acceptable salt thereof;

(8) NMDA receptor antagonist, for example, dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinone or cis-4-(phosphonomethyl)-2-pipehdinecarboxylic acid or a pharmaceutically acceptable salt thereof;

(9) α-adrenergic, for example, doxazosin, tamsulosin, clonidine or 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyhdyl) quinazoline;

(10) tricyclic antidepressant, for example, desipramine,

imipramine, clomipramine, doxepin, amythptiline or nortriptiline;

(11) anticonvulsant, for example, carbamazepine, lamotrigine or valproate;

(12) tachykinin (NK) antagonist (particularly an NK-3, NK-2 or NK-1 antagonist), for example, 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(thfluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-thazol-3-one, lanepitant, dapitant or 3-[[2-methoxy-5-(thfluoromethoxy)phenyl]methylamino]-2-phenyl-piperidine (2S,3S);

(13) muscarinic antagonist, for example, oxybutin, tolterodine, propiverine, tropsium chloride or darifenacin;

(14) COX-2 inhibitor, for example, celecoxib, rofecoxib or valdecoxib;

(15) non-selective COX inhibitor (preferably, having a protective effect on the gastrointestinal tract), for example, nitroflurbiprofen;

(16) coal-tar analgesic, particularly paracetamol;

(17) neuroleptic, for example, droperidol;

(18) vanilloid receptor agonist (e.g., resinferatoxin) or antagonist (e.g., capsazepine);

(19) β-adrenergic, for example, propranolol;

(20) local anaesthetic, for example, mexiletine、tocainide or lidocaine;

(21) corticosteriod, for example, dexamethasone or prednisone;

(22) serotonin receptor agonist or antagonist;

(23) cholinergic (nicotinic) analgesic;

(24) tramadol hydrochloride;

(25) PDEV inhibitor, such as sildenafil, vardenafil or taladafil;

(26) α-2-δ ligand, for example, gabapentin or pregabalin;

(27) canabinoid; and

(28) antidepressant (e.g., amitriptyline, trazodone, duloxetine, milnacipran, fluoxetine, paroxetine, sertraline、

citalopram and imipramine), anticonvulsant (e.g., phenytoin or carbamazepine), narcotic drug (e.g., methadone, tramadol) , Chinese herbal medicine (e.g., gosha-jinki-gan, shakuyaku-kanzoh-toh) and vitamin.

[0213]

For combined use, the administration time of the compound of the present invention and the concomitant drug is not restricted, and the compound of the present invention or the concomitant drug can be administered to an administration subject simultaneously, or may be administered at different times. The dosage of the concomitant drug may be determined according to the dose clinically used, and can be appropriately selected depending on an administration subject, administration route, disease, combination and the like.

The administration form of the combined use is not particularly limited, and the compound of the present invention and a concomitant drug only need to be combined on administration. Examples of such administration mode include the following:

(1) administration of a single preparation obtained by simultaneously processing the compound of the present invention and the concomitant drug, (2) simultaneous administration of two kinds of preparations of the compound of the present invention and the concomitant drug, which have been separately produced, by the same administration route, (3) administration of two kinds of preparations of the compound of the present invention and the concomitant drug, which have been separately produced, by the same administration route in a staggered manner, (4) simultaneous administration of two kinds of preparations of the compound of the present invention and the concomitant drug, which have been separately produced, by different administration routes, (5) administration of two kinds of preparations of the compound of the present invention and the concomitant drug, which have been separately produced, by different

administration routes in a staggered manner (e.g., administration in the order of the compound of the present invention and the concomitant drug, or in the reverse order) and the like.

The mixing ratio of the compound of the present invention and a concomitant drug in the combination agent of the present invention can be appropriately selected based on the subject of administration, administration route, disease and the like.

For example, while the content of the compound of the present invention in the combination agent of the present invention varies depending on the preparation form, it is generally about 0.01 - 100 wt%, preferably about 0.1 - 50 wt%, more preferably about 0.5 - 20 wt%, of the whole preparation.

[0214]

The content of the concomitant drug in the combination agent of the present invention varies depending on the preparation form, and generally about 0.01 to 100% by weight, preferably about 0.1 to 50% by weight, further preferably about 0.5 to 20% by weight, of the entire preparation.

While the content of the additive such as a carrier and the like in the combination agent of the present invention varies depending on the form of a preparation, it is generally about 1 to 99.99% by weight, preferably about 10 to 90% by weight, based on the preparation.

When the compound of the present invention and the concomitant drug are separately prepared, the same content may be adopted.

The dose of the combination agent varies depending on the kind of the compound of the present invention, administration route, symptom, age of patients and the like. For example, for oral administration to patients (body weight about 60 kg) with inflammatory bowel disease (IBD), about 0.1 mg/kg body weight - about 30 mg/kg body weight, preferably about 1 mg/kg body weight - 20 mg/kg body weight, of compound (I) can be administered once to several portions per day.

The dose of the pharmaceutical composition of the present invention as a sustained-release preparation varies depending on the kind and content of compound (I), dosage form, period of sustained drug release, subject animal of administration (e.g., mammals such as mouse, rat, hamster, guinea pig, rabbit, cat, dog, bovine, horse, swine, sheep, monkey, human etc.), and administration object. For example, for application by parenteral administration, about 0.1 to about 100 mg of compound (I) needs to be released from the administered preparation per 1 week.

[0215]

Any amount of the concomitant drug can be adopted as long as the side effects do not cause a problem. The daily dosage in terms of the concomitant drug varies depending on the severity, age, sex, body weight, sensitivity difference of the subject, administration period, interval, and nature, pharmacology, kind of the pharmaceutical preparation, kind of effective ingredient, and the like, and not particularly restricted, and the amount of a drug is, in the case of oral administration for example, generally about 0.001 to 2000 mg, preferably about 0.01 to 500 mg, further preferably about 0.1 to 100 mg, per 1 kg of a mammal and this is generally administered once to 4-times, divided in a day.

When the combination agent of the present invention is administered, the compound of the present invention and the concomitant drug can be administered simultaneously, or may be administered in a staggered manner. When administered at a time interval, the interval varies depending on the effective ingredient, dosage form and administration method, and, for example, when the concomitant drug is administered first, a method in which the compound of the present invention is administered within time range of from 1 minute to 3 days, preferably from 10 minutes to 1 day, more preferably from 15 minutes to 1 hour, after administration of the concomitant drug is an example. When the compound of the present invention

is administered first, a method in which the concomitant drug is administered within time range of from 1 minute to 1 day, preferably from 10 minutes to 6 hours, more preferably from 15 minutes to 1 hour after administration of the compound of the present invention is an example.

Examples

[0216]

The present invention is explained in detail in the following by referring to Preparations, Examples, Experimental Examples and Formulation Examples, which are not to be construed as limitative, and the invention may be changed within the scope of the present invention.

[0217]

In the following Examples, the "room temperature" generally means about 10°C to about 35°C. The ratios indicated for mixed solvents are volume mixing ratios, unless otherwise specified. % means wt%, unless otherwise specified.

[0218]

In silica gel column chromatography, basic silica gel means use of aminopropylsilane-bound silica gel. In HPLC (high performance liquid chromatography), C18 means use of octadecyl-bound silica gel. The ratios of elution solvents are volume mixing ratios, unless otherwise specified.

[0219]

^{1}H NMR (proton nuclear magnetic resonance spectrum) was measured by Fourier-transform type NMR. For the analysis, ACD/SpecManager (trade name) and the like were used. Peaks with very mild protons such as a hydroxy group, an amino group and the like are not described.

[0220]

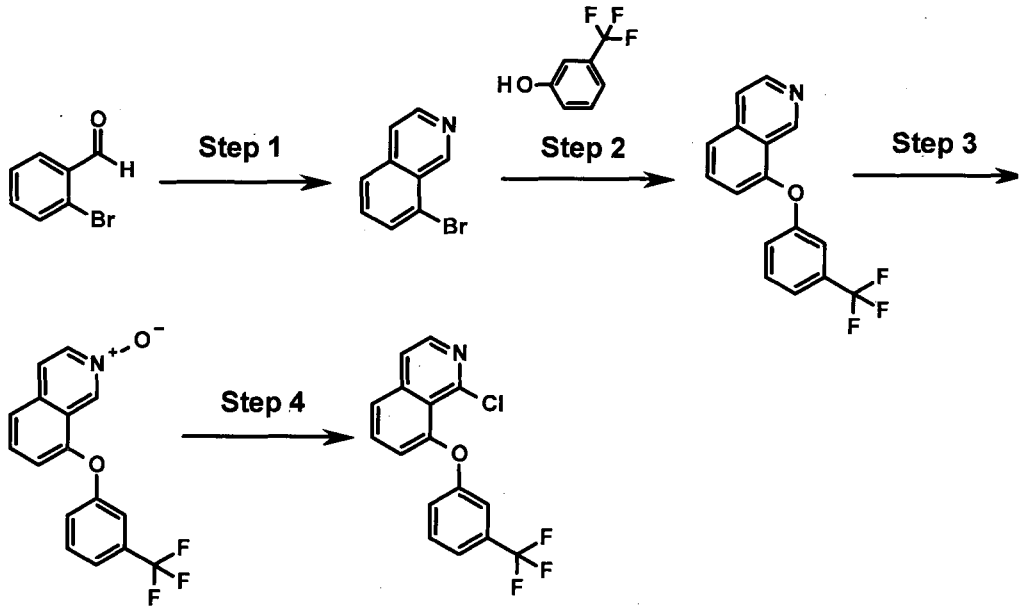
MS (mass spectrum) was measured by LC/MS (liquid chromatography mass spectrometer). As ionization method, ESI (Electro Spray Ionization) method or APCI (Atomospheric Pressure Chemical Ionization) method was used. The data indicates those found. Generally, a molecular ion peak is

observed. In the case of a salt, a molecular ion peak or fragment ion peak of free form is generally observed.

[0221]

Preparation 1: 1-Chloro-8-[3-(trifluoromethyl)phenoxy]isoquinoline

[0222]



[0223]

Step 1: 8-Bromoisoquinoline

A mixture of 2-bromobenzaldehyde (50 g, 270 mmol), aminoacetaldehyde dimethyl acetal (28.4 g, 270 mmol) and toluene (400 mL) was refluxed under argon. Dehydration was carried out using dean stark for 2.0 hours. After removal of calculated amount of water, the reflux was continued for 1.0 hour. The toluene was evaporated under reduced pressure, the residue was dissolved in dichloromethane (600 mL), and the solution was cooled to 0°C. To the cooled solution was slowly added aluminium chloride (118.9 g, 891.7 mmol) under argon. The reaction mixture was stirred at 45°C for 2.0 hours. After the completion of the reaction was confirmed by TLC, the mixture was cooled to room temperature and slowly poured into an ice water. The mixture was basified with 10% sodium hydroxide solution, and the dichloromethane layer was separated. The aqueous layer was re-extracted with

dichloromethane (2 x 100 mL). The combined dichloromethane layers were washed with brine, and dried over sodium sulfate. The dichloromethane was evaporated, and the residue was purified by silica gel (100-200 mesh) column chromatography with 8-12% ethyl acetate in hexane as a mobile phase to give the title compound as an off-white solid (28 g, 49.8%). MS(ESI)m/z: 208 [M (^{79}Br)+1] ,210 [M (^{81}Br)+1]; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.17 (t, *J* = 7.8 Hz, 1H); 7.91 (d, *J* = 6.0 Hz, 1H); 8.02 (d, *J* = 8.4 Hz, 1H); 8.05 (d, *J* = 8.8 Hz, 1H); 8.65 (d, *J* = 5.2 Hz, 1H) 9.48 (s, 1H).

[0224]

Step 2: 8-[3-(Trifluoromethyl)phenoxy]isoquinoline

A mixture of 8-bromoisoquinoline (1.0 g, 4.8 mmol), 3-trifluoromethylphenol (1.55 g, 9.6 mmol), cesium carbonate (3.9 g, 12 mmol) and dimethylsulfoxide (10 mL) was degassed with argon for 30 min, and to the mixture were added copper(I) iodide (0.91 g, 4.8 mmol), copper powder (0.30 g, 4.8 mmol) and 2,2,6,6-tetramethyl-3,5-heptanedione (0.49 mL, 2.5 mmol). Degassing was continued for additional 20 min. The resulting mixture was heated at 100°C for 4 hours under argon atmosphere. The reaction mixture was cooled to room temperature, and to the mixture were added water (50 mL) followed by 10% aqueous sodium hydroxide solution (50 mL). The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water (25 mL) and brine (50 mL), and dried over sodium sulfate. The organic layer was concentrated under vacuum, and the residue was purified by combiflash with 8-12% ethyl acetate in hexane as a mobile phase to give the title compound as an off-white solid (0.65 g., 47%). MS(ESI)m/z: 290.1 (M+1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, *J* = 7.2 Hz, 1H); 7.45 (dd, *J* = 1.6 & 7.6 Hz, 1H);7,56-7.60 (m, 2H); 7.66-7.70 (m, 1H); 7.73-7.81 (m, 2H); 7.92 (d, *J* = 5.6 Hz, 1H); 8.61 (bs, 1H) 9.51 (bs, 1H).

[0225]

Step 3: 8-[3-(Trifluoromethyl)phenoxy]isoquinoline *N*-oxide

To a solution of 8-[3-(trifluoromethyl)phenoxy]isoquinoline (0.65 g, 2.24 mmol) in dichloromethane (25 mL) was added 3-chloroperbenzoic acid (0.969 g, 3.37 mmol) at 0°C. The mixture was stirred at room temperature overnight (for 18 hours). After the completion of the reaction was confirmed by TLC, aqueous saturated sodium bicarbonate solution (25 mL) was added thereto, and the stirring was continued for 2.0 hours. The dichloromethane layer was separated, and the aqueous layer was re-extracted with dichloromethane (2 x 25 mL). The combined organic layers were washed with brine, and dried over sodium sulfate. The organic layer was concentrated under vacuo, and the obtained crude product was used in the next step without further purification. MS(ESI)m/z: 306.1 (M+1).

[0226]

Step 4: 1-Chloro-8-[3-(trifluoromethyl)phenoxy]isoquinoline

A mixture of 8-[3-(trifluoromethyl)phenoxy]isoquinoline *N*-oxide (0.60 g, 1.96 mmol) and phosphorous oxychloride (6 mL) was heated at 100°C for 5 hours. After the completion of the reaction by TLC, the phosphorous oxychloride was evaporated, and the obtained residue was dissolved in ethyl acetate. The ethyl acetate layer was washed with saturated sodium bicarbonate and water brine, and dried over sodium sulfate. The ethyl acetate layer was concentrated, and the obtained residue was purified on combiflash with 6-8% ethyl acetate in hexane as a mobile phase to give the title compound as an off-white solid (0.5 g, 79%). MS(ESI)m/z: 324.1, [M(^{35}Cl)+1] 326.1 [M(^{37}Cl)+1]; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.23 (dd, *J* = 2.4 & 8.4 Hz, 1H); 7.34 (s, 1H); 7.41 (d, *J* = 7.6 Hz, 1H); 7.50 (d, J = 7.6, 1H); 7.62 (t, *J* = 8.0 Hz, 1H); 7.88 (t, *J* = 8.0 Hz, 1H); 7.98-8.00 (m, 2H); 8.36 (d, *J* = 5.6 Hz, 1H)

[0227]

Preparations 2 to 22:

The compounds of Preparations 2 to 22 were synthesized in analogous manner to that of preparation 1.

[0228]

Table 1

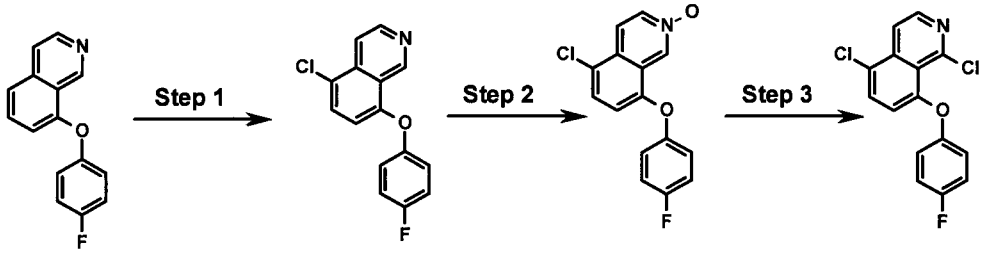
Prep. No.	IUPAC Name	MS(EI)m/z: (M+1)
2	1-Chloro-8-(4-fluorophenoxy)isoquinoline	274.0 (^{35}Cl), 276.0 (^{37}Cl)
3	1-Chloro-8-(3-fluorophenoxy)isoquinoline	274.1 (^{35}Cl), 276.0 (^{37}Cl)
4	1-Chloro-8-[4-(trifluoromethyl)phenoxy]isoquinoline	324.1 (^{35}Cl), 326.1 (^{37}Cl)
5	1-Chloro-8-[3-(trifluoromethoxy)phenoxy]isoquinoline	340.1 (^{35}Cl), 342.1 (^{37}Cl)
6	1-Chloro-8-(4-chlorophenoxy)isoquinoline	290.0 (^{35}Cl), 292.0 (^{37}Cl)
7	1-Chloro-8-(3-chlorophenoxy)isoquinoline	290.0 (^{35}Cl), 292.1 (^{37}Cl)
8	1-Chloro-8-[4-(trifluoromethoxy)phenoxy]isoquinoline	340.1 (^{35}Cl), 342.1 (^{37}Cl)
9	1-Chloro-8-(4-methylphenoxy)isoquinoline	270.1 (^{35}Cl), 272.1 (^{37}Cl)
10	1-Chloro-8-(3-methylphenoxy)isoquinoline	270.1 (^{35}Cl), 272.1 (^{37}Cl)
11	1-Chloro-8-(4-methoxyphenoxy)isoquinoline	286.1 (^{35}Cl), 288.1 (^{37}Cl)
12	1-Chloro-8-(3-methoxyphenoxy)isoquinoline	286.1 (^{35}Cl), 288.1 (^{37}Cl)
13	4-[(1-Chloro-8-isoquinolyl)oxy]benzonitrile	281.1 (^{35}Cl), 283.1 (^{37}Cl)
14	1-Chloro-8-(2,3-difluorophenoxy)isoquinoline	291.8 (^{35}Cl), 293.8 (^{37}Cl)
15	1-Chloro-8-(2,4-difluorophenoxy)isoquinoline	291.8 (^{35}Cl), 293.8 (^{37}Cl)
16	1-Chloro-8-(3,4-difluorophenoxy)isoquinoline	291.8 (^{35}Cl), 293.8 (^{37}Cl)

17	1-Chloro-8-(3,5-difluorophenoxy)isoquinoline	291.8 (^{35}Cl), 293.8 (^{37}Cl)
18	1-Chloro-8-(2-fluorophenoxy)isoquinoline	291.8 (^{35}Cl), 293.8 (^{37}Cl)
19	1-Chloro-8-(2-chlorophenoxy)isoquinoline	289.8 (^{35}Cl), 291.8 (^{37}Cl)
20	1-Chloro-8-[4-fluoro-3-(trifluoromethyl)phenoxy]isoquinoline	341.8 (^{35}Cl), 343.8 (^{37}Cl)
21	1-Chloro-8-(3,4-dichlorophenoxy)isoquinoline	325.7 (^{35}Cl), 327.7 (^{37}Cl)
22	1-Chloro-8-[(5-chloro-3-pyridyl)oxy]isoquinoline	291.0 (^{35}Cl), 293.0 (^{37}Cl)

[0229]

Preparation 23: 1,5-Dichloro-8-(4-fluorophenoxy)isoquinoline

[0230]



[0231]

Step 1: 5-Chloro-8-(4-fluorophenoxy)isoquinoline

N-Chlorosuccinimide (0.67 g, 2.0 mmol) was added in portion wise to a solution of 8-(4-fluorophenoxy)isoquinoline (0.6 g, 2.5 mmol) in sulfuric acid (3 mL) at 0°C. The reaction mixture was then warmed to room temperature and stirred at for 2 hours. After the completion of the reaction was confirmed by TLC, the reaction mixture was cooled to 0°C and quenched with ice cold water, and the precipitate thus obtained was collected by filtration and washed with cold n-hexane to give the title compound (0.5 g, 73%). MS(EI)m/z: 274.1[M(^{35}Cl)+1], 276.1 [M(^{37}Cl)+1]; ^{1}H NMR DMSO-*d6*: δ 6.83 (d, *J* = 8.0 Hz, 1H); 7.35-7.43 (m, 2H); 7.53-7.57 (m, 1H); 7.75-7.78 (m, 1H); 7.96 (d, *J* = 8.0 Hz, 1H); 8.20 (d, *J* = 6.4 Hz, 1H); 8.82 (d, *J* = 6.0 Hz, 1H), 9.3 (s, 1H).

[0232]

Step 2: 5-Chloro-8-(4-fluorophenoxy)-isoquinoline *N*-oxide

To a solution of 5-chloro-8-(4-fluorophenoxy)isoquinoline (0.4 g, 1.46 mmol) in dichloromethane (10 mL) was added 3-chloroperbenzoic acid (0.78 g, 2.93 mmol) at 0°C. The mixture was stirred at room temperature overnight (for 18 hours). After the completion of the reaction was confirmed by TLC, aqueous saturated sodium bicarbonate solution (15 mL) was added thereto, and the stirring was continued for 2.0 hours. The dichloromethane layer was separated, and the aqueous layer was re-extracted with dichloromethane (2 x 25 mL). The combined organic layers were washed with brine, and dried over sodium sulfate. The organic layer was concentrated under vacuo, and the obtained crude product was used in the next reaction without further purification.

[0233]

Step 3: 1,5-Dichloro-8-(4-fluorophenoxy)isoquinoline

A mixture of 5-chloro-8-(4-fluorophenoxy)-isoquinoline *N*-oxide and phosphorous oxychloride (10 mL) was heated at 100°C for 16 hours. After the completion of the reaction was confirmed by TLC, the phosphorous oxychloride was evaporated, and the obtained residue was dissolved in ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, water and brine, and dried over sodium sulfate. The organic layer was concentrated, and the obtained residue was purified on combiflash with 2-6% ethyl acetate in hexane as a mobile phase to give the title compound as an off-white solid (0.435 g, 95% in two steps). MS(ESI)m/z: 308.0[M(^{35}Cl)+1] ,310.0 [M(^{37}Cl)+1].

[0234]

Preparation 24:

The compound of Preparation 24 was synthesized in analogous manner to that of preparation 23.

[0235]

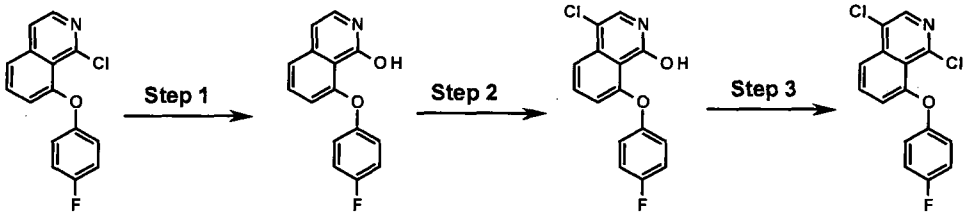
Table 2

Prep. No.	IUPAC Name	MS(EI)m/z: (M+1)
24	1,5-Dichloro-8-[3-(trifluoromethyl)phenoxy]isoquinoline	357.7 (^{35}Cl), 359.7 (^{37}Cl)

[0236]

Preparation 25: 1,4-Dichloro-8-(4-fluorophenoxy)isoquinoline

[0237]



[0238]

Step 1: 8-(4-Fluorophenoxy)isoquinolin-1-ol

A mixture of 1-chloro-8-(4-fluorophenoxy)isoquinoline (0.5 g, 1.82 mmol) and sodium acetate (1.4 g, 18.2 mmol) in acetic acid (15 mL) was heated at 100°C for 4 hours. After the completion of the reaction was confirmed by TLC, the reaction mixture was poured into ice cold water, and the solid thus obtained was collected by filtration, washed with water and n-hexane, and dried to give the title compound as a pale-brownish solid (0.430g, 92%). MS(ESI)m/z: 255.9 (M+1); ^{1}H NMR DMSO-d_6: δ 6.51 (d, J = 7.2 Hz, 1H); 6.85-6.91 (m, 3H); 7.12-7.17 (m, 3H); 7.44 (d, J = 8.0 Hz, 1H); 7.63 (t, J = 8.0 Hz, 1H); 11.0 (bs, 1H).

[0239]

Step 2: 4-Chloro-8-(4-fluorophenoxy)isoquinolin-1-ol

N-Chlorosuccinimide (0.22 g, 1.66 mmol) was added in portion wise to a solution of 8-(4-fluorophenoxy)isoquinolin-1-ol (0.42 g, 1.66 mmol) in N,N-dimethylacetamide (15 mL) at 0°C. The reaction mixture was warmed to room temperature and stirred at 30-35°C for 3 hours. After the completion of the reaction was confirmed by TLC, the reaction mixture was cooled to 0°C and quenched with ice cold water, and the precipitate thus obtained was collected by filtration and washed with cold

solution of n-hexane to give the title compound (0.4 g, 83%). MS(ESI)m/z: 289.8[M(^{35}Cl)+1], 291.8 [M(^{37}Cl)+1]; ^{1}H NMR DMSO-d_6: δ 6.89-6.93 (m, 2H); 7.05 (d, J = 8.4 Hz, 1H); 7.14-7.18 (m, 2H); 7.48 (d, J = 5.2 Hz, 1H); 7.63 (d, J = 8.4 Hz, 1H); 7.81 (t, J = 8.4 Hz, 1H); 11.32 (bs, 1H).

[0240]

Step 3: 1,4-Dichloro-8-(4-fluorophenoxy)isoquinoline

A mixture of 4-chloro-8-(4-fluorophenoxy)isoquinolin-1-ol (0.4 g, 1.38 mmol) and phosphorous oxychloride (8 mL) was refluxed for 16 hours. After the completion of the reaction mixture was confirmed by TLC, the reaction mixture was cooled to room temperature, and concentrated. The residue was diluted with aqueous sodium bicarbonate solution (20 mL), and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with water and brine, and dried over sodium sulfate. The organic layer was concentrated, and the obtained crude product was purified by silica gel (100-200 mesh) column chromatography with 2-4% ethyl acetate in hexane as a mobile phase to give the title compound as an off-white solid (0.3 g, 70%). MS(ESI)m/z: 307.8 [M(^{35}Cl)+1], 309.7 [M(^{37}Cl)+1]; ^{1}H NMR DMSO-d_6: δ 6.98-7.03 (m, 2H); 7.08-7.28 (m, 3H); 7.73 (d, J = 7.6 Hz, 1H); 8.02 (dd, J = 1.2, 8.4 Hz, 1H); 8.37 (s, 1H).

[0241]

Preparations 26 and 27:

The compounds of Preparations 26 and 27 were synthesized in analogous manner to that of preparation 25.

[0242]

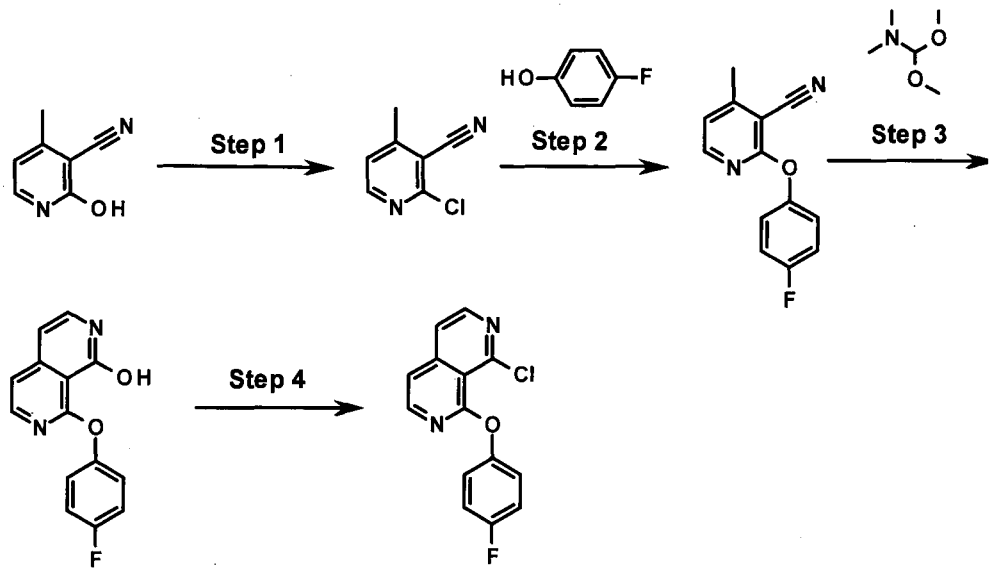
Table 3

Prep. No.	IUPAC Name	MS(EI)m/z: (M+1)
26	1,4-Dichloro-8-(3-fluorophenoxy)isoquinoline	307.8 (^{35}Cl), 309.8 (^{37}Cl)
27	1,4-Dichloro-8-[3-(trifluoromethyl)phenoxy]isoquinoline	357.7 (^{35}Cl), 359.7 (^{37}Cl)

[0243]

Preparation 28: 1-Chloro-8-(4-fluorophenoxy)-2,7-naphthyridine

[0244]



[0245]

Step 1: 2-Chloro-4-methylpyridine-3-carbonitrile

A mixture of 2-hydroxy-4-methylpyridine-3-carbonitrile (3.0 g, 22.38 mmol; obtained as described in WO 2011/088201), phosphoryl chloride (6.26 mL, 67.16 mmol) and phosphorus pentachloride (1.4 g, 6.71 mmol) was refluxed for 2 hours. The reaction mixture was cooled to room temperature, and then concentrated under vacuo to dryness. The obtained residue was diluted with aqueous sodium bicarbonate solution. The precipitate thus obtained was collected by filtration and dried to give the title compound as an off-white solid (3.0 g, 88%). MS(ESI)m/z: 153.1 (M+1); ^{1}H NMR $CDCl_3$: δ 8.43 (d, J = 5.2 Hz, 1H), 7.22 (d, J = 4.8 Hz, 1H), 2.8 (s, 3H).

[0246]

Step 2: 2-(4-Fluorophenoxy)-4-methylpyridine-3-carbonitrile

To a mixture of 2-chloro-4-methylpyridine-3-carbonitrile (1.0 g, 6.57 mmol) and 4-fluorophenol (0.81 g, 7.23 mmol) in N,N-dimethylformamide (10 mL) was added potassium carbonate (1.8 g, 13.15 mmol). The reaction mixture was heated at 80°C for 12 hours, then cooled to room temperature, and poured into ice cold water to obtain precipitate. The precipitate was

collected by filtration and dried to give the title compound as a white solid (1.2 g, 80%). MS(ESI)m/z: 228.9 (M+1); ^{1}H NMR DMSO-d_6: δ 2.54 (s, 3H); 7.24 (d, J = 5.6 Hz, 1H); 7.27-7.29 (m, 4H); 8.21 (d, J = 5.2 Hz, 1H).

[0247]

Step 3: 8-(4-Fluorophenoxy)-2,7-naphthyridin-1-ol

A mixture of 2-(4-fluorophenoxy)-4-methylpyridine-3-carbonitrile (1.2 g, 5.26 mmol), N,N-dimethylformamide dimethyl acetal (0.7 mL, 5.26 mmol) and DMF (15 mL) was refluxed for 12 hours. After the disappearance of the starting material was confirmed by TLC, the reaction mixture was cooled to room temperature and concentrated to dryness. To the residue were added acetic acid (5 mL) and sulfuric acid (5 mL), and the mixture was heated to 50°C for 2 hours. The reaction mixture was cooled to room temperature, and poured into an ice cold solution of aqueous sodium bicarbonate to obtain precipitate. The precipitate was collected by filtration, and washed with n-hexane to give the title compound as a white powder (1.2 g 89% yield). MS(ESI)m/z: 256.9 (M+1); ^{1}H NMR DMSO-d_6: δ 6.48 (d, J = 6.8 Hz, 1H), 7.10-7.20 (m, 2H), 7.21-7.31 (m, 3H), 7.43 (t, J = 6.4 Hz, 1H), 8.07 (d, J = 6.0 Hz, 1H), 11.5 (bs, 1H).

[0248]

Step 4: 1-Chloro-8-(4-fluorophenoxy)-2,7-naphthyridine

A mixture of 8-(4-fluorophenoxy)-2,7-naphthyridin-1-ol (400 mg, 1.56 mmol) and phosphoryl chloride (4 mL, 15.85 mmol) was heated at 130°C for 20 min, cooled to room temperature and concentrated to dryness. The obtained crude product (0.4 g) was used in the next step without any purification. MS(ESI)m/z: (M+1) 274.9 [M(^{35}Cl)+1], 276.8 [M(^{37}Cl)+1]; ^{1}H NMR DMSO: δ 7.14-7.25 (m, 4H), 7.29 (d, J = 5.2 Hz, 1H), 7.53 (d, J = 5.6 Hz, 1H), 8.14 (d, J = 6.0 Hz, 1H), 8.46 (d, J = 6.0 Hz, 1H).

[0249]

Preparations 29 to 52:

The compounds of Preparations 29 to 52 were synthesized in analogous manner to that of preparation 28.

[0250]

Table 4

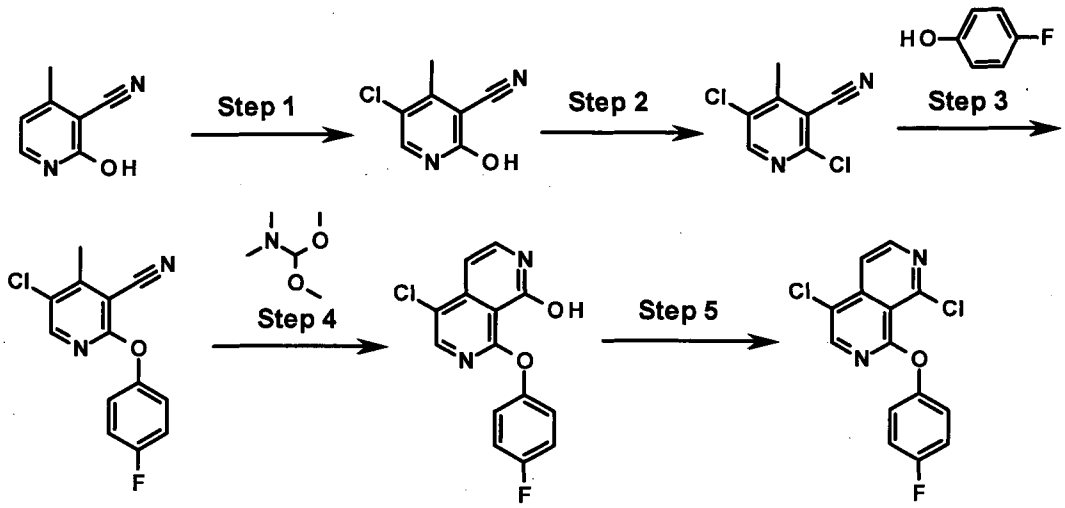
Prep. No.	IUPAC Name	MS(EI)m/z: (M+1)
29	1-Chloro-8-(3-fluorophenoxy)-2,7-naphthyridine	274.8 (^{35}Cl), 276.8 (^{37}Cl)
30	1-Chloro-8-[3-(trifluoromethyl)phenoxy]-2,7-naphthyridine	324.8 (^{35}Cl), 326.8 (^{37}Cl)
31	1-Chloro-8-(3-chlorophenoxy)-2,7-naphthyridine	291.0 (^{35}Cl), 293.0(^{37}Cl)
32	1-Chloro-8-(3,5-difluorophenoxy)-2,7-naphthyridine	293.0 (^{35}Cl), 295.0 (^{37}Cl)
33	1-Chloro-8-(2,5-difluorophenoxy)-2,7-naphthyridine	293.1 (^{35}Cl), 295.1 (^{37}Cl)
34	1-Chloro-8-(2,6-difluorophenoxy)-2,7-naphthyridine	293.0 (^{35}Cl), 295.0 (^{37}Cl)
35	1-Chloro-8-(2,4-difluorophenoxy)-2,7-naphthyridine	293.1 (^{35}Cl), 295.0 (^{37}Cl)
36	1-Chloro-8-(3,4-difluorophenoxy)-2,7-naphthyridine	293.0 (^{35}Cl), 295.0 (^{37}Cl)
37	1-Chloro-8-[2-fluoro-3-(trifluoromethyl)phenoxy]-2,7-naphthyridine	343.1 (^{35}Cl), 345.1 (^{37}Cl)
38	1-Chloro-8-[4-fluoro-3-(trifluoromethyl)phenoxy]-2,7-naphthyridine	343.0 (^{35}Cl), 345.0 (^{37}Cl)
39	1-Chloro-8-[4-fluoro-2-(trifluoromethyl)phenoxy]-2,7-naphthyridine	343.0 (^{35}Cl), 345.0 (^{37}Cl)
40	1-Chloro-8-[2-fluoro-5-(trifluoromethyl)phenoxy]-2,7-naphthyridine	343.0 (^{35}Cl), 345.0 (^{37}Cl)

41	1-Chloro-8-(2-fluoro-4-methoxy-phenoxy)-2,7-naphthyridine	305.1 (^{35}Cl), 307.1 (^{37}Cl)
42	1-Chloro-8-(4-fluoro-2-methoxy-phenoxy)-2,7-naphthyridine	305.1 (^{35}Cl), 307.0 (^{37}Cl)
43	1-Chloro-8-[2-chloro-3-(trifluoromethyl)phenoxy]-2,7-naphthyridine	359.0 (^{35}Cl), 361.0 (^{37}Cl
44	1-Chloro-8-(4-chloro-2-methoxy-phenoxy)-2,7-naphthyridine	321.0 (^{35}Cl), 323.0 (^{37}Cl)
45	1-Chloro-8-[4-(trifluoromethyl)phenoxy]-2,7-naphthyridine	325.0 (^{35}Cl), 327.0 (^{37}Cl)
46	1-Chloro-8-(4-chlorophenoxy)-2,7-naphthyridine	291.0 (^{35}Cl), 293.0(^{37}Cl)
47	1-Chloro-8-(4-fluoro-3-methyl-phenoxy)-2,7-naphthyridine	289.1 (^{35}Cl), 291.1(^{37}Cl)
48	1-Chloro-8-(2-chloro-4-fluoro-phenoxy)-2,7-naphthyridine	309.0 (^{35}Cl), 311.0 (^{37}Cl)
49	1-Chloro-8-(3-chloro-4-fluoro-phenoxy)-2,7-naphthyridine	309.0 (^{35}Cl), 311.0 (^{37}Cl)
50	1-Chloro-8-[3-(trifluoromethoxy)phenoxy]-2,7-naphthyridine	341.0 (^{35}Cl), 343.0 (^{37}Cl)
51	1-Chloro-8-[4-(trifluoromethoxy)phenoxy]-2,7-naphthyridine	341.1 (^{35}Cl), 343.1 (^{37}Cl)
52	1-Chloro-8-[(5-fluoro-3-pyridyl)oxy]-2,7-naphthyridine	276.0 (^{35}Cl), 278.1 (^{37}Cl)

[0251]

Preparation 53: 4,8-Dichloro-1-(4-fluorophenoxy)-2,7-naphthyridine

[0252]



[0253]

Step 1: 5-Chloro-2-hydroxy-4-methylpyridine-3-carbonitrile

To a mixture of 2-hydroxy-4-methylpyridine-3-carbonitrile (2.5 g, 18.6 mmol) in N,N-dimethylacetamide (1 mL) was added *N*-chlorosuccinimide (2.48 g, 18.65 mmol) in portion wise at 0°C under nitrogen. The reaction mixture was stirred at 30-35°C for 3 hours. The reaction mixture was cooled to room temperature, and then poured into ice cold water, and the solid was collected by filtration. The solid was washed with n-hexane to give the title compound as an off-white solid (2.0 g, 64%). MS(ESI)m/z: (M+1) 168.9 [M(^{35}Cl)+1], 170.9 [M(^{37}Cl)+1]; ^{1}H NMR DMSO-d_6: δ 2.4 (s, 3H), 8.02 (s, 1H), 12.78 (bs, 1H).

[0254]

Step 2: 2,5-Dichloro-4-methylpyridine-3-carbonitrile

A mixture of 5-chloro-2-hydroxy-4-methylpyridine-3-carbonitrile (2.0 g, 11.9 mmol), phosphoryl chloride (3.33 mL, 35.71 mmol) and phosphorus pentachloride (0.74 g, 3.57 mmol) was refluxed for 1 hour. The reaction mixture was cooled to room temperature and then concentrated to dryness. The obtained residue was diluted with aqueous sodium bicarbonate solution. The precipitate thus obtained was collected by filtration, and dried to give the title compound as an off-white solid (1.8 g, 81%). MS(ESI)m/z: 186.9 [M(^{35}Cl)+1], 188.9 [M(^{37}Cl)+1]; ^{1}H NMR $CDCl_3$: δ 2.8 (s, 3H), 8.48 (s, 1H).

[0255]

Step 3: 5-Chloro-2-(4-fluorophenoxy)-4-methylpyridine-3-carbonitrile

To a mixture of 2,5-dichloro-4-methylpyridine-3-carbonitrile (1.3 g, 6.95 mmol) and 4-fluorophenol (0.85 g, 7.64 mmol) in N,N-dimethylformamide (15 mL) was added potassium carbonate (1.9 g, 13.9 mmol). The reaction mixture was heated at 80°C for 16 hours, cooled to room temperature, and poured into an ice cold water to obtain precipitate. The precipitate was collected by filtration, and dried to give the title compound as a white solid (1.2 g, 67%). MS(ESI)m/z: 262.8 (M+1); ^{1}H NMR $CDCl_3$: δ 2.6 (s, 3H), 7.07-7.15 (m, 4H), 8.17 (s, 1H)

[0256]

Step 4: 5-Chloro-8-(4-fluorophenoxy)-2,7-naphthyridin-1-ol

A mixture of 5-chloro-2-(4-fluorophenoxy)-4-methylpyridine-3-carbonitrile (1.2 g, 4.56 mmol) and N,N-dimethylformamide dimethyl acetal (0.6 ml, 4.56 mmol) in DMF (12 mL) was refluxed for 12 hours. After the disappearance of the starting material was confirmed by TLC, the reaction mixture was cooled to room temperature and concentrated to dryness. To the residue were added acetic acid (6 mL) and sulfuric acid (6 mL), and the mixture was heated to 50°C for 2 hours. The reaction mixture was cooled to room temperature, and poured into an ice cold solution of aq. sodium bicarbonate to obtain precipitate. The precipitate was collected by filtration to give the title compound as a white powder (1.0 g, 76%). MS(ESI)m/z: 290.8 [M(^{35}Cl)+1], 292.8 [M(^{37}Cl)+1]; ^{1}H NMR DMSO-*d6*: δ 6.59 (d, *J* = 7.2 Hz, 1H), 7.16-7.21 (m, 2H), 7.22-7.30 (m, 2H), 7.63 (t, *J* = 6.8 Hz, 1H), 8.25 (s, 1H), 11.8 (bs, 1H).

[0257]

Step 5: 4,8-Dichloro-1-(4-fluorophenoxy)-2,7-naphthyridine

A mixture of 5-chloro-8-(4-fluorophenoxy)-2,7-naphthyridin-1-ol (0.7 g, 2.40 mmol) and phosphoryl chloride

(14 mL) was heated at 130°C for 1 hour. The reaction mixture was cooled to room temperature and concentrated to dryness. The obtained residue was diluted with sodium bicarbonate solution (20 mL), and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuo to give a crude product. The crude product was purified by silica gel (100-200 mesh size) column chromatography using 2% ethyl acetate in hexane as mobile phase to give the title compound (0.5 g, 67%). MS(ESI)m/z: 308.7 [M(^{35}Cl)+1], 310.8 [M(^{37}Cl)+1]; ^{1}H NMR $CDCl_3$: δ 7.1-7.25 (m, 4H), 7.92 (d, *J* = 6 Hz, 1H), 8.19 (s, 1H), 8.60 (d, *J* = 6 Hz, 1H).

[0258]

Preparations 54 and 55:

The compounds of Preparations 54 and 55 were synthesized in analogous manner to that of preparation 53.

[0259]

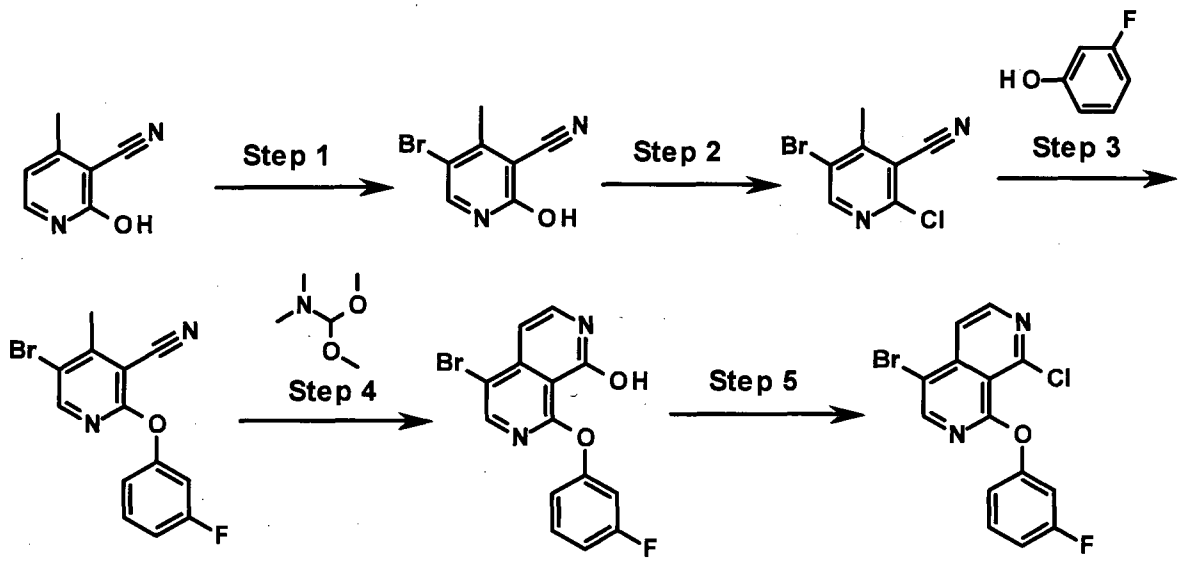
Table 5

Prep. No.	IUPAC Name	MS(EI)m/z: (M+1)
54	4,8-Dichloro-1-(3-fluorophenoxy)-2,7-naphthyridine	309.1 (^{35}Cl), 311.0 (^{37}Cl)
55	4,8-Dichloro-1-[4-(trifluoromethyl)phenoxy]-2,7-naphthyridine	359.3 (^{35}Cl), 361.1 (^{37}Cl)

[0260]

Preparation 56: 4-Bromo-8-chloro-1-(3-fluorophenoxy)-2,7-naphthyridine

[0261]



[0262]

Step 1: 5-Bromo-2-hydroxy-4-methylpyridine-3-carbonitrile

To a mixture of 2-hydroxy-4-methylpyridine-3-carbonitrile (2.20 g, 16.40 mmol) in N,N-dimethylacetamide (22.0 mL) was added *N*-bromosuccinimide (3.21 g, 18.04 mmol) in portion wise at 0°C under nitrogen. The reaction mixture was stirred at 40°C for 2 hours. The reaction mixture was cooled to room temperature, and then poured into ice cold water, and the solid was collected by filtration. The solid was washed with n-hexane to give the title compound as an off-white solid (2.7 g, 77%). MS(ESI)m/z: (M+1) 212.9 [M(^{79}Br)+1], 214.9 [M(^{81}Br)+1]; ^{1}H NMR DMSO-d_6: δ 2.42 (s, 3H), 8.08 (s, 1H), 12.78 (br s, 1H).

[0263]

Step 2: 5-Bromo-2-chloro-4-methyl-pyridine-3-carbonitrile

A mixture of 5-bromo-2-hydroxy-4-methylpyridine-3-carbonitrile (2.0 g, 9.38 mmol), phosphoryl chloride (2.62 mL 28.16 mmol) and phosphorus pentachloride (0.58 g, 2.81 mmol) was refluxed for 2 hour. The reaction mixture was cooled to room temperature and then concentrated to dryness. The obtained residue was diluted with aqueous sodium bicarbonate solution. The precipitate thus obtained was collected by filtration, and dried to give the title compound as an off-

white solid (2.0 g, 92%). MS(ESI)m/z: 230.9 [M(^{79}Br)+1], 232.9 [M(^{81}Br)+1]; ^{1}H NMR DMSO-d_6: δ 2.59 (s, 3H), 8.82 (s, 1H)

[0264]

Step 3: 5-Bromo-2-(3-fluorophenoxy)-4-methyl-pyridine-3-carbonitrile

To a mixture of 5-bromo-2-chloro-4-methyl-pyridine-3-carbonitrile (2.0 g, 8.64 mmol) and 3-fluorophenol (1.18 mL, 12.9 mmol) in N,N-dimethylformamide (20 mL) was added potassium carbonate (2.38 g, 17.2 mmol). The reaction mixture was heated at 100°C for 16 hours, cooled to room temperature, and poured into an ice cold water, and the mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuo to give a crude product. The crude product was purified by silica gel (100-200 mesh size) column chromatography using 5% ethyl acetate in hexane as mobile phase to give the title compound (2.0 g, 75%). MS(ESI)m/z: 307.0 [M(^{79}Br)+1], 309.0 [M(^{81}Br)+1]; ^{1}H NMR $CDCl_3$: δ 2.63 (s, 3H), 6.91-7.02 (m, 3H)7.36-7.42 (m, 1H), 8.32 (s, 1H).

[0265]

Step 4: 5-Bromo-8-(3-fluorophenoxy)-2,7-naphthyridin-1-ol

A mixture of 5-bromo-2-(3-fluorophenoxy)-4-methyl-pyridine-3-carbonitrile (2.4g, 7.81 mmol) and N,N-dimethylformamide dimethyl acetal (3.12 ml, 23.44 mmol) in DMF (15 mL) was refluxed for 12 hours. After the disappearance of the starting material was confirmed by TLC, the reaction mixture was cooled to room temperature and concentrated to dryness. To the residue were added acetic acid (7.8 mL) and sulfuric acid (7.8 mL), and the mixture was heated to 50°C for 2 hours. The reaction mixture was cooled to room temperature, and poured into an ice cold solution of aq. sodium bicarbonate, and the mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuo to give a crude product. The crude product was as such used for next reaction

(2.2 g, 75%). MS(ESI)m/z: 334.9. [M(^{79}Br)+1], 337.0 [M(^{81}Br)+1].

[0266]

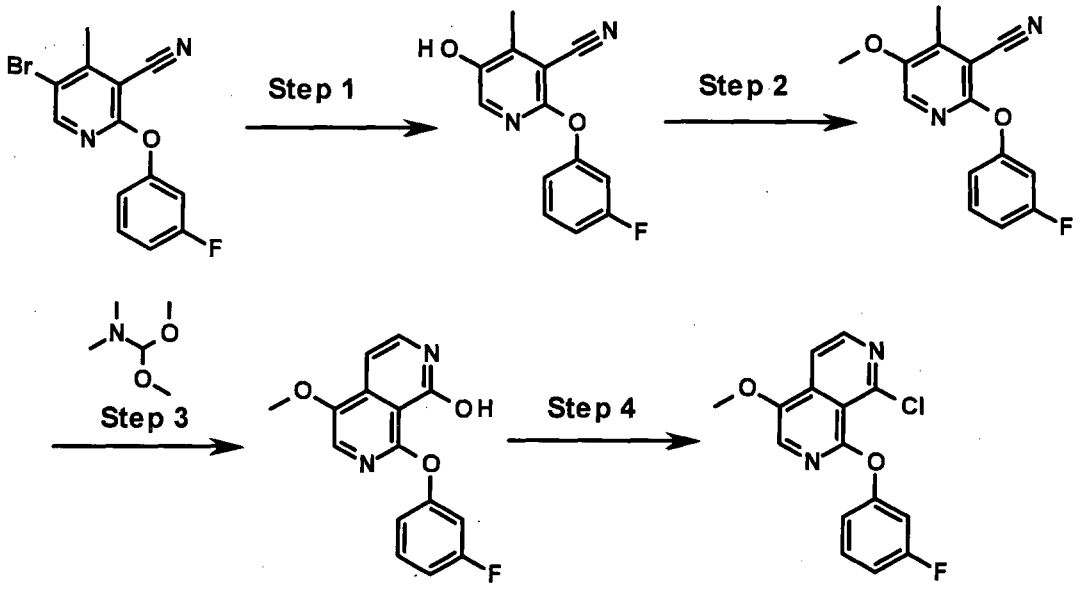
Step 5: 4-Bromo-8-chloro-1-(3-fluorophenoxy)-2,7-naphthyridine

A mixture of 5-bromo-8-(3-fluorophenoxy)-2,7-naphthyridin-1-ol (2.2 g, 6.56 mmol) and phosphoryl chloride (20 mL) was heated at 130°C for 1 hour. The reaction mixture was cooled to room temperature and concentrated to dryness. The obtained residue was diluted with sodium bicarbonate solution (20 mL), and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuo to give a crude product. The crude product was purified by silica gel (100-200 mesh size) column chromatography using 7% ethyl acetate in hexane as mobile phase to give the title compound (1.5 g, 64%). MS(ESI)m/z: 353.0 [M(^{79}Br)+1], 354.9 [M(^{81}Br)+1]; ^{1}H NMR $CDCl_3$: δ 6.99-7.06 (m, 3H). 7.41-7.45 (m, 1H), 7.91 (d, *J* = 5.6 Hz, 1H), 8.34 (s, 1H), 8.60 (d, *J* = 5.6 Hz, 1H).

[0267]

Preparation 57: 8-Chloro-1-(3-fluorophenoxy)-4-methoxy-2,7-naphthyridine

[0268]



[0269]

Step 1: 2-(3-Fluorophenoxy)-5-hydroxy-4-methyl-pyridine-3-carbonitrile

A mixture of 5-bromo-2-(3-fluorophenoxy)-4-methyl-pyridine-3-carbonitrile (0.63 g, 2.72 mmol, synthesized as described in Step 3 of preparation 56) and 1,4-dioxane (6.5 mL) was degassed with argon for 0.5 hours. To the mixture were added potassium acetate (0.80 g, 8.16 mmol), bispinacoloto diborane (0.83 g, 3.26 mmol) and $PdCl_2$(dppf) DCM complex (0.067 g, 0.08 mmol). The mixture was heated for 2 hours. The disappearance of the starting material was confirmed by TLC. Then the reaction mixture was cooled to 0°C, treated with hydrogen peroxide (30%) solution (0.92 mL, 8.16 mmol) and stirred for 1 hour. The reaction mixture was diluted with DCM and poured into water. The aqueous layer was extracted with DCM (3 x 15 mL). The combined organic layers were washed with saturated sodium thiosulphate solution (10 mL), then brine (20 mL), dried over sodium sulfate and concentrated under vacuo to give a crude product. The crude product was as such used for next reaction (0.5 g, 89%). MS(ESI)m/z: 245.0 [M+1]

[0270]

Step 2: 2-(3-Fluorophenoxy)-5-methoxy-4-methyl-pyridine-3-carbonitrile

To a mixture of 2-(3-fluorophenoxy)-5-hydroxy-4-methyl-pyridine-3-carbonitrile (0.7 g, 2.86 mmol) in N,N-dimethylacetamide (10.0 mL) were added cesium carbonate (2.79 g, 8.59 mmol) and methyl iodide (0.89 mL, 14.34 mmol) at room temperature under nitrogen. The reaction mixture was stirred at 65°C for 18 hours. The reaction mixture was cooled to room temperature, and then poured into ice cold water, and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuo to give a crude product. The crude product was purified by silica gel (100-200 mesh size) column chromatography using 7% ethyl acetate in hexane as mobile phase to give the title compound (0.7 g, 94%).

MS(ESI)m/z: 259.1. [M+1],; ^{1}H NMR DMSO-d_6: δ 2.40 (s, 3H), 3.92 (s, 3H), 7.03-716 (m, 3H), 7.44-7.50 (m, 1H), 8.09(s, 1H).

[0271]

Step 3: 8-(3-Fluorophenoxy)-5-methoxy-2,7-naphthyridin-1-ol

A mixture of 2-(3-fluorophenoxy)-5-methoxy-4-methyl-pyridine-3-carbonitrile (0.7 g, 7.81 mmol) and N,N-dimethylformamide dimethyl acetal (1.08 ml, 8.13 mmol) in DMF (7 mL) was refluxed for 12 hours. The disappearance of the starting material was confirmed by TLC, then the reaction mixture was cooled to room temperature and concentrated to dryness. The obtained residue was diluted with acetic acid (2.7 mL) and sulfuric acid (2.7 mL), and the mixture was heated to 50°C for 2 hours. The reaction mixture was cooled to room temperature, and poured into an ice cold solution of aq. sodium bicarbonate, and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuo to give a crude product. The crude product was as such used for next reaction (0.3 g, 38%). MS(ESI)m/z: 287.0 [M)+1]

[0272]

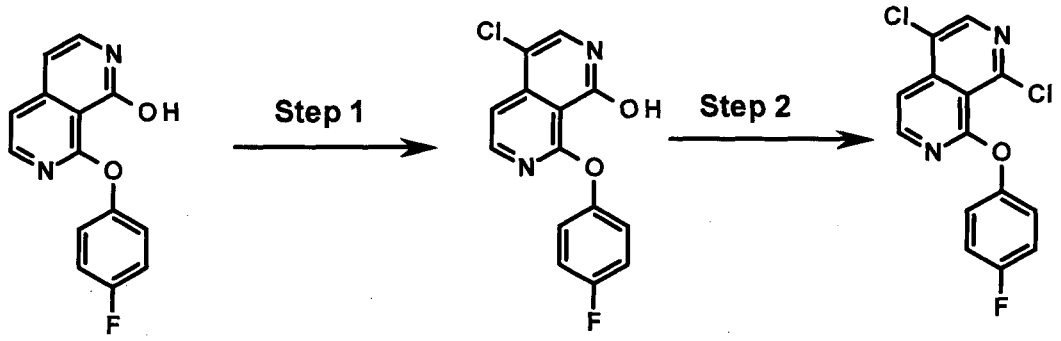
Step 4: 8-Chloro-1-(3-fluorophenoxy)-4-methoxy-2,7-naphthyridine

A mixture of 8-(3-fluorophenoxy)-5-methoxy-2,7-naphthyridin-1-ol (0.3 g, 1.04 mmol) and phosphoryl chloride (1.0 mL) was heated at 100°C for 16 hours. The reaction mixture was cooled to room temperature and concentrated to dryness. The obtained residue was diluted with sodium bicarbonate solution (20 mL), and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuo to give a crude product. The crude product was purified by silica gel (100-200 mesh size) column chromatography using 7% ethyl acetate in hexane as mobile phase to give the title compound (0.05 g, 16%). MS(ESI)m/z: 305.0 [M+1].

[0273]

Preparation 58: 1,4-Dichloro-8-(4-fluorophenoxy)-2,7-naphthyridine

[0274]



[0275]

Step 1: 4-Chloro-8-(4-fluorophenoxy)-2,7-naphthyridin-1-ol

To a mixture of 8-(4-fluorophenoxy)-2,7-naphthyridin-1-ol (Step 3 of Preparation 28, 0.65 g, 2.53 mmol) in N,N-dimethylacetamide (20 mL) was added *N*-chlorosuccinimide (0.33 g, 2.53 mmol) in portion wise at 0°C under nitrogen. The reaction mixture was stirred at 30-35°C for 1 hour. The reaction mixture was cooled to room temperature, and then poured into ice cold water. The solid was collected by filtration, and washed with n-hexane to give the title compound as an off-white solid (0.4 g, 55%). MS(ESI)m/z: 291.1 [M(^{35}Cl)+1], 293.1 [M(^{37}Cl)+1]; ^{1}H NMR DMSO-d_6: δ 7.10-7.30 (m, 4H), 7.35 (d, J = 5.2 Hz, 1H), 7.78 (d, J = 6.4 Hz, 1H), 8.26 (d, J = 5.6 Hz, 1H), 11.9 (bs, 1H).

[0276]

Step 2: 1,4-Dichloro-8-(4-fluorophenoxy)-2,7-naphthyridine

A mixture of 4-chloro-8-(4-fluorophenoxy)-2,7-naphthyridin-1-ol (0.4 g, 1.38 mmol) and phosphoryl chloride (8 mL) was heated at 130°C for 2 hour. The reaction mixture was cooled to room temperature and concentrated to dryness. The obtained residue was diluted with sodium bicarbonate solution (20 mL), and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under

vacuo to give a crude product. The crude product was used in next reaction without further purification.

[0277]

Preparations 59 and 60:

The compounds of Preparations 59 and 60 were synthesized in analogous manner to that of preparation 58.

[0278]

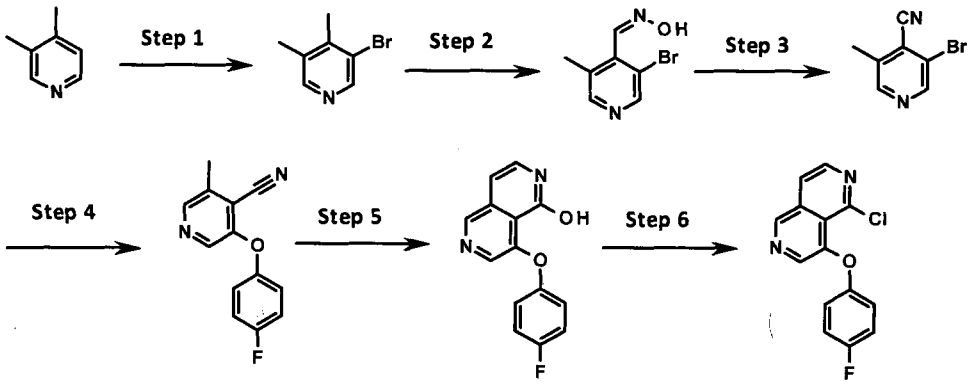
Table 6

Prep. No.	IUPAC Name	MS(EI)m/z: (M+1)
59	1,4-Dichloro-8-(3-fluorophenoxy)-2,7-naphthyridine	309.0 (^{35}Cl)+1], 311.0 (^{37}Cl)
60	4-Bromo-1-chloro-8-(3-fluorophenoxy)-2,7-naphthyridine	352.9 M(^{79}Br)+1], 355 [M(^{81}Br)+1]

[0279]

Preparation 61: 1-Chloro-8-(4-fluorophenoxy)-2,6-naphthyridine

[0280]



[0281]

Step 1: 3-Bromo-4,5-dimethyl-pyridine

To a mixture of 3,4-dimethylpyridine (5.0 g, 46.6 mmol) in conc sulfuric acid (50.0 mL) was added N-bromosuccinimide (9.31 g, 51.32 mmol) in portion wise at room temperature under nitrogen. The reaction mixture was stirred at 60°C for 18 hours. The reaction mixture was cooled to room temperature, then poured into ice cold water, and basified with 10% NaOH solution. The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with

brine, dried over sodium sulfate and concentrated under vacuo to give a crude product. The crude product was purified by silica gel (100-200 mesh size) column chromatography using 5% ethyl acetate in hexane as mobile phase to give the title compound (0.8 g, 9.3%). MS(ESI)m/z: 186.0 [M(^{79}Br)+1], 188.0 [M(^{81}Br)+1]; ^{1}H NMR $CDCl_3$: δ 2.31 (s, 3H), 2.36 (s, 3H), 8.23 (s, 1H), 8.51 (s, 1H).

[0282]

Step 2: 3-Bromo-5-methyl-pyridine-4-carbaldehyde oxime

A solution of 3-bromo-4,5-dimethyl-pyridine (1.0 g, 5.37 mmol) and butyl nitrite (0.72 g, 6.98 mmol) in N,N-dimethylformamide (10.0 mL) was cooled to -78°C. To the mixture was added a solution of potassium *tert*-butoxide (1.39 g, 12.36 mmol) in N,N-dimethylformamide (5.0 mL). The reaction mixture was stirred at -50°C for an hour, and then a mixture of glacial acetic acid (1.5 mL) and water (2.5 mL) was added thereto. The reaction mixture was poured into ice cold water, and the solid was collected by filtration. The solid was washed with water to give the title compound as off-white solid (0.75 g, 64.7%). MS(ESI)m/z: (M+1) 215.0 [M(^{79}Br)+1], 216.9 [M(^{81}Br)+1].

[0283]

Step 3: 3-Bromo-5-methyl-pyridine-4-carbonitrile

A mixture of 3-bromo-5-methyl-pyridine-4-carbaldehyde oxime (0.65 g, 3.02 mmol) and acetic anhydride (3.0 mL) was heated at 120°C for 4 hours. The reaction mixture was cooled to room temperature and then concentrated to dryness. The obtained residue was diluted with dichloromethane, and the mixture was washed with water, brine, dried over sodium sulfate and concentrated under vacuo to give a crude product which was used as such for next reaction. MS(ESI)m/z: 197.0 [M(^{79}Br)+1], 198.9 [M(^{81}Br)+1].

[0284]

Step 4: 3-(4-Fluorophenoxy)-5-methyl-pyridine-4-carbonitrile

A mixture of 3-bromo-5-methyl-pyridine-4-carbonitrile

(2.0 g, 10.1 mmol), 3-fluorophenol (1.85 mL, 20.3 mmol) and cesium carbonate (9.89 g, 30.4 mmol) in dimethylsulfoxide (20 mL) was degassed with argon for 30 min. To the mixture were added copper(I) iodide (1.93 g, 10.1 mmol), copper powder (0.65 g, 10.1 mmol) and 2,2,6,6-tetramethyl-3.5-heptanedione (1.05 mL, 5.0 mmol). The mixture was continued degassing for another 20 min. The resulting mixture was heated at 100°C for 18 hours under argon atmosphere. The mixture was cooled to room temperature and diluted with water (100 mL) followed by 10% aqueous sodium hydroxide solution (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water (50 mL) and brine (100 mL), dried over sodium sulfate and concentrated under vacuo to give a crude product. The crude product was purified by combiflash with 8-12% ethyl acetate in hexane as a mobile phase to give the title compound as off white solid (0.80 g, 35%). MS(ESI)m/z: 229.1; ^{1}H NMR DMSO-*d6* 2.52 (s, 3H), 7.02-7.05 (m, 1H), 7.09-7.19 (m, 1H), 7.47- 7.53 (m 1H), 8.30 (s,1H), 8.56, (s, 1H).

[0285]

Step 5: 8-(4-Fluorophenoxy)-2,6-naphthyridin-1-ol

A mixture of 3-(4-fluorophenoxy)-5-methyl-pyridine-4-carbonitrile (0.5 g, 2.19 mmol) and N,N-dimethylformamide dimethyl acetal (0.88 mL, 6.57 mmol) in DMF (6 mL) was refluxed for 24 hours. After confirming the disappearance of the starting material by TLC, the reaction mixture was cooled to room temperature and concentrated to dryness. To the residue were added ethanol (3 mL) and 50% aq. hydrobromic acid (3 mL), and the mixture was heated to 80°C for 18 hours. The reaction mixture was cooled to room temperature, and concentrated, and the mixture was poured into an ice cold solution of aq. sodium bicarbonate. The aqueous layer was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuo to give a crude product. The crude

product was as such used for next reaction (0.5 g).
MS(ESI)m/z: 257.1. [M+1].

[0286]

Step 6: 1-Chloro-8-(4-fluorophenoxy)-2,6-naphthyridine

A mixture of 8-(4-fluorophenoxy)-2,6-naphthyridin-1-ol (0.5 g, 1.95 mmol) and phosphoryl chloride (5 mL) was heated at 130°C for 3 hour. The reaction mixture was cooled to room temperature and concentrated to dryness. The obtained residue was diluted with sodium bicarbonate solution (10 mL), and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuo to give a crude product. The crude product was purified by silica gel (100-200 mesh size) column chromatography using 7% ethyl acetate in hexane as mobile phase to give the title compound (0.105 g, 20%). MS(ESI)m/z: 275.0 [M(^{35}Cl)+1], 277.0 [M(^{37}Cl)+1]; ^{1}H NMR $CDCl_3$: δ 6.70-6.90 (m, 3H), 7.27-7.36 (m, 1H), 7.77 (d, *J* = 5.6Hz, 1H), 8.43 (br s, 1H), 8.52 (d, *J* = 5.6 Hz, 1H), 9.17 (bs, 1H).

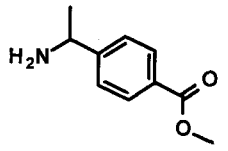
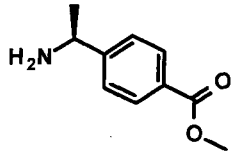
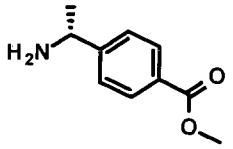
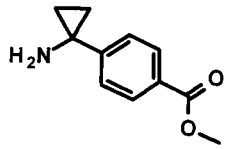
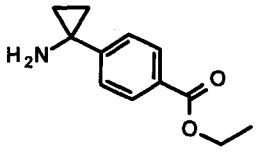
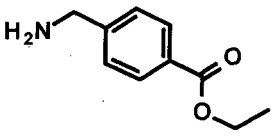
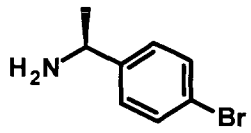
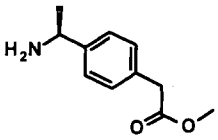
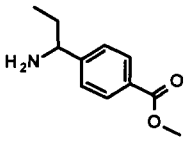
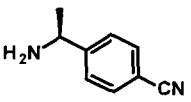
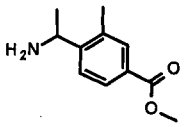
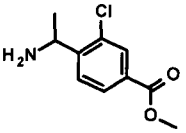
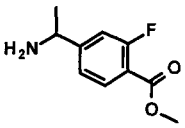
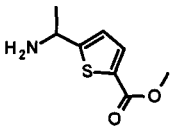
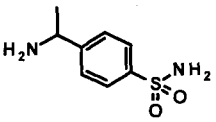
[0287]

Preparations 62-76

The compounds of Preparations 62-76 were either obtained from commercial source or prepared as per literature method.

[0288]

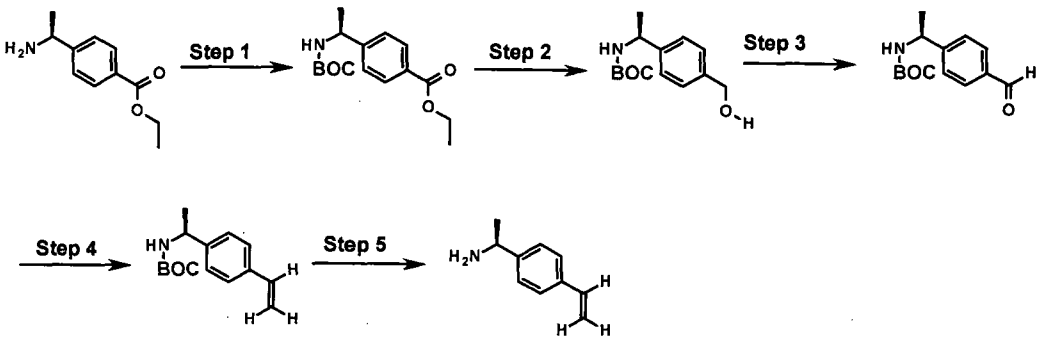
Table 7

 Preparation 62	 Preparation 63	 Preparation 64
 Preparation 65 *J. Org. Chem.* **2010,** *75*(12), 4078-85	 Preparation 66 *J. Org. Chem.* **2010,** *75*(12), 4078-85	 Preparation 67
 Preparation 68	 Preparation 69	 Preparation 70 WO 2009/139373
 Preparation 71	 Preparation 72 WO 2011/106632	 Preparation 73 WO 2009/139373
 Preparation 74 WO 2011/106632	 Preparation 75 WO 2011/106627	 Preparation 76 WO 2011/003418 & WO 2009/007015

[0289]

Preparation 77: (1S)-1-(4-Vinylphenyl)ethanamine

[0290]



[0291]

Step 1: Ethyl 4-[(1S)-1-(tert-butoxycarbonylamino)ethyl]benzoate

To a mixture of ethyl 4-[(1S)-1-aminoethyl]benzoate (5.0 g, 25.90 mmol) in DCM (50 mL) were added triethylamine (10.8 mL, 77.72 mmol) and BOC anhydride (6.77 g, 31.08 mmol). The reaction mixture was stirred at room temperature for 16 hours. The reaction completion was confirmed by TLC, then diluted with water (50 mL) and extracted with dichloromethane (2 x 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuo to give a crude product. The crude product was purified by silica gel column chromatography using 5-10% ethyl acetate in hexane to give the title compound (5.0 g, 60%).

[0292]

Step 2: tert-Butyl N-[(1S)-1-[4-(hydroxymethyl)phenyl]ethyl]carbamate

To a solution of ethyl 4-[(1S)-1-(tert-butoxycarbonylamino)ethyl]benzoate (5.0 g, 17 mmol) in THF (50 mL) was added lithium aluminium hydride (34 mL, 34 mmol) (1.0 M slution in THF) at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 1 hour, and the product formation was confirmed by TLC. The mixture was quenched by aq. sodium sulfate solution, and the solid obtained was flitered, and the filtrate was concentrated to dryness to give the title compound (3.3 g, 77%). MS(EI)m/z: 196.2 (M-56 + 1); ^{1}H NMR (400 MHz, , $CDCl_3$): δ 1.42 (s, 12H), 4.68 (s, 2H), 4.78 (br s, 2H), 7.28-7.35 (m, 4H).

[0293]

Step 3: tert-Butyl N-[(1S)-1-(4-formylphenyl)ethyl]carbamate

To a solution of tert-butyl N-[(1S)-1-[4-(hydroxymethyl)phenyl]ethyl]carbamate (3.3 g, 13.1 mmol) in DCM (60 mL) was added manganese oxide (14 g, 157.7 mmol), and the reaction mixture was stirred at room temperature for 1.5 hours. The product formation was confirmed by TLC. The mixture was flitered through celite pad, then the filtrate was concentrated under vacuo to give the title compound (3.0 g, 92%). MS(EI)m/z: 194.2 (M-56 + 1); ^{1}H NMR (400 MHz, , $CDCl_3$): δ 1.33 (s, 12H), 4.84 (br s, 1H), 7.32 (d, J = 4.8 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 9.99 (s, 1H).

[0294]

Step 4: tert-Butyl N-[(1S)-1-(4-vinylphenyl)ethyl]carbamate

To a solution of tert-butyl N-[(1S)-1-(4-formylphenyl)ethyl]carbamate (3.0 g, 12.04 mmol) in 1,4-dioxane (30 mL) were added potassium carbonate (3.3 g, 24.00 mmol) and methyltriphenylphosphonium bromide (5.16 g, 14.45 mmol). The resulting mixture was heated at 110°C for 16 hours under argon atmosphere. The reaction was cooled to room temperature, then diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water (25 mL), brine (50 mL), dried over sodium sulfate and concentrated under vacuo to give a crude product. The crude product was purified by combiflash column chromatography using 10-20% ethyl acetate in hexane as a mobile phase to give the title compound. (2.5 g, 84%) MS(ESI)m/z: 192.1 (M-56 + 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 12H), 4.77 (br s, 2H), 5.22 (d, J = 7.6 Hz, 1H), 5.73 (d, J = 18.0 Hz, 1H), 6.66-6.73 (m, 1H), 7.24 (s, 1H), 7.26 (s, 1H), 7.37 (d, J = 8.4 Hz, 2H).

[0295]

Step 5: (1S)-1-(4-Vinylphenyl)ethanamine

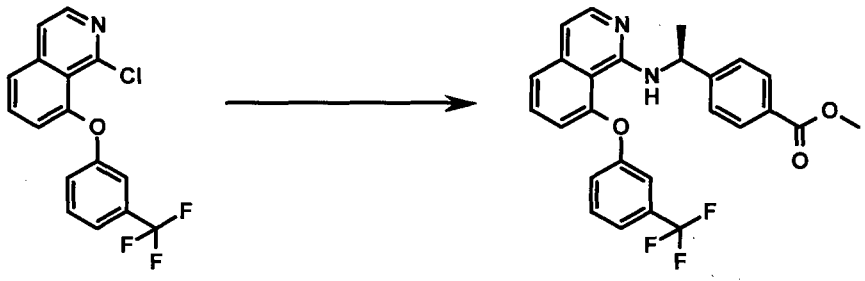
To a solution of tert-butyl N-[(1S)-1-(4-

vinylphenyl)ethyl]carbamate (2.5 g, 10.12 mmol) in DCM (25 mL) was added TFA (5 mL), and the reaction mixture was heated at 70°C for 4 hours. The product formation was confirmed by TLC. The mixture was diluted with DCM followed by aq. $NaHCO_3$ solution (50 mL) and extracted with dichloromethane (2 x 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuo to give the title compound (1.28 g, 86%). ^1H NMR (400 MHz, , DMSO-d6): δ 1.48 (d, J = 6.8 Hz, 3H), 4.41 (br s, 1H), 5.30 (d, J = 11.6 Hz, 1H), 5.88 (d, J = 18.0 Hz, 1H); 6.71-6.78 (m, 1H), 7.45 (d, J = 8.0 Hz, 2H); 7.54 (d, J = 8.0 Hz, 2H); 8.26 (bs, 2H).

[0296]

Example A1: Methyl 4-[(1S)-1-[[8-[3-(trifluoromethyl)phenoxy]-1-isoquinolyl]amino]ethyl]benzoate

[0297]



[0298]

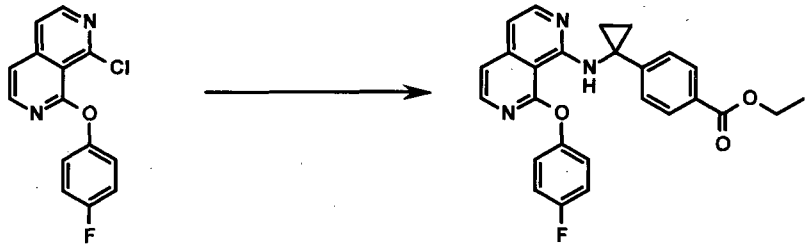
A mixture of 1-chloro-8-[3-(trifluoromethhyl)phenoxy]isoquinoline (0.1 g, 0.31 mmol; Preparation 1) and methyl 4-[(1*S*)-1-aminoethyl]benzoate (0.083 g, 0.46 mmol, Preparation 63) was heated at 140°C for 2.0 hours. The residue was purified by combiflash with 6-8% ethyl acetate in hexane as a mobile phase to give the title compound as an off white solid (0.11 g, 76%). MS(ESI) m/z: 467.2 (M+1); ^1H NMR $CDCl_3$: δ 1.43 (d, *J* = 6.8 Hz, 3H); 3.81 (s, 3H); 5.30-5.35 (m, 1H); 6.96 (d, *J* = 5.6 Hz, 1H); 7.03 (dd, *J* = 1.8 & 7.0 Hz, 1H),7.33 (d, *J* = 8.4 Hz, 3H); 7.46 (d, *J* = 6.8 Hz, 1H); 7.54-7.65 (m, 4H); 7.67 (t, *J* = 7.6, 1H); 7.77-8.00 (m, 3H).

[0299]

Example A2: Ethyl 4-[1-[[8-(4-fluorophenoxy)-2,7-naphthyridin-

1-yl]amino]cyclopropyl]benzoate

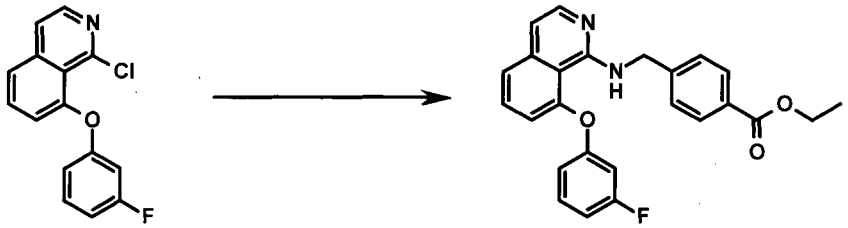
[0300]



The Example A2 was performed in analogous manner to that of Example A1 using 1-chloro-8-(4-fluorophenoxy)-2,7-naphthyridine (0.2 g, 0.73 mmol, Preparation 28) and ethyl 4-(1-aminocyclopropyl)benzoate (0.18 g, 0.88 mmol; Preparation 66) to give the title compound (0.04 g, 12%). MS(ESI) m/z: 444.1 (M+1); ^{1}H NMR DMSO-d_6: δ 1.36 (t, J = 7.2 Hz, 3H); 1.45-1.55 (m, 4H); 4.34 (q, J = 7.2 Hz, 2H); 6.80 (d, J = 5.6 Hz, 1H); 7.11 (d, J = 5.6 Hz, 1H); 7.15-7.26 (m, 4H); 7.29 (d, J = 8.8 Hz, 2H), 7.92-7.96 (m, 3H), 8.12 (d, J = 5.6 Hz, 2H).

[0301]

Example A3: Ethyl 4-[[[8-(3-fluorophenoxy)-1-isoquinolyl]amino]methyl]benzoate

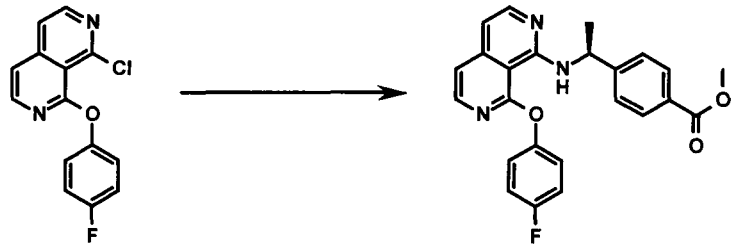


The Example A3 was performed in analogous manner to that of Example A1 using 1-chloro-8-(3-fluorophenoxy)isoquinoline (0.15 g, 0.54 mmol, Preparation 3) and ethyl 4-(aminomethyl)benzoate (0.27 g, 1.6 mmol; Preparation 67) to give the title compound (0.07 g, 30%). MS(ESI) m/z: 417.2 (M+1); ^{1}H NMR DMSO-d_6: δ 1.29 (t, J = 7.2 Hz, 3H); 4.28 (q, J = 7.2 Hz, 2H); 4.78 (d, J = 6.0 Hz, 2H); 6.85 (d, J = 7.2 Hz, 1H); 6.94 (t, J = 5.2 Hz, 2H); 7.10 (d, J = 9.2 Hz, 2H); 7.35 (d, J = 7.6 Hz, 2H); 7.47-7.54 (m, 3H); 7.80 (s, 1H); 7.82 (d, J = 4.0 Hz, 2 H); 7.96 (s, 1H)

[0302]

Example A4: Methyl 4-[(1S)-1-[[8-(4-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate

[0303]



[0304]

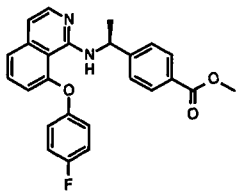
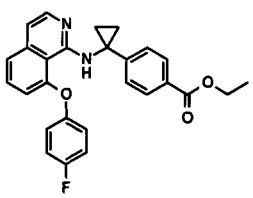
The Example A4 was performed in a similar manner to that of Example A1 using 1-chloro-8-(4-fluorophenoxy)-2,7-naphthyridine (0.2 g, 0.73 mmol; Preparation 28) and methyl 4-[(1*S*)-1-aminoethyl]benzoate (0.19 g, 1.09 mmol, Preparation 63) to give the title compound (0.2 g, 66%). MS(ESI) m/z: 417.2 (M+1); ^{1}H NMR DMSO-d_6: δ 1.62 (d, *J* = 6.8 Hz, 3H); 3.89 (s, 3H), 5.54-5.57 (m, 1H); 6.74 (d, *J* = 6.0 Hz, 1H); 7.08 (d, *J* = 6.0 Hz, 1H); 7.15-7.24 (m, 4H); 7.48 (d, *J* = 8.0 Hz, 2H); 7.79 (d, *J* = 6.8 Hz, 1H); 7.93 (d, *J* = 5.2 Hz, 1H); 7.98 (d, *J* = 8.8 Hz, 2H); 8.05 (d, *J* = 5.2 Hz, 1H).

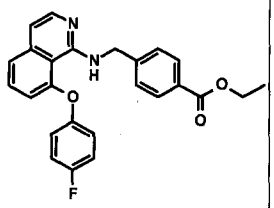
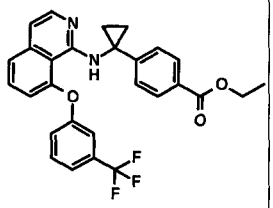
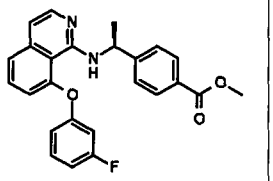
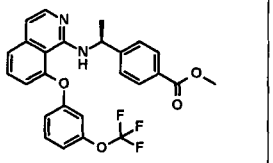
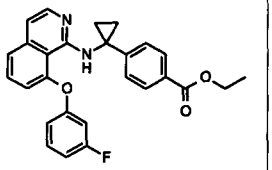
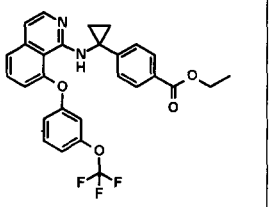
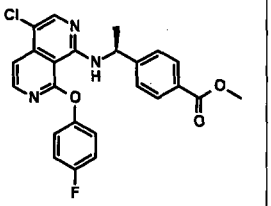
[0305]

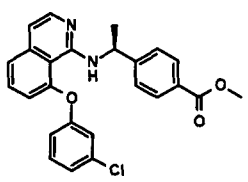
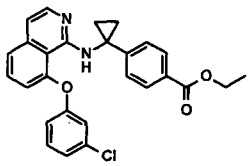
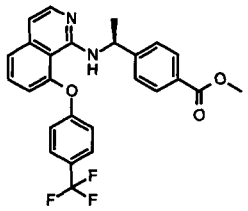
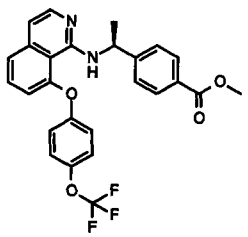
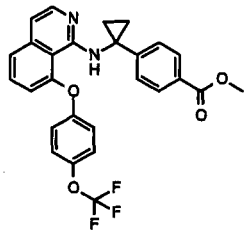
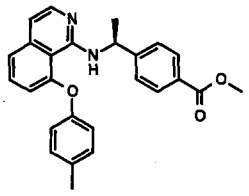
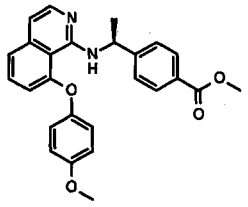
The compounds of Examples A5 to A84 and A86 were synthesized in a similar manner to that of Example A1.

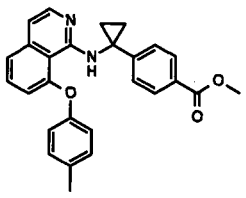
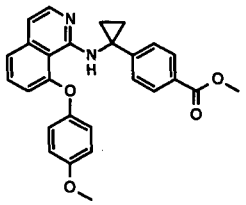
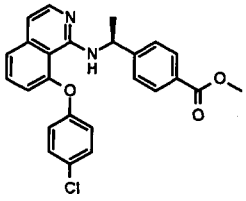
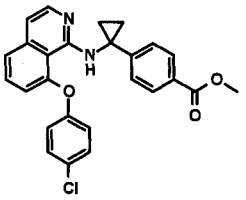
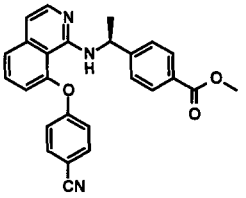
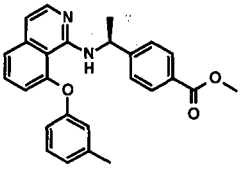
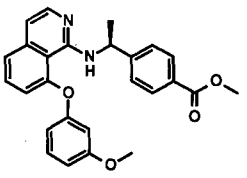
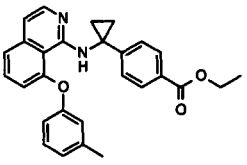
[0306]

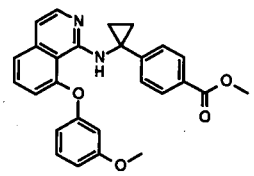
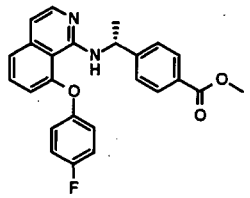
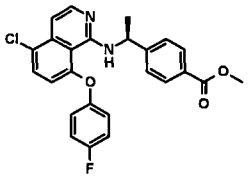
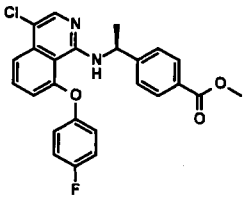
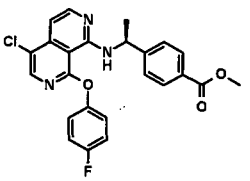
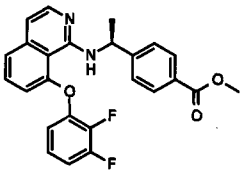
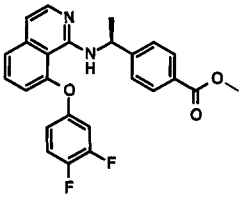
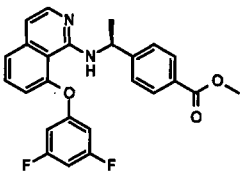
Table 8

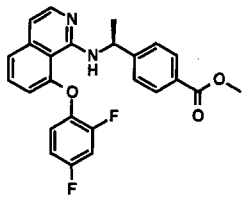
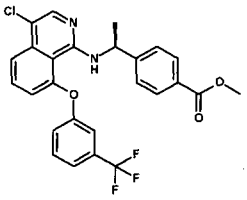
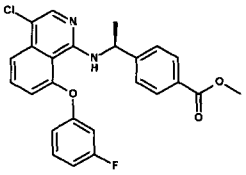
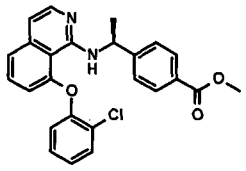
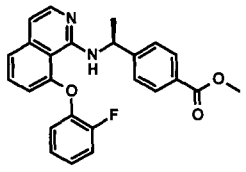
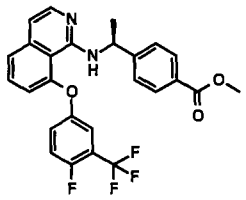
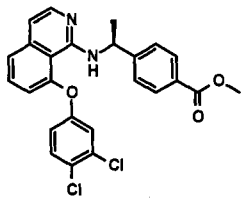
Ex.No.	Structure	IUPAC Name	MS(ESI)m/z: (M+1)
A5		Methyl 4-[(1*S*)-1-[[8-(4-fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoate	417.0
A6		Ethyl 4-[1-[[8-(4-fluorophenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoate	443.1

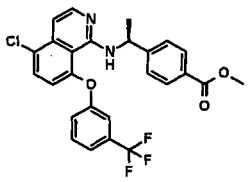
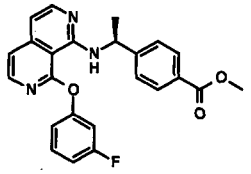
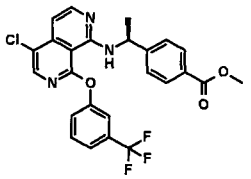
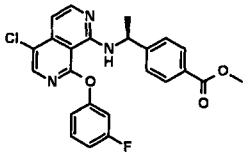
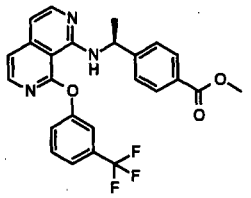
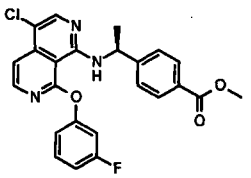
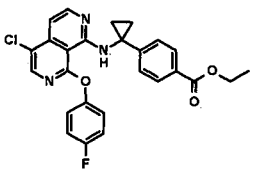
A7		Ethyl 4-[[[8-(4-fluorophenoxy)-1-isoquinolyl]amino]methyl]benzoate	417.1
A8		Ethyl 4-[1-[[8-[3-(trifluoromethyl)phenoxy]-1-isoquinolyl]amino]cyclopropyl]benzoate	493.2
A9		Methyl 4-[(1S)-1-[[8-(3-fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoate	417.2
A10		Methyl 4-[(1S)-1-[[8-[3-(trifluoromethoxy)phenoxy]-1-isoquinolyl]amino]ethyl]benzoate	483.2
A11		Ethyl 4-[1-[[8-(3-fluorophenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoate	443.2
A12		Ethyl 4-[1-[[8-[3-(trifluoromethoxy)phenoxy]-1-isoquinolyl]amino]cyclopropyl]benzoate	509.2
A13		Methyl 4-[(1S)-1-[[4-chloro-8-(4-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	452.2 (^{35}Cl), 454.2 (^{37}Cl)

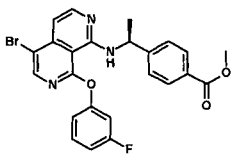
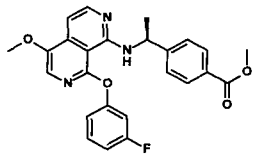
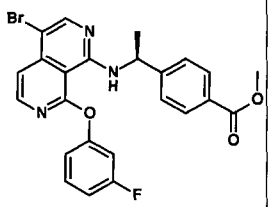
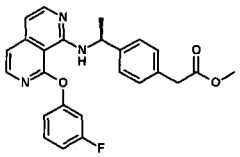
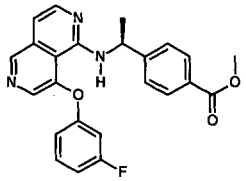
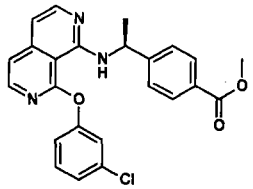
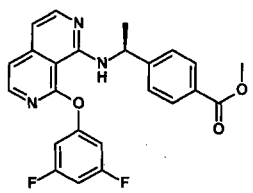
A14		Methyl 4-[(1S)-1-[[8-(3-chlorophenoxy)-1-isoquinolyl]amino]ethyl]benzoate	433.2 (^{35}Cl), 435.2 (^{37}Cl)
A15		Ethyl 4-[1-[[8-(3-chlorophenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoate	459.2
A16		Methyl 4-[(1S)-1-[[8-[4-(trifluoromethyl)phenoxy]-1-isoquinolyl]amino]ethyl]benzoate	467.2
A17		Methyl 4-[(1S)-1-[[8-[4-(trifluoromethoxy)phenoxy]-1-isoquinolyl]amino]ethyl]benzoate	483.2
A18		Methyl 4-[1-[[8-[4-(trifluoromethoxy)phenoxy]-1-isoquinolyl]amino]cyclopropyl]benzoate	495.2
A19		Methyl 4-[(1S)-1-[[8-(4-methylphenoxy)-1-isoquinolyl]amino]ethyl]benzoate	413.2
A20		Methyl 4-[(1S)-1-[[8-(4-methoxyphenoxy)-1-isoquinolyl]amino]ethyl]benzoate	429.2

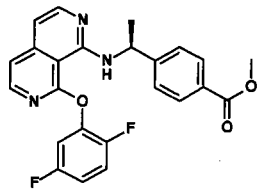
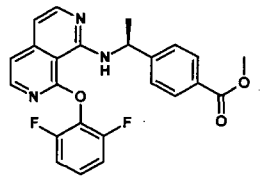
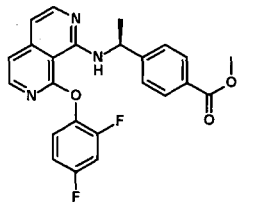
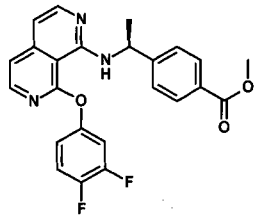
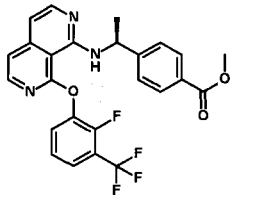
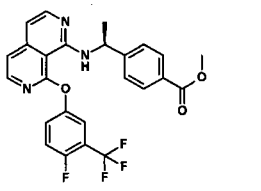
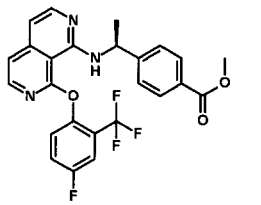
A21		Methyl 4-[1-[[8-(4-methylphenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoate	425.2
A22		Methyl 4-[1-[[8-(4-methoxyphenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoate	441.2
A23		Methyl 4-[(1S)-1-[[8-(4-chlorophenoxy)-1-isoquinolyl]amino]ethyl]benzoate	433.1 (^{35}Cl), 435.1 (^{37}Cl)
A24		Methyl 4-[1-[[8-(4-chlorophenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoate	445.1
A25		Methyl 4-[(1S)-1-[[8-(4-cyanophenoxy)-1-isoquinolyl]amino]ethyl]benzoate	424.1
A26		Methyl 4-[(1S)-1-[[8-(3-methylphenoxy)-1-isoquinolyl]amino]ethyl]benzoate	413.2
A27		Methyl 4-[(1S)-1-[[8-(3-methoxyphenoxy)-1-isoquinolyl]amino]ethyl]benzoate	429.2
A28		Ethyl 4-[1-[[8-(3-methylphenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoate	439.2

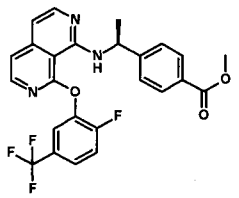
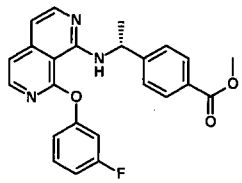
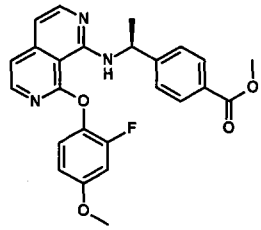
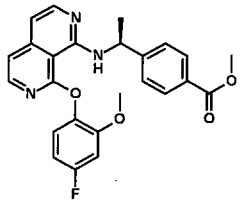
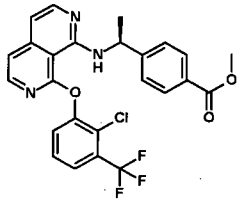
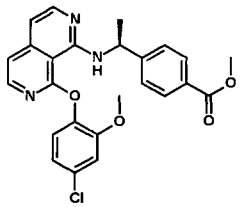
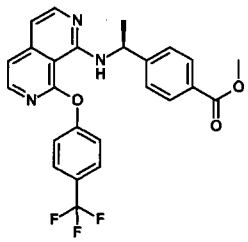
A29		Methyl 4-[1-[[8-(3-methoxyphenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoate	441.2
A30		Methyl 4-[(1R)-1-[[8-(4-fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoate	417.2
A31		Methyl 4-[(1S)-1-[[5-chloro-8-(4-fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoate	451.2 (^{35}Cl), 453.2 (^{37}Cl)
A32		Methyl 4-[(1S)-1-[[4-chloro-8-(4-fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoate	450.8
A33		Methyl 4-[(1S)-1-[[5-chloro-8-(4-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	451.8
A34		Methyl 4-[(1S)-1-[[8-(2,3-difluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoate	434.8
A35		Methyl 4-[(1S)-1-[[8-(3,4-difluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoate	434.8
A36		Methyl 4-[(1S)-1-[[8-(3,5-difluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoate	434.8

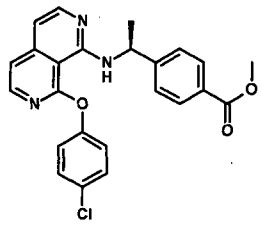
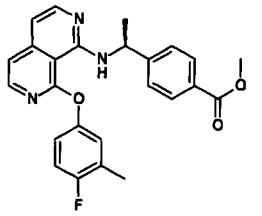
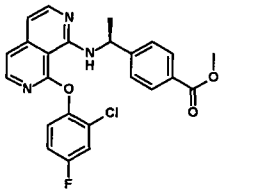
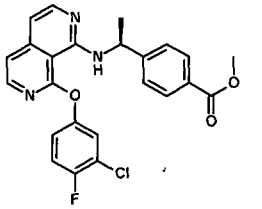
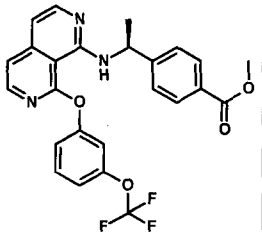
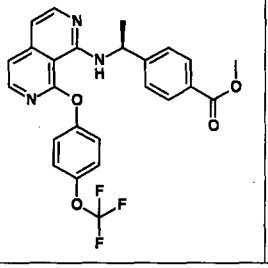
A37		Methyl 4-[(1S)-1-[[8-(2,4-difluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoate	434.8
A38		Methyl 4-[(1S)-1-[[4-chloro-8-[3-(trifluoromethyl)phenoxy]-1-isoquinolyl]amino]ethyl]benzoate	500.8
A39		Methyl 4-[(1S)-1-[[4-chloro-8-(3-fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoate	450.8
A40		Methyl 4-[(1S)-1-[[8-(2-chlorophenoxy)-1-isoquinolyl]amino]ethyl]benzoate	432.8 (^{35}Cl), 434.8 (^{37}Cl)
A41		Methyl 4-[(1S)-1-[[8-(2-fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoate	416.9
A42		Methyl 4-[(1S)-1-[[8-[4-fluoro-3-(trifluoromethyl)phenoxy]-1-isoquinolyl]amino]ethyl]benzoate	484.7
A43		Methyl 4-[(1S)-1-[[8-(3,4-dichlorophenoxy)-1-isoquinolyl]amino]ethyl]benzoate	466.7 (^{35}Cl), 468.7 (^{37}Cl)

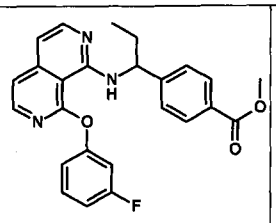
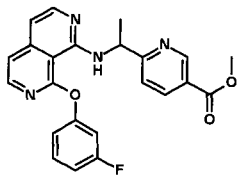
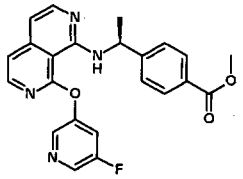
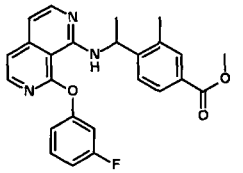
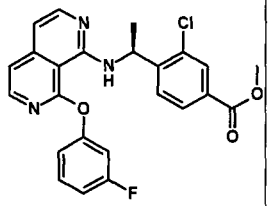
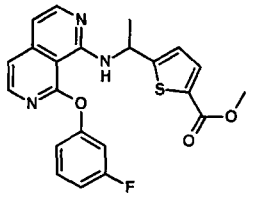
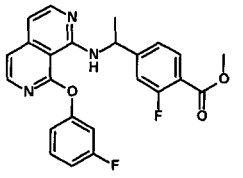
A44		Methyl 4-[(1S)-1-[[5-chloro-8-[3-(trifluoromethyl)phenoxy]-1-isoquinolyl]amino]ethyl]benzoate	500.8
A45		Methyl 4-[(1S)-1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	418.1
A46		Methyl 4-[(1S)-1-[[5-chloro-8-[3-(trifluoromethyl)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	502.0
A47		Methyl 4-[(1S)-1-[[5-chloro-8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	451.9
A48		Methyl 4-[(1S)-1-[[8-[3-(trifluoromethyl)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	468.2
A49		Methyl 4-[(1S)-1-[[4-chloro-8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	452.1 (^{35}Cl), 454.1 (^{37}Cl)
A50		Ethyl 4-[1-[[5-chloro-8-(4-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]cyclopropyl]benzoate	478.1

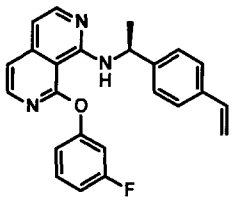
A51		Methyl 4-[(1S)-1-[[5-bromo-8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	496.1 (^{79}Br), 498.1 (^{81}Br)
A52		Methyl 4-[(1S)-1-[[8-(3-fluorophenoxy)-5-methoxy-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	448.1
A53		Methyl 4-[(1S)-1-[[4-bromo-8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	496.0 (^{79}Br), 498.0 (^{81}Br)
A54		Methyl 2-[4-[(1S)-1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]phenyl]acetate	432.2
A55		Methyl 4-[(1S)-1-[[8-(3-fluorophenoxy)-2,6-naphthyridin-1-yl]amino]ethyl]benzoate	418.1
A56		Methyl 4-[(1S)-1-[[8-(3-chlorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	434.1
A57		Methyl 4-[(1S)-1-[[8-(3,5-difluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	436.2

A58		Methyl 4-[(1S)-1-[[8-(2,5-difluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	436.2
A59		Methyl 4-[(1S)-1-[[8-(2,6-difluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	436.1
A60		Methyl 4-[(1S)-1-[[8-(2,4-difluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	436.2
A61		Methyl 4-[(1S)-1-[[8-(3,4-difluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	436.2
A62		Methyl 4-[(1S)-1-[[8-[2-fluoro-3-(trifluoromethyl)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	486.2
A63		Methyl 4-[(1S)-1-[[8-[4-fluoro-3-(trifluoromethyl)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	486.2
A64		Methyl 4-[(1S)-1-[[8-[4-fluoro-2-(trifluoromethyl)phenoxy]-2,7-naphthyridin-1-	486.2

		yl]amino]ethyl]benzoate	
A65		Methyl 4-[(1S)-1-[[8-[2-fluoro-5-(trifluoromethyl)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	486.1
A66		Methyl 4-[(1R)-1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	418.2
A67		Methyl 4-[(1S)-1-[[8-(2-fluoro-4-methoxy-phenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	448.2
A68		Methyl 4-[(1S)-1-[[8-(4-fluoro-2-methoxy-phenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	448.2
A69		Methyl 4-[(1S)-1-[[8-[2-chloro-3-(trifluoromethyl)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	502.2
A70		Methyl 4-[(1S)-1-[[8-(4-chloro-2-methoxy-phenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	464.2
A71		Methyl 4-[(1S)-1-[[8-[4-(trifluoromethyl)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	468.2

A72		Methyl 4-[(1S)-1-[[8-(4-chlorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	NA
A73		Methyl 4-[(1S)-1-[[8-(4-fluoro-3-methyl-phenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	432.2
A74		Methyl 4-[(1S)-1-[[8-(2-chloro-4-fluoro-phenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	452.1
A75		Methyl 4-[(1S)-1-[[8-(3-chloro-4-fluoro-phenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	452.1
A76		Methyl 4-[(1S)-1-[[8-[3-(trifluoromethoxy)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	484.2
A77		Methyl 4-[(1S)-1-[[8-[4-(trifluoromethoxy)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	NA

A78		Methyl 4-[1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]propyl]benzoate	432.2
A79		Methyl 6-[1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]pyridine-3-carboxylate	419.2
A80		Methyl 4-[(1S)-1-[[8-[(5-fluoro-3-pyridyl)oxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	419.2
A81		Methyl 4-[1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]-3-methyl-benzoate	432.2
A82		Methyl 3-chloro-4-[(1S)-1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	452.1
A83		Methyl 5-[1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]thiophene-2-carboxylate	424.2
A84		Methyl 2-fluoro-4-[1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	436.2

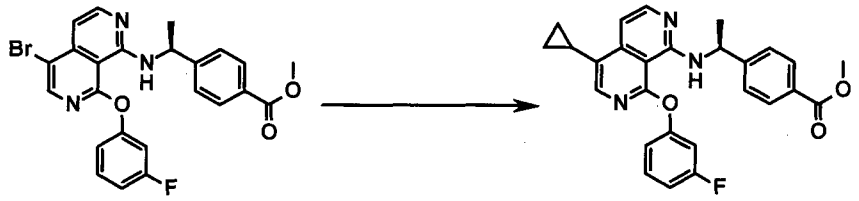
A86		8-(3-Fluorophenoxy)-N-[(1S)-1-(4-vinylphenyl)ethyl]-2,7-naphthyridin-1-amine	386.1

NA: not available

[0307]

Example B1: Methyl 4-[(1S)-1-[[5-cyclopropyl-8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate

[0308]



[0309]

A mixture of methyl 4-[(1S)-1-[[5-bromo-8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate (0.2 g, 0.4 mmol, Preparation A51), cyclopropyl boronic acid (0.103 g, 1.20 mmol), potassium phosphate (0.299 g, 1.41 mmol), water (0.2 mL) and toluene (4 mL) was degassed with argon for 30 min. To the mixture were added palladium acetate (0.009 g, 0.04 mmol) and tricyclohexylphosphine (0.022 g, 0.08 mmol), and the mixture was degassed for another 20 min. The resulting mixture was heated at 100 °C for 18 hours under argon atmosphere. The reaction was cooled to room temperature and filtered through celite pad. The filtrate was concentrated under vacuum, and the residue was purified by combiflash with 8-12% ethyl acetate in hexane as a mobile phase to give the title compound (0.167 g, 91.75,%). MS(EI)m/z: 458.2 (M+1); ^{1}H NMR $CDCl_3$: δ 0.61-0.64 (m, 2H), 0.96-1.01 (m, 2H), 1.61 (d, *J* = 6.8Hz, 3H), 1.91-1.95 (m, 1H), 5.54-5.58 (m, 1H), 6.98-7.01 (m, 3H), 7.20 (d, *J* = 6.0 Hz, 1H), 7.40-7.48 (m, 3H), 7.77 (d, *J* = 6.8Hz, 1H), 7.80 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 2H), 8.14 (d, *J* = 6.0 Hz, 1H).

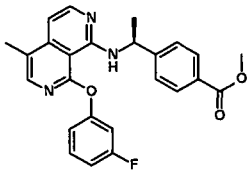
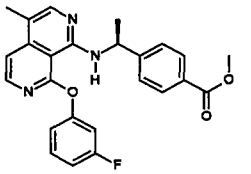
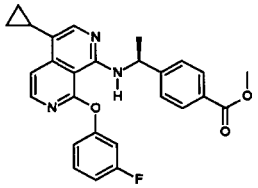
[0310]

The compounds of Examples B2 to B4 were synthesized in a

similar manner to that of Example B1.

[0311]

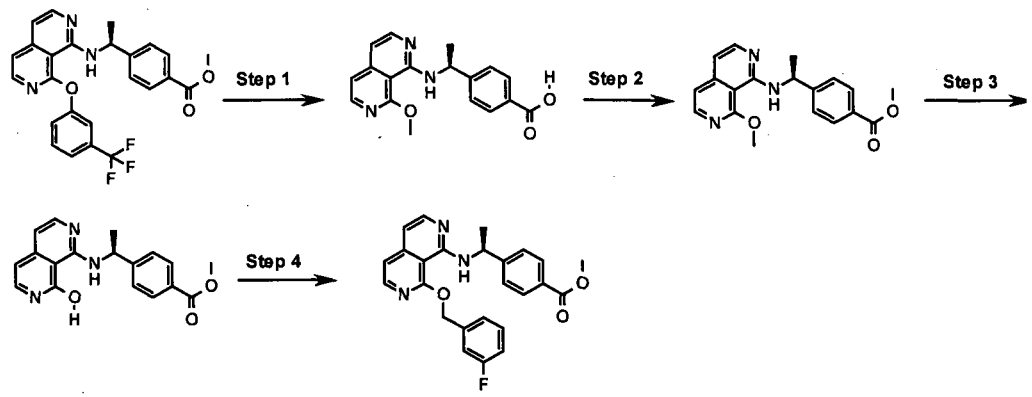
Table 9

Ex.No.	Structure	IUPAC Name	MS(ESI)m/z: (M+1)
B2		Methyl 4-[(1S)-1-[[8-(3-fluorophenoxy)-5-methyl-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	432.1
B3		Methyl 4-[(1S)-1-[[8-(3-fluorophenoxy)-4-methyl-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	432.1
B4		Methyl 4-[(1S)-1-[[4-cyclopropyl-8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	458.2

[0312]

Example C1: Methyl 4-[(1S)-1-[[8-[(3-fluorophenyl)methoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoate

[0313]



[0314]

Step 1: 4-[(1S)-1-[(8-Methoxy-2,7-naphthyridin-1-yl)amino]ethyl]benzoic acid

A mixture of methyl 4-[(1S)-1-[[8-[3-(trifluoromethyl)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoate (5.5 g, 2.40 mmol, Preparation A48) and lithium hydroxide monohydrate (4.8 g, 118 mol) in mixture of THF:MeOH:H_2O (2:3:1, 110 mL) was strirred at room temprature for 3 days. The product formation was confirmed by TLC, then the reaction mixture was concentrated to dryness, then to the mixture was added water (20 mL), and the mixture was acidified by 2N HCl (pH = 2-3), and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuo to give the ttle compound (3.5 g, 92%). MS(ESI) m/z: 324.1 (M+1)

[0315]

Step 2: Methyl 4-[(1S)-1-[(8-methoxy-2,7-naphthyridin-1-yl)amino]ethyl]benzoate

To a solution of 4-[(1S)-1-[(8-methoxy-2,7-naphthyridin-1-yl)amino]ethyl]benzoic acid (3.5 g, 10.83 mmol) in DMF (35 mL) were added potassium carbonate (3.0 g, 21.67 mmol) and methyl iodide (1.0 mL, 16.25 mmol). The resulting mixture was strirred at room temprature for 1 hour under argon atmosphere. The product formation was confirmed by TLC, then the reaction mixture was diluted with water (350 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried over sodium sulfate and evaporated under vacuum to give the title compound (3.5 g, 96%). MS(ESI) m/z: 338.1 (M+1); ^{1}H NMR (400 MHz, DMSO-d6): δ 1.58 (d, J = 6.8 Hz, 3H); 3.82 (s, 3H), 4.13 (s, 3H), 5.40-5.44 (m, 1H), 6.79 (d, J = 6.0 Hz, 1H); 7.16 (d, J = 6.0 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H); 7.90-7.95 (m, 4H), 8.07 (d, J = 5.2 Hz, 1H).

[0316]

Step 3: Methyl 4-[(1S)-1-[(8-hydroxy-2,7-naphthyridin-1-yl)amino]ethyl]benzoate

To a solution of methyl 4-[(1S)-1-[(8-methoxy-2,7-naphthyridin-1-yl)amino]ethyl]benzoate (3.5 g, 10.38 mmol) in

acetonitrile (35 mL) were added sodium iodide (1.55 g, 10.38 mmol) and chlorotrimethylsilane (1.32 mL, 10.38 mmol). The resulting mixture was strirred at room temprature for 1 hour under argon atmosphere. The product formation was confirmed by TLC, then the reaction mixture was diluted with aqueous sodium bicarbonate (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried over sodium sulfate and evaporated under vacuum to give a crude product. The crude product was purified by combiflash column chromatography using 50-55% ethyl acetate in hexane as a mobile phase to give the title compound (2.5 g, 75%). MS(ESI) m/z: 324.1 (M+1); ^{1}H NMR (400 MHz, DMSO-d6): δ 1.49 (d, *J* = 7.2 Hz, 3H); 3.80 (s, 3H), 5.32-5.35 (m, 1H), 6.34-6.36 (m, 1H); 6.54 (d, *J* = 5.2 Hz, 1H), 7.27-7.30 (m, 1H); 7.48 (d, *J* = 8.4 Hz, 2H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.92 (d, J = 5.6 Hz, 1H), 9.82 (d, *J* = 7.6 Hz, 1H), 11.51 (d, *J* = 5.2 Hz, 1H).

[0317]

Step 4: Methyl 4-[(1S)-1-[[8-[(3-fluorophenyl)methoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoate

To a solution of methyl 4-[(1S)-1-[(8-hydroxy-2,7-naphthyridin-1-yl)amino]ethyl]benzoate (0.25 g, 0.77 mmol) in tolune (10 mL) were added silver carbonate (0.42 g, 1.55 mmol) and 3-fluorobenzyl bromide (0.11 mL, 0.93 mmol). The resulting mixture was stirred and heated at 120°C for 16 hours, and the product formation was confirmed by TLC. The reaction mixture was cooled to room temperature, then filtetred on celite pad and washed with ethyl acetate (20 mL). The organic layer was concentrated under vacuum, and the residue was purified by combiflash column chromatography using 10-15% ethyl acetate in hexane as a mobile phase to give the title compound (0.18 g, 54%). MS(ESI) m/z: 432.2 (M+1); ^{1}H NMR (400 MHz, CDCl3): δ 1.41 (d, *J* = 6.4 Hz, 3H); 3.89 (s, 3H), 5.39-5.44 (m, 1H), 5.53 (s, 2H), 6.63 (d, *J* = 5.6 Hz, 1H); 6.68 (d, *J* = 5.6 Hz, 1H), 6.84-6.88 (m, 1H), 7.03 (d, *J* = 6.0 Hz, 1H); 7.06-7.11 (m,

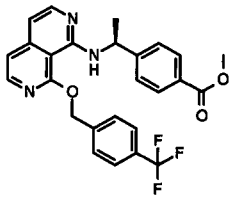
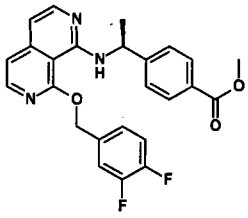
1H), 7.20-7.23 (m, 1H), 7.26-7.29 (m, 2H), 7.34-7.37 (m, 1H), 7.88-7.90 (m, 3H), 7.96-8.03 (m, 1H).

[0318]

The compounds of Examples C2 and C3 were synthesized in a similar manner to that of Example C1.

[0319]

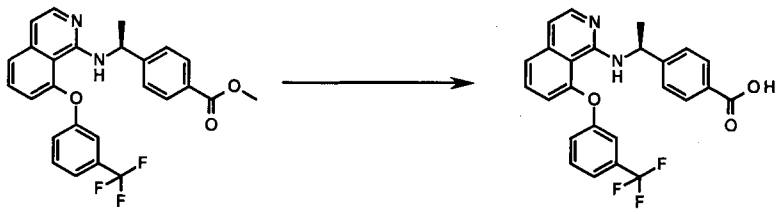
Table 10

Ex.No.	Structure	IUPAC Name	MS(ESI)m/z: (M+1)
C2		Methyl 4-[(1S)-1-[[8-[[4-(trifluoromethyl)phenyl]methoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	482.2
C3		Methyl 4-[(1S)-1-[[8-[(3,4-difluorophenyl)methoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoate	450.2

[0320]

Example D1: 4-[(1S)-1-[[8-[3-(Trifluoromethyl)phenoxy]-1-isoquinolyl]amino]ethyl]benzoic acid

[0321]



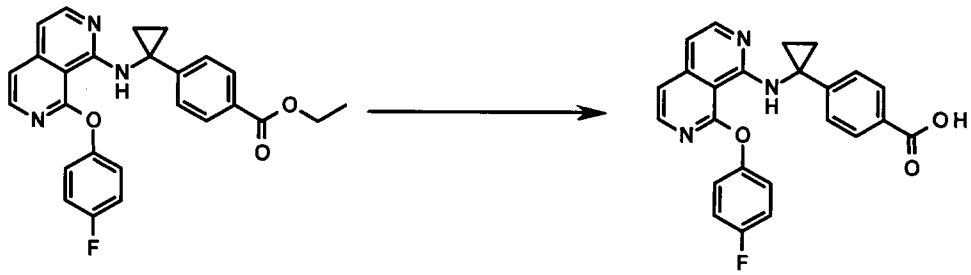
[0322]

To a solution of methyl 4-[(1S)-1-[[8-[3-(trifluoromethyl)phenoxy]-1-isoquinolyl]amino]ethyl]benzoate (110 mg, 0.23 mmol, Example A1) in mixture of solvent THF:methanol:H_2O (3:2:2, 7 mL) was added lithium hydroxide (49 mg, 1.13 mmol). The reaction mixture was stirred at room

temperature overnight, and the product formation was confirmed by TLC. The mixture was concentrated in vacuum and neutralized with 1N HCl. The solid thus obtained was collected by filtration under vacuum and dried to give the title compound. MS(EI)m/z: 453.1 (M+1); ^{1}H NMR (400 MHz, DMSO-*d6*): δ 1.44 (d, *J* = 7.2Hz, 3H); 5.32-5.35 (m, 1H); 6.98-6.99 (d, *J* = 5.2Hz, 1H); 7.04 (dd, *J* = 1.6 & 7.2Hz, 1H); 7.30-7.36 (m, 3H); 7.57-7.70 (m, 6H); 7.76-7.80 (m, 3H); 12.80 (bs, 1H).

Example D2: 4-[1-[[8-(4-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]cyclopropyl]benzoic acid

[0323]

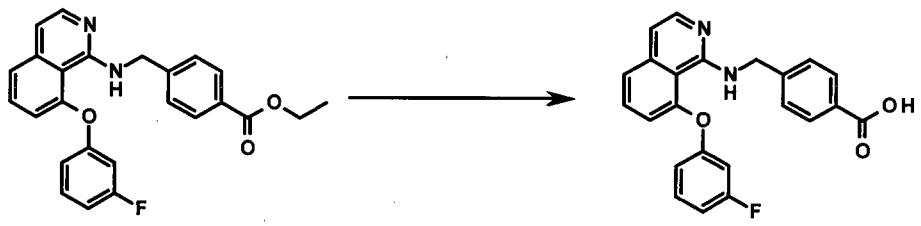


[0324]

The Example D2 was performed in a similar manner to that of Example D1 using the compound mentioned in Example A2 (0.04 g, 0.09 mmol) to give the title compound (0.014 g, 36%). MS(EI) m/z: 416.1 (M+); ^{1}H NMR DMSO: δ 1.42-1.47 (m, 4H); 6.93 (d, *J* = 6.0 Hz, 1H); 7.29-7.33 (m, 5H); 7.38-7.42 (m, 2H); 7.80 (d, *J* = 8.4 Hz, 2H); 7.96 (d, *J* = 5.6 Hz, 1H); 8.04 (d, *J* = 5.6 Hz, 1H); 8.27 (s, 1H); 12.70 (bs, 1H).

Example D3: 4-[[[8-(3-Fluorophenoxy)-1-isoquinolyl]amino]methyl]benzoic acid

[0325]



[0326]

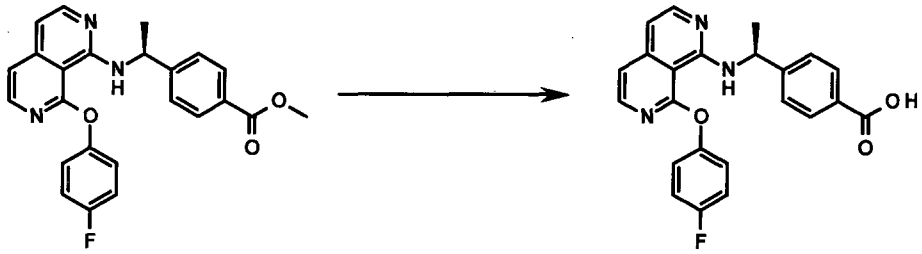
The Example D3 was performed in a similar manner to that

of Example D1 using the compound mentioned in Example A3 (0.07 g, 0.017 mmol) to give the title compound (0.033 g, 51%). MS(EI) m/z: 389.1 (M+1); ^{1}H NMR DMSO: δ 4.80 (d, *J* = 6.0 Hz, 2H); 6.86 (dd, *J* = 1.2 & 7.6Hz, 1H); 6.93 (d, *J* = 6.0 Hz, 2H); 7.10 (dd, *J* = 9.2 & 1.2 Hz, 2H); 7.31 (d, *J* = 8.4 Hz, 2H); 7.47-7.56 (m, 3H); 7.79 (d, *J* = 8.4 Hz, 2H); 7.82 (d, *J* = 6.0 Hz, 1H); 7.94 (t, *J* = 5.6 Hz, 1H); 12.8 (bs, 1H).

[0327]

Example D4: 4-[(1S)-1-[[8-(4-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid

[0328]



[0329]

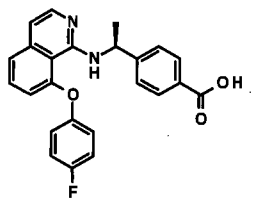
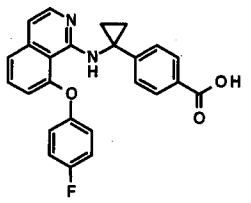
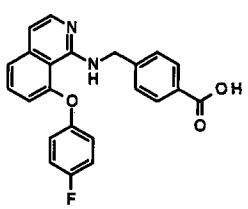
To a solution of methyl 4-[(1S)-1-[[8-(4-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate (0.2 g, 0.47 mmol, Example A4) in 8 mL of combined solvent THF:H_2O (3:1) was added potassium hydroxide (0.053 g, 0.95 mmol). The reaction mixture was stirred at 80°C for 18 hours, and the product formation was confirmed by TLC. The mixture was concentrated in vacuum and neutralized with 1N HCl. The solid thus obtained was collected by filtration under vacuum and dried to give the title compound as a white solid (0.12 g, 62%). MS(EI)m/z: 404 (M+1); ^{1}H NMR DMSO: δ 1.55 (d, *J* = 7.2Hz, 3H); 5.46-5.47 (m, 1H); 6.88 (d, *J* = 5.6 Hz, 1H); 7.28 (d, *J* = 5.6 Hz, 1H); 7.30-7.34 (m, 2H); 7.40-7.43 (m, 2H); 7.55 (d, *J* = 8.0 Hz, 2H); 7.83.-7.88 (m, 3H); 7.96 (d, *J* = 5.6 Hz, 1H); 8.02 (d, *J* = 5.6 Hz, 1H); 12.85 (bs, 1H)

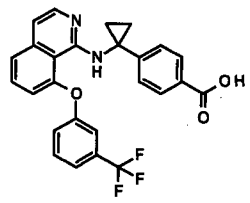
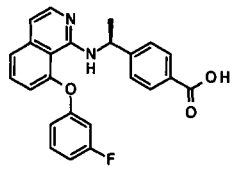
[0330]

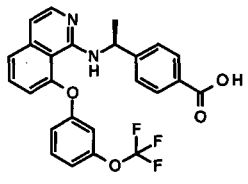
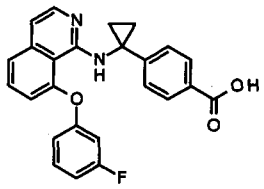
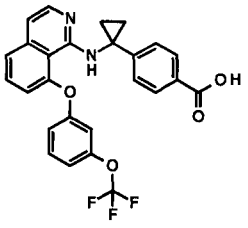
The compounds of Examples D5-D92 were synthesized in a similar manner to that of Example D1 or D4.

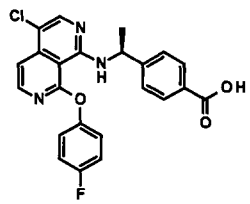
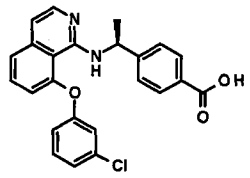
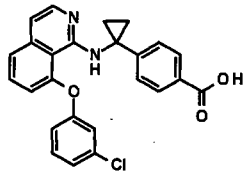
[0331]

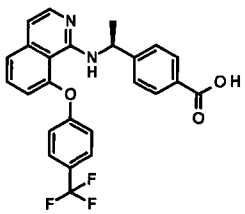
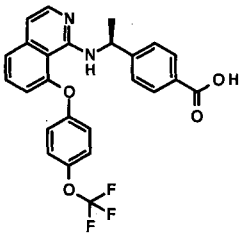
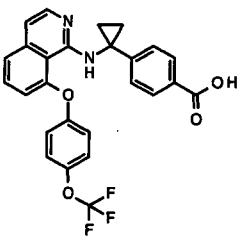
Table 11

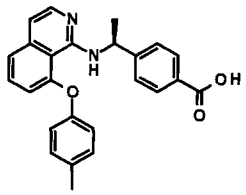
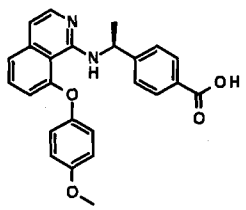
Ex. No.	Structure	IUPAC Name ^{1}H NMR data	MS(ESI)m/z: (M+1)
D5		4-[(1*S*)-1-[[8-(4-Fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.45 (d, *J* = 6.8 Hz, 3H), 5.37 (q, *J* = 6.8 Hz, 1H), 6.83-6.85 (m, 1H), 6.92 (d, *J* = 5.6 Hz, 1H), 7.22-7.25 (m, 2H), 7.30-7.35 (m, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 5.6 Hz, 1H), 7.78 (d, *J* = 6.0 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 12.80 (bs, 1H).	403.2
D6		4-[1-[[8-(4-Fluorophenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoic acid ^{1}H NMR $CDCl_3$: δ 1.56-1.62 (m, 2H); 1.74-1.76 (m, 2H), 6.83 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 6.4 Hz, 1H), 7.16-7.22 (m, 6H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.95 (d, *J* = 6.8 Hz, 1H), 9.16 (bs, 1H).	415.2
D7		4-[[[8-(4-Fluorophenoxy)-1-isoquinolyl]amino]methyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 4.87 (d, *J* = 5.2 Hz, 2H), 6.67-6.6.70 (m,	389.2

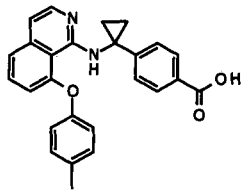
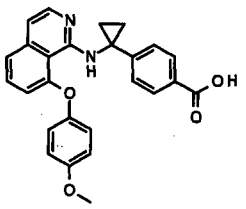
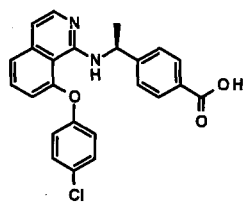
		1H), 6.91 (d, J = 5.6 Hz, 1H), 7.23-7.33 (m, 4H), 7.37-7.43 (m, 3H), 7.49 (t, J = 8.0 Hz, 1H), 7.80-7.83 (m, 3H), 8.10 (t, J = 6.0 Hz, 1H), 12.87 (bs, 1H).	
D8		4-[1-[[8-[3-(Trifluoromethyl)phenoxy]-1-isoquinolyl]amino]cyclopropyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.17-1.20 (m, 2H); 1.36-1.39 (m, 2H); 6.95 (dd, J = 2.8, 6.4 Hz, 1H), 7.00 (d, J = 6.0 Hz, 1H); 7.17 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.57-7.61 (m, 4H), 7.65-7.70 (m, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 6.0 Hz, 1H), 7.95 (s, 1H), 12.75 (bs, 1H).	465.1
D9		4-[(1S)-1-[[8-(3-Fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.43 (d, J = 6.8 Hz, 3H), 5.32-5.35 (m, 1H), 6.90-6.95 (m, 2H), 7.02 (dd, J = 1.6, 6.8 Hz, 1H), 7.07-7.12 (m, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.47-7.61 (m, 4H), 7.77-7.79 (m, 3H), 12.80 (bs, 1H).	403.2

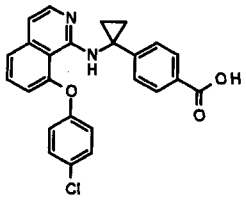
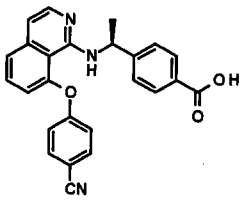
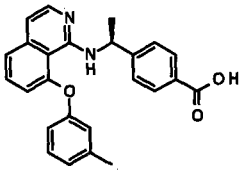
D10		4-[(1*S*)-1-[[8-[3-(Trifluoromethoxy)phenoxy]-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.42 (d, *J* = 7.2 Hz, 3H), 5.30-5.33 (m, 1H), 6.96 (d, *J* = 6.0 Hz, 1H), 7.01-7.03 (m, 1H), 7.07 (dd, *J* = 1.6, 7.2 Hz, 1H);, 7.23-7.28 (m, 4H), 7.42 (d, *J* = 6.8 Hz, 1H), 7.54-7.64 (m, 3H), 7.49-7.79 (m, 3H), 12.80 (bs, 1H).	469.2
D11		4-[1-[[8-(3-Fluorophenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.21-1.23 (m, 2H), 1.39 (s, 2H), 6.93-7.00 (m, 3H), 7.07-7.18 (m, 4H), 7.46-7.59 (m, 3H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 5.6Hz, 1H), 7.90 (s, 1H), 12.75 (bs, 1H).	415.2
D12		4-[1-[[8-[3-(Trifluoromethoxy)phenoxy]-1-isoquinolyl]amino]cyclopropyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.18 (s, 2H), 1.38 (s, 2H), 6.98-7.00 (m, 2H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.22-7.25 (m, 2H), 7.54-7.61 (m, 3H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 5.6 Hz, 1H), 7.88 (s, 1H), 12.75 (bs, 1H).	481.1

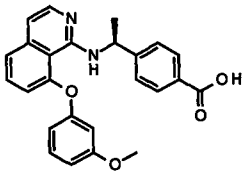
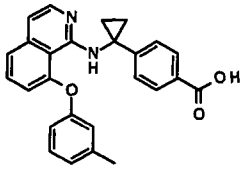
D13		4-[(1*S*)-1-[[4-Chloro-8-(4-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.57 (d, *J* = 6.8 Hz, 3H), 5.43 (t, *J* = 7.2 Hz, 1H), 7.33 (t, *J* = 8.4 Hz, 2H), 7.42-7.45 (m, 3H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.98 (d, *J* = 7.2 Hz, 1H), 8.15 (s, 1H), 8.16 (s, 1H); 12.85 (bs, 1H).	438.4
D14		4-[(1*S*)-1-[[8-(3-Chlorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.43 (d, *J* = 6.8 Hz, 3H), 5.31-5.35 (m, 1H), 6.95 (d, *J* = 6.0 Hz, 1H), 7.01 (dd, *J* = 7.2 & 1.6 Hz, 1H), 7.06 (dd, *J* = 7.2 & 1.6 Hz, 1H), 7.25 (t, *J* = 2.5 Hz, 1H), 7.31-7.32 (m, 3H), 7.45-7.50 (m, 2H), 7.55-7.62 (m, 2H), 7.77-7.79 (m, 3H), 12.80 (bs, 1H).	419.2
D15		4-[1-[[8-(3-Chlorophenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.22-1.23 (m, 2H), 1.38-1.41 (m, 2H), 6.94 (dd, *J* = 7.2 & 1.6 Hz, 1H), 7.00 (d, *J* = 6.0 Hz, 1H), 7.08-7.10 (m, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.30-7.32 (m,	431.2

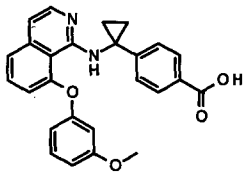
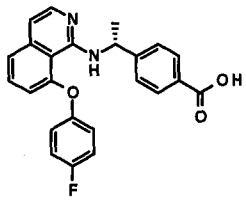
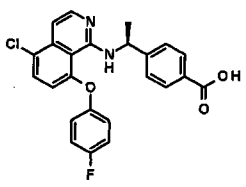
		2H), 7.45-7.49 (m, 1H), 7.54-7.60 (m, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 5.6 Hz, 1H), 7.91 (s, 1H), 12.75 (bs, 1H).	
D16		4-[(1*S*)-1-[[8-[4-(Trifluoromethyl)phenoxy]-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.41 (d, *J* = 6.8 Hz, 3H), 5.28-5.31 (m, 1H), 6.98 (d, *J* = 5.6 Hz, 1H), 7.13 (dd, *J* = 2.4, 6.4 Hz, 1H), 7.20-7.25 (m, 4H), 7.33 (bs, 1H), 7.62-7.67 (m, 2H), 7.73 (d, *J* = 8.0Hz, 2H), 7.78-7.82 (m, 3H), 12.80 (bs, 1H).	453.2
D17		4-[(1*S*)-1-[[8-[4-(Trifluoromethoxy)phenoxy]-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.43 (d, *J* = 7.2 Hz, 3H), 5.32-5.35 (m, 1H), 6.94 (d, *J* = 5.2 Hz, 1H), 6.99 (d, *J* = 6.8 Hz, 1H), 7.24 (d, *J* = 9.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.46-7.62 (m, 5H), 7.67-7.78 (m, 3H), 12.80 (bs, 1H).	469.2
D18		4-[1-[[8-[4-(Trifluoromethoxy)phenoxy]-1-isoquinolyl]amino]cyclopropyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.22-1.23 (m, 2H); 1.37-1.40 (m, 2H), 6.92	481.2

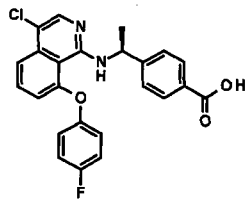
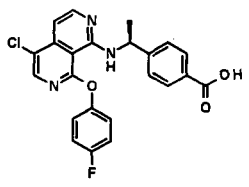
		(d, J = 7.6 Hz, 1H), 6.99 (d, J = 6.0 Hz, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H), 7.54-7.60 (m, 2H), 7.73 (d, J = 8.8 Hz, 2H), 7.81 (d, J = 6.0 Hz, 1H), 7.94 (s, 1H), 12.75 (bs, 1H).	
D19		4-[(1*S*)-1-[[8-(4-Methylphenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.46 (d, J = 6.8 Hz, 3H), 2.33 (s, 3H), 5.34-5.38 (m, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 4.8 Hz, 1H), 7.07 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H); 7.48 (d, J = 7.2 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.75 (d, J = 6.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 3H), 12.80 (bs, 1H).	399.2
D20		4-[(1*S*)-1-[[8-(4-Methoxyphenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.48 (d, J = 6.4 Hz, 3H), 3.78 (s, 3H), 5.34-5.38 (m, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.91 (d, J = 4.8 Hz, 1H), 7.05 (d, J = 9.2 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.0 Hz, 3H), 7.50 (t, J = 7.6 Hz, 1H), 7.75	415.2

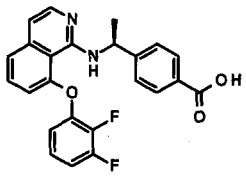
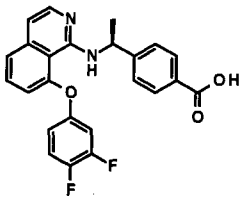
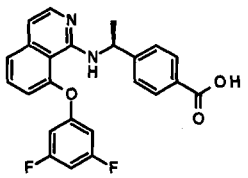
		(d, J = 5.6 Hz, 1H), 7.83 (d, J = 8.8 Hz, 3H), 12.80 (bs, 1H).	
D21		4-[1-[[8-(4-Methylphenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoic acid ^{1}H NMR (400 MHz, DMSO-*d6*): δ 1.23 (s, 2H), 1.39 (s, 2H), 2.32 (s, 3H), 6.79 (d, J = 7.6 Hz, 1H), 6.96 (d, J = 5.2 Hz, 1H), 7.09 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.45-7.54 (m, 2H), 7.74 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 5.2 Hz, 1H), 8.08 (s, 1H), 12.75 (bs, 1H).	411.2
D22		4-[1-[[8-(4-Methoxyphenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.23-1.28 (m, 2H), 1.38-1.41 (m, 2H), 3.77 (s, 3H), 6.70 (d, J = 7.6 Hz, 1H), 6.94 (d, J = 6.0 Hz, 1H), 7.03-7.06 (m, 2H), 7.16-7.21 (m, 4H), 7.42 (d, J = 7.6 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.79 (d, J = 5.2 Hz, 1H), 8.16 (s, 1H), 12.75 (bs, 1H).	427.2
D23		4-[(1S)-1-[[8-(4-Chlorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}HN MR DMSO-d_6: δ 1.43 (d, J = 6.8 Hz, 3H), 5.32-5.36 (m,	419.2

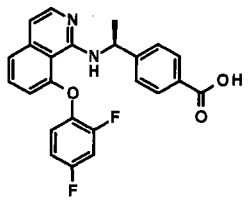
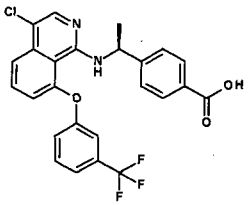
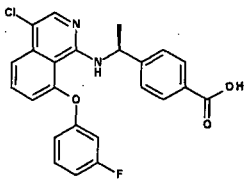
		1H), 6.92-6.96 (m, 2H), 7.16 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.50-7.59 (m, 5H), 7.77-7.80 (m, 3H), 12.80 (bs, 1H).	
D24		4-[1-[[8-(4-Chlorophenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.20-1.23 (m, 2H); 1.37-1.41 (m, 2H), 6.90 (dd, *J* = 6.8 & 1.6 Hz, 1H),6.98 (d, *J* = 5.2 Hz, 1H), 7.15-7.20 (m, 4H), 7.50-7.59 (m, 4H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.80 (d, *J* = 5.6 Hz 1H), 7.94 (s, 1H), 12.75 (bs, 1H).	430.8
D25		4-[(1*S*)-1-[[8-(4-Cyanophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.38 (d, *J* = 6.8 Hz, 3H), 5.32-5.36 (m, 1H), 6.97 (d, *J* = 6.0 Hz, 1H), 7.13-7.15 (m, 1H), 7.19-7.25 (m, 5H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.73 (bs, 2H), 7.80 (d, *J* = 6.0 Hz, 1H), 7.91 (d, *J* = 8.8 Hz, 2H), 12.80 (bs, 1H).	409.8
D26		4-[(1*S*)-1-[[8-(3-Methylphenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.43 (d, *J* = 6.8 Hz, 3H), 2.31 (s, 3H), 5.32-5.36 (m, 1H), 6.88-6.95	399.2

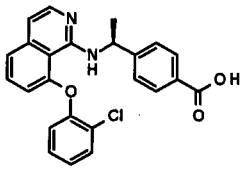
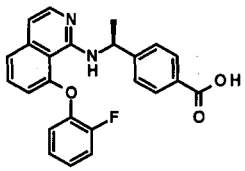
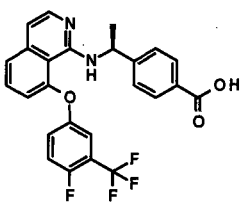
		(m, 4H), 7.07 (d, *J* = 7.2 Hz, 1H), 7.32-7.37 (m, 3H), 7.47-7.57 (m, 2H), 7.65 (d, *J* = 6.8 Hz, 1H), 7.76-7.80 (m, 3H), 12.80 (bs, 1H).	
D27		4-[(1*S*)-1-[[8-(3-Methoxyphenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.44 (d, *J* = 6.8 Hz, 3H), 3.75 (s, 3H), 5.32-5.36 (m, 1H), 6.61 (dd, *J* = 1.8, 7.4 Hz, 1H), 6.76 (t, *J* = 2.2 Hz, 1H), 6.83 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.92 (d, *J* = 6.0 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 7.32-7.38 (m, 3H), 7.50-7.60 (m, 3H), 7.76-7.79 (m, 3H), 12.80 (bs, 1H).	415.4
D28		4-[1-[[8-(3-Methylphenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.20-1.26 (m, 2H), 1.37-1.45 (m, 2H), 2.32 (s, 3H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 6.0 Hz, 2H), 7.03 (s, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.48-7.56 (m, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 6.0 Hz, 1H), 8.04 (s, 1H), 12.75 (bs, 1H).	411.2

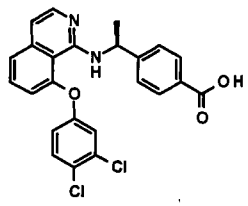
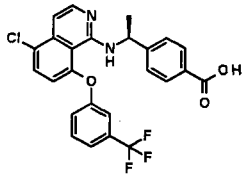
D29		4-[1-[[8-(3-Methoxyphenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.20-1.23 (m, 2H), 1.35-1.38 (m, 2H), 3.76 (s, 3H), 6.67 (d, J = 8.0 Hz, 1H), 6.81-6.84 (m, 2H), 6.90 (d, J = 7.2 Hz, 1H), 6.97 (d, J = 6.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.35 (t, J = 8.0 Hz, 1H), 7.50-7.58 (m, 2H), 7.74 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 6.0Hz, 1H), 7.99 (s, 1H), 12.75 (bs, 1H).	427.2
D30		4-[(1*R*)-1-[[8-(4-Fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.46 (d, J = 7.2 Hz, 3H), 5.37 (q, J = 6.8 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.93 (d, J = 5.6 Hz, 1H), 7.23 (d, J = 4.8 Hz, 1H), 7.25 (d, J = 4.4 Hz, 1H), 7.32 (t, J = 8.4 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.67 (bs, 1H), 7.76-7.82 (m, 3H), 12.75 (bs, 1H).	403.2
D31		4-[(1*S*)-1-[[5-Chloro-8-(4-fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.47 (d, J = 6.8 Hz, 3H), 5.39 (q, J = 6.8	437.1

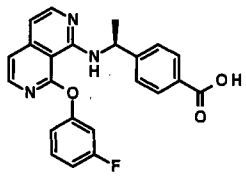
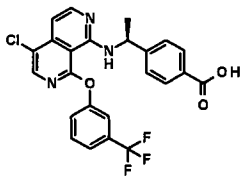
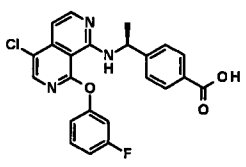
		Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 7.08 (d, *J* = 5.6 Hz, 1H), 7.27-7.42 (m, 6H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 6.8 Hz, 1H), 7.95 (d, *J* = 6.0 Hz, 1H).	
D32		4-[(1*S*)-1-[[4-Chloro-8-(4-fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.47 (d, *J* = 7.2 Hz, 3H), 5.34 (q, *J* = 6.8 Hz, 1H), 6.97 (dd, *J* = 6.0 & 2.8 Hz, 1H); 7.27-7.6 (m, 4H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.70-7.73 (m, 2H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.87 (d, *J* = 6.8 Hz, 1H), 7.91 (s, 1H), 12.80 (bs, 1H).	436.8
D33		4-[(1S)-1-[[5-Chloro-8-(4-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.57 (d, *J* = 6.8 Hz, 3H), 5.49 (q, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 6.0 Hz, 1H), 7.33 (t, *J* = 8.4 Hz, 2H), 7.42-7.46 (m, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.98 (d, *J* = 6.8 Hz, 1H), 8.16 (s, 1H), 8.20 (d, *J* = 5.2 Hz, 1H), 12.82 (bs, 1H).	437.8

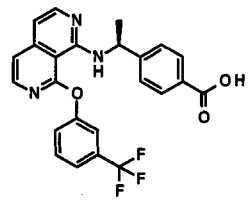
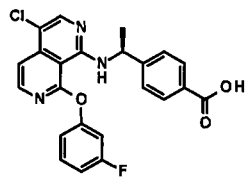
D34		4-[(1*S*)-1-[[8-(2,3-Difluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.49 (d, *J* = 6.8 Hz, 3H), 5.39-5.42 (m, 1H), 6.91 (dd, *J* = 1.8, 7.4 Hz, 1H), 6.94 (d, *J* = 6.0 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 7.29-7.33 (m, 1H), 7.37-7.43 (m, 3H), 7.51-7.56 (m, 3H), 7.79-7.81(m, 3H), 12.80 (bs, 1H).	421.2
D35		4-[(1*S*)-1-[[8-(3,4-Difluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.46 (d, *J* = 6.8 Hz, 3H), 5.35-5.38 (m, 1H), 6.91-6.99 (m, 3H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.43-7.58 (m, 5H), 7.78-7.82 (m, 3H), 12.80 (bs, 1H).	421.2
D36		4-[(1S)-1-[[8-(3,5-Difluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.50 (d, *J* = 6.8 Hz, 3H), 5.42-5.45 (m, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 5.6 Hz, 1H), 7.21-7.26 (m, 1H), 7.44-7.52 (m, 5H), 7.57-7.69 (m, 1H), 7.68 (d, *J* = 6.8 Hz, 1H), 7.79 (d, *J* = 5.6 Hz, 1H), 7.84 (d,	421.2

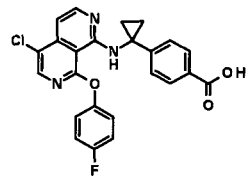
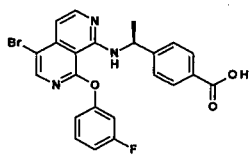
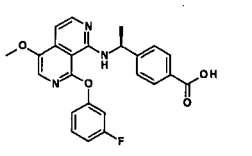
		J = 8.4 Hz, 2H), 12.80 (bs, 1H).	
D37		4-[(1S)-1-[[8-(2,4-Difluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.44 (d, J = 6.8 Hz, 3H), 5.32-5.35 (m, 1H), 6.90 (dd, J = 1.8, 8.2 Hz, 2H), 6.96 (d, J = 6.0 Hz, 1H), 7.09-7.15 (m, 2H), 7.31-7.35 (m, 3H), 7.59-7.62 (m, 2H), 7.78-7.80 (m, 3H), 12.80 (bs, 1H).	421.2
D38		4-[(1*S*)-1-[[4-Chloro-8-[3-(trifluoromethyl)phenoxy]-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.45 (d, J = 6.8 Hz, 3H), 5.30 (q, J = 7.2 Hz, 1H), 7.15 (dd, J = 6.4 & 3.6 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.0 Hz, 1H), 7.62-7.71 (m, 4H), 7.76-7.81 (m, 4H), 7.93 (s, 1H), 12.82 (bs, 1H).	487.1
D39		4-[(1*S*)-1-[[4-Chloro-8-(3-fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.45 (d, J = 6.8 Hz, 3H), 5.31 (q, J = 6.8 Hz, 1H), 6.97 (dd, J = 8.4 & 2.0 Hz, 1H), 7.09-7.17 (m, 3H), 7.34 (d, J = 8.4 Hz, 2H),	437.1

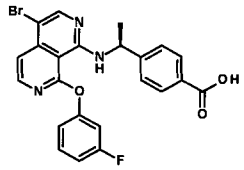
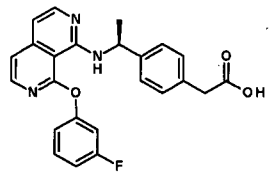
		7.51 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 5.6 Hz, 1H), 7.75-7.80 (m, 4H), 7.92 (s, 1H), 12.75 (bs, 1H).	
D40		4-[(1*S*)-1-[[8-(2-Chlorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.48 (d, J = 7.2 Hz, 3H), 5.40-5.44 (m, 1H), 6.75 (dd, J = 1.6, 7.2 Hz, 1H), 6.93 (d, J = 6.0 Hz, 1H), 7.22 (dd, J = 8.4 & 1.6 Hz, 1H), 7.26-7.39 (m, 3H), 7.44-7.55 (m, 3H), 7.63 (d, J = 6.8 Hz, 1H), 7.71 (dd, J = 8.2 & 1.8 Hz, 1H), 7.78-7.81 (m, 3H), 12.80 (bs, 1H).	419.1
D41		4-[(1S)-1-[[8-(2-Fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.60 (d, J = 4.4 Hz, 3H), 5.46-5.48 (m, 1H), 6.87 (d, J = 8.0 Hz, 1H), 7.01 (bs, 1H), 7.33-7.67 (m, 9H), 7.73 (d, J = 6.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 12.80 (bs, 1H).	403.2
D42		4-[(1*S*)-1-[[8-[4-Fluoro-3-(trifluoromethyl)phenoxy]-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.46 (d, J = 6.8 Hz, 3H), 5.35-5.38 (m,	471.1

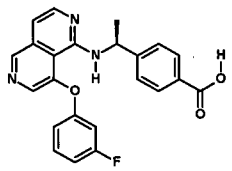
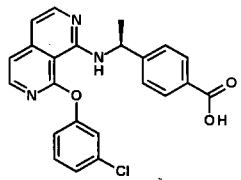
		1H), 6.92-6.95 (m, 2H), 7.38 (d, *J* = 8.0 Hz, 2H) , 7.42-7.62 (m, 5H), 7.69 (dd, *J* = 5.6 & 3.2 Hz, 1H), 7.78-7.80 (m, 3H), 12.80 (bs, 1H).	
D43		4-[(1*S*)-1-[[8-(3,4-Dichlorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.45 (d, *J* = 6.8 Hz, 3H), 5.32-5.35 (m, 1H), 6.95 (d, *J* = 6.0 Hz, 1H), 7.03 (dd, *J* = 1.6 & 7.2 Hz, 1H), 7.08 (dd, *J* = 8.8 & 2.4 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 2.8 Hz, 1H), 7.53-7.62 (m, 2H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 3H), 12.80 (bs, 1H).	
D44		4-[(1*S*)-1-[[5-Chloro-8-[3-(trifluoromethyl)phenoxy]-1-isoquinolyl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.44 (d, *J* = 6.8 Hz, 3H), 5.35 (q, *J* = 6.8 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 1H), 7.11 (d, *J* = 6.4 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 9.2 Hz, 1H), 7.62-7.70 (m, 4H), 7.75-7.80 (m, 3H), 7.96 (d, *J* = 5.6 Hz, 1H), 12.75 (bs, 1H).	487.1

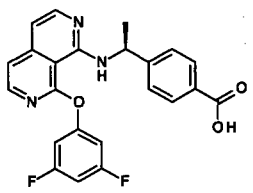
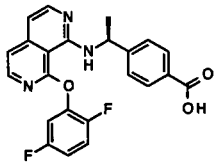
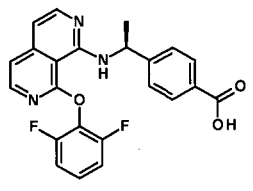
D45		4-[(1*S*)-1-[[8-(3-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.56 (d, *J* = 6.8 Hz, 3H), 5.46 (q, *J* = 6.8 Hz, 1H), 6.90 (d, *J* = 5.6 Hz, 1H); 7.18-7.20 (m, 1H), 7.23 (dd, *J* = 8.4 & 1.6 Hz, 1H), 7.31 (d, *J* = 6.0 Hz, 1H), 7.35-7.38 (m, 1H), 7.50-7.57 (m, 3H), 7.79 (d, *J* = 6.8 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 5.6 Hz, 1H), 8.02 (d, *J* = 5.6 Hz, 1H), 12.80 (bs, 1H).	404.0
D46		4-[(1*S*)-1-[[5-Chloro-8-[3-(trifluoromethyl)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.58 (d, *J* = 6.8 Hz, 3H), 5.50 (q, *J* = 6.8 Hz, 1H), 7.01 (d, *J* = 5.6 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.69-7.75 (m, 3H), 7.86-7.88 (m, 3H), 7.96 (d, *J* = 7.2 Hz, 1H), 8.18 (s, 1H), 8.21 (d, *J* = 6.0 Hz, 1H), 12.81 (bs, 1H).	488.1
D47		4-[(1*S*)-1-[[5-Chloro-8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.57 (d, *J* = 7.6 Hz, 3H), 5.48 (q, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 5.2 Hz,	438.1

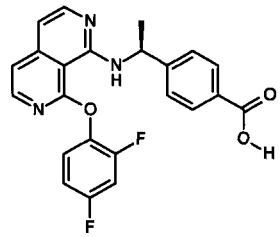
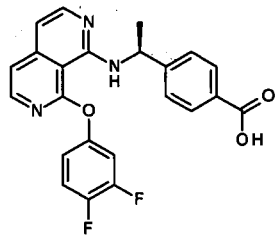
		1H), 7.18 (dt, J = 8.4 & 2.0 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.37-7.41 (m, 1H), 7.51-7.57 (m, 3H), 7.87 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 6.8 Hz, 1H), 8.19 (s, 1H), 8.20 (d, J = 2.0 Hz, 1H), 12.82 (bs, 1H).	
D48		4-[(1*S*)-1-[[8-[3-(Trifluoromethyl)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.57 (d, J = 6.8 Hz, 3H), 5.47 (q, J = 6.8 Hz, 1H), 6.89 (d, J = 5.2 Hz, 1H), 7.12 (d, J = 6.0 Hz, 1H), 7.58 (d, J = 7.6 Hz, 2H), 7.70-7.74 (m, 3H), 7.82 (d, J = 7.2 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.97 (d, J = 5.6 Hz, 1H), 8.03 (d, J = 6.0 Hz, 1H), 12.82 (bs, 1H).	454.0
D49		4-[(1*S*)-1-[[4-Chloro-8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.57 (d, J = 7.2 Hz, 3H), 5.43 (q, J = 6.8 Hz, 1H), 7.18-7.22 (m, 1H), 7.25 (dd, J = 2.0 & 8.4 Hz, 1H), 7.37-7.41 (m, 1H), 7.47 (d, J = 6.0 Hz, 1H), 7.52-7.57 (m, 3H), 7.87 (d, J = 8.0 Hz, 2H), 8.93 (d, J = 6.8 Hz, 1H), 8.16 (s, 1H), 8.18 (d, J = 5.6 Hz, 1H), 12.82 (bs, 1H).	438.0

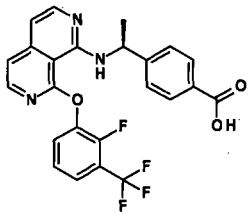
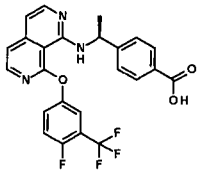
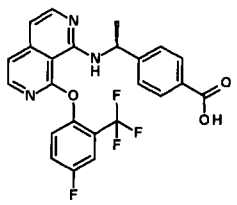
D50		4-[1-[[5-Chloro-8-(4-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]cyclopropyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.43-1.47 (m, 4H), 7.05 (d, J = 5.6 Hz, 1H), 7.29-7.34 (m, 4H), 7.40-7.44 (m, 2H), 7.79 (d, J = 8.4 Hz, 2H), 8.16 (s, 1H), 8.22 (d, J = 5.6 Hz, 1H), 8.44 (s, 1H), 13.0 (bs, 1H).	450
D51		4-[(1S)-1-[[5-Bromo-8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR (400 MHz, DMSO-$d6$): δ 1.55 (d, J = 6.8 Hz, 3H), 5.44-5.48 (m, 1H), 6.95 (d, J = 5.2 Hz, 1H), 7.15-7.19 (m, 1H), 7.24 (dd, J = 7.6, 1.6 & 7.6 Hz, 1H), 7.36-7.39 (m, 1H), 7.50 (d, J = 8 Hz, 1H), 7.49-7.55 (m, 3H), 7.54 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 6.8 Hz, 1H), 8.17 (d, J = 6.0 Hz, 1H), 8.26 (s, 1H), 12.80 (br s, 1H).	481.9
D52		4-[(1S)-1-[[8-(3-Fluorophenoxy)-5-methoxy-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR (400 MHz, DMSO-$d6$): δ	434.0

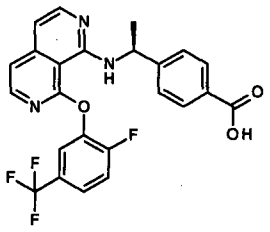
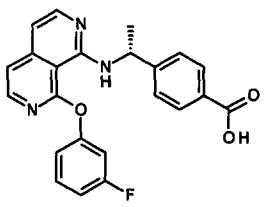
		1.55 (d, *J* = 7.2 Hz, 3H), 3.92 (s, 3H), 5.43-5.45 (m, 1H), 7.00 (d, *J* = 5.2 Hz, 1H), 7.14-7.18 (m, 2H), 7.28-7.31 (m, 1H), 7.49-7.54 (m, 3H), 7.71 (s, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 8.07 (d, *J* = 6.0 Hz, 1H), 12.80 (br s, 1H).	
D53		4-[(1S)-1-[[4-Bromo-8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR (400 MHz, DMSO-*d6*): δ 1.55 (d, J = 6.8 Hz, 3H), 5.44-5.48 (m, 1H), 7.17-7.22 (m, 1H), 7.24 (dd, J = 1.6 & 8.0, 1.6 Hz, 1H), 7.37-7.41 (m, 1H), 7.43 (d, J = 5.2 Hz, 1H), 7.51-7.57 (m, 3H), 7.87 (d, J = 8.4 Hz, 2H), 7.95 (d, J = 7.2 Hz, 1H), 8.17 (d, J = 6.0 Hz, 1H), 8.25 (s, 1H), 12.80 (br s, 1H).	481.9
D54		2-[4-[(1S)-1-[[8-(3-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]phenyl]acetic acid ^{1}H NMR (400 MHz, DMSO-*d6*): δ 1.53 (d, J = 7.2 Hz, 3H), 3.51 (s, 2H), 5.39-5.45 (m, 1H), 6.88 (d, J= 5.6 Hz, 1H), 7.15-7.23 (m, 4H), 7.30 (d, J = 6.0 Hz, 1H), 7.33-7.36 (m, 3H),	418.0

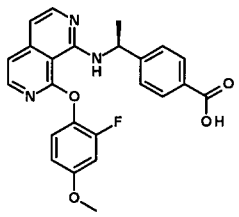
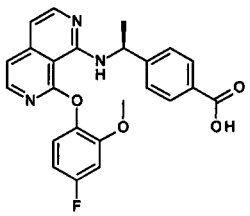
		7.49-7.55 (m, 1H), 7.73 (d,J = 6.8 Hz, 1H), 7.97 (d, J = 5.2 Hz, 1H), 8.05 (d, J = 5.6 Hz, 1H), 12.23 (br. s, 1H)).	
D55		4-[(1S)-1-[[8-(3-Fluorophenoxy)-2,6-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR (400 MHz, DMSO-*d6*): δ 1.45 (d, J = 6.8 Hz, 3H), 5.31-5.35 (m, 1H), 6.99 (dd, J = 1.6, 8.0, 1.6 Hz, 1H), 7.10-7.20 (m, 3H), 7.33 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 6.8 Hz, 1H), 7.48-7.53 (m, 1H), 7.79 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 5.6 Hz, 1H), 8.16 (s, 1H), 8.98 (s, 1H), 12.80 (br s, 1H).	404.0
D56		4-[(1S)-1-[[8-(3-Chlorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.56 (d, *J* = 6.8 Hz, 3H), 5.44-5.47 (m, 1H), 6.89 (d, *J* = 6.0 Hz, 1H), 7.30 (d, *J* = 5.6 Hz, 1H), 7.35-7.41 (m, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.55.-7.58 (m, 3H), 7.79 (d, *J* = 6.8 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 5.2 Hz, 1H), 8.02 (d, *J* = 5.2 Hz, 1H), 12.85 (bs, 1H).	420.1
D57		4-[(1S)-1-[[8-(3,5-	422.1

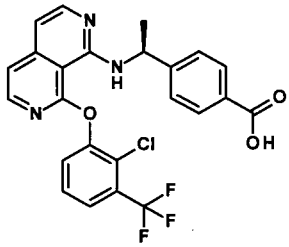
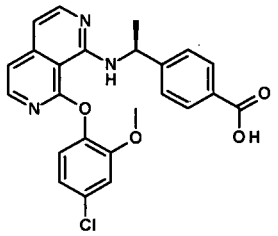
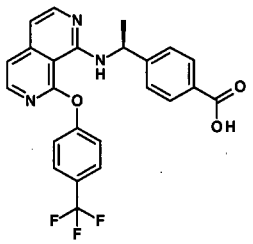
		Difluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.60 (d, J = 7.2 Hz, 3H), 5.45-5.49 (m, 1H), 6.97 (d, J = 5.2 Hz, 1H), 7.22-7.30 (m, 3H), 7.39 (d, J = 5.6 Hz, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 8.0 Hz, 3H), 8.00 (d, J = 6.0 Hz, 1H), 8.07 (d, J = 5.2 Hz, 1H), 12.85 (bs, 1H).	
D58		4-[(1S)-1-[[8-(2,5-Difluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.58 (d, J = 6.8 Hz, 3H), 5.49-5.53 (m, 1H), 6.92 (d, J = 5.6 Hz, 1H), 7.23-7.27 (m, 1H), 7.35 (d, J = 6.0 Hz, 1H), 7.47-7.54 (m, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.62-7.67 (m, 1H), 7.78-7.79 (m, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.99 (d, J = 6.0 Hz, 1H), 8.04 (d, J = 5.6 Hz, 1H), 12.80 (bs, 1H).	422.1
D59		4-[(1S)-1-[[8-(2,6-Difluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.57 (d, J = 7.2 Hz, 3H), 5.49-5.53 (m, 1H), 6.91 (d, J = 5.2 Hz, 1H), 7.22-7.25 (m, 1H), 7.33 (d, J	422.1

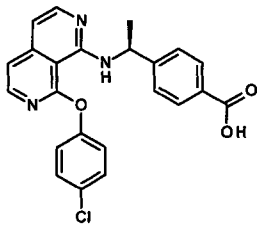
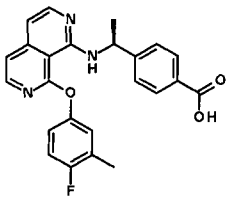
		= 6.0 Hz, 1H), 7.49-7.56 (m, 3H), 7.63-7.69 (m, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.97 (d, *J* = 6.0 Hz, 1H), 8.04 (d, *J* = 6.0 Hz, 1H), 12.85 (bs, 1H).	
D60		4-[(1S)-1-[[8-(2,4-Difluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.59 (d, J = 6.8 Hz, 3H), 5.56-5.58 (m, 1H), 6.93 (d, J = 5.6 Hz, 1H), 7.33-7.38 (m, 3H), 7.39-7.44 (m, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.84-7.89 (m, 3H), 7.98 (d, J = 6.0 Hz, 1H), 8.07 (d, J = 5.6 Hz, 1H), 12.80 (bs, 1H).	422.1
D61		4-[(1S)-1-[[8-(3,4-Difluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.58 (d, *J* = 6.4 Hz, 3H), 5.44-5.48 (m, 1H), 6.94 (d, *J* = 5.2 Hz, 1H), 7.27-7.29 (m, 1H), 7.34 (d, *J* = 6.0 Hz, 1H), 7.54-7.61 (m, 4H), 7.63-7.69 (m, 1H), 7.89 (d, *J* = 8.8 Hz, 2H), 8.00-8.03 (m, 2H), 12.82 (bs, 1H).	422.1

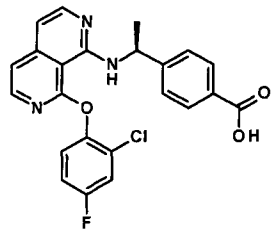
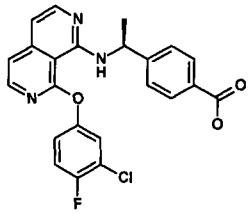
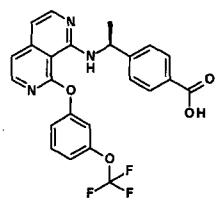
D62		4-[(1S)-1-[[8-[2-Fluoro-3-(trifluoromethyl)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.59 (d, J = 6.8 Hz, 3H), 5.52-5.56 (m, 1H), 6.92 (d, J = 5.6 Hz, 1H), 7.35 (d, J = 6.0 Hz, 1H), 7.54-7.59 (m, 3H), 7.75-7.78 (m, 1H), 7.83-7.89 (m, 3H), 7.94-7.98 (m, 2H), 8.05 (d, J = 5.6 Hz, 1H), 12.80 (br s, 1H).	472.0
D63		4-[(1S)-1-[[8-[4-Fluoro-3-(trifluoromethyl)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.57 (d, J = 7.2 Hz, 3H), 5.45-5.49 (m, 1H), 6.90 (d, J = 6.0 Hz, 1H), 7.31 (d, J = 6.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.63-7.68 (m, 1H), 7.78-7.81 (m, 2H), 7.88 (d, J = 8.4 Hz, 2H), 7.91 (dd, J = 5.6 & 2.4 Hz, 1H), 7.97 (d, J = 5.6 Hz, 1H), 8.02 (d, J = 5.2 Hz, 1H), 12.80 (bs, 1H).	472.0
D64		4-[(1S)-1-[[8-[4-Fluoro-2-(trifluoromethyl)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.52 (d, J = 7.2 Hz, 3H), 5.45-5.49 (m, 1H), 6.92 (d, J = 5.2 Hz, 1H),	472.0

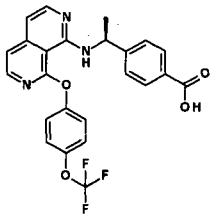
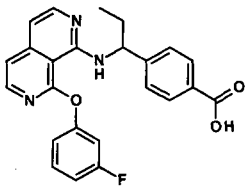
		7.34 (d, J = 5.6 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 7.2 Hz, 1H), 7.71-7.73 (m, 2H), 7.80 (dd, J = 8.4 & 2.4 Hz, 1H), 7.86 (d, J = 8.8 Hz, 2H), 7.96 (d, J = 5.2 Hz, 1H), 8.04 (d, J = 6.0 Hz, 1H), 12.80 (bs, 1H).	
D65		4-[(1S)-1-[[8-[2-Fluoro-5-(trifluoromethyl)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.59 (d, J = 6.8 Hz, 3H), 5.51-5.55 (m, 1H), 6.92 (d, J = 6.0 Hz, 1H), 7.35 (d, J = 5.2 Hz, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.68-7.71 (m, 1H), 7.79-7.83 (m, 2H), 7.88 (d, J = 8.0 Hz, 2H), 7.97 (d, J = 5.2 Hz, 1H), 8.05 (d, J = 6.0 Hz, 1H), 8.13 (dd, J = 6.4 & 1.6 Hz, 1H), 12.80 (bs, 1H).	472.1
D66		4-[(1R)-1-[[8-(3-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR (400 MHz, DMSO-d6): δ 1.56 (d, J = 7.2 Hz, 3H), 5.44-5.47 (m, 1H), 6.90 (d, J = 5.2 Hz, 1H), 7.15-7.20 (m, 1H), 7.23 (dd, J = 8, 1.6 Hz, 1H), 7.31 (d, J = 5.6 Hz, 1H), 7.32-7.39 (m, 1H), 7.50-7.57 (m, 3H), 7.79-7.81 (m, 1H),	404

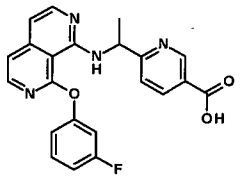
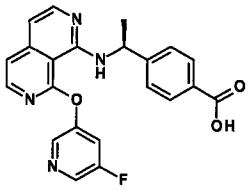
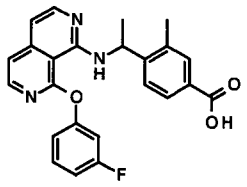
		7.88 (d, J = 8 Hz, 2H), 7.99 (d, J = 6 Hz, 1H), 8.02 (d, J = 5.2 Hz, 1H), 12.85 (bs, 1H).	
D67		4-[(1S)-1-[[8-(2-Fluoro-4-methoxy-phenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR (400 MHz, DMSO-d6): δ 1.57 (d, J = 6.8 Hz, 3H), 3.81 (s, 3H), 5.47-5.51 (m, 1H), 6.87-6.90 (m, 2H), 7.07 (dd, J = 12.4, 2.8 Hz, 1H), 7.30 (d, J = 5.6 Hz, 1H), 7.48 (t, J = 8.8 Hz, 1H), 7.55 (d, J = 8 Hz, 2H), 7.83-7.89 (m, 3H), 7.96 (d, J = 5.2 Hz 1H), 8.03 (d, J = 5.6 Hz, 1H), 12.85 (bs, 1H).	434.0
D68		4-[(1S)-1-[[8-(4-Fluoro-2-methoxy-phenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR (400 MHz, DMSO-d6): δ 1.55 (d, J = 7.2 Hz, 3H), 3.75 (s, 3H), 5.48-5.51 (m, 1H), 6.85-6.90 (m, 2H), 7.15 (dd, J = 10.8, 3.2 Hz, 1H), 7.25 (d, J = 5.2 Hz, 1H), 7.44- 7.48 (m, 1H), 7.54 (d, J = 8 Hz, 2H), 7.89 (d, J = 8.4 Hz, 2H), 7.95 (d, J = 6 Hz, 2H), 8.01 (d, J = 5.2 Hz, 1H), 12.85 (bs, 1H).	434.0

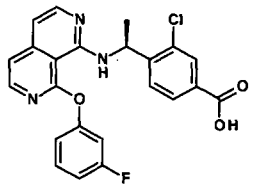
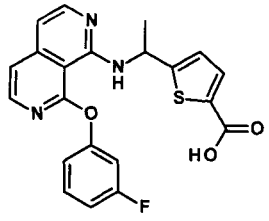
D69		4-[(1S)-1-[[8-[2-Chloro-3-(trifluoromethyl)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR (400 MHz, DMSO-d6): δ 1.58 (d, J = 7.2 Hz, 3H), 5.53-5.57 (m, 1H), 6.92 (d, J = 5.6 Hz, 1H), 7.34 (d, J = 6 Hz, 1H), 7.58 (d, J = 8 Hz, 2H), 7.72 (t, 8.4 Hz, 1H), 7.85- 7.89 (m, 4H), 7.95 (t, J = 5.6 Hz, 2H), 8.05 (d, J = 5.2 Hz, 1H), 12.81 (bs, 1H).	488.0
D70		4-[(1S)-1-[[8-(4-Chloro-2-methoxy-phenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR (400 MHz, DMSO-d6): δ 1.55 (d, *J* = 7.2 Hz, 3H), 3.76 (s, 3H), 5.48-5.52 (m, 1H), 6.89 (d, *J* = 5.3 Hz, 1H), 7.12 (dd, *J* = 2.4 Hz, *J* = 8.4 Hz, 1H), 7.27-7.31 (m, 2H), 7.48 (d, *J* =8.8 Hz, 1H), 7.54 (d, *J* = 8 Hz, 2H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.95 (d, *J* = 5.6 Hz, 2H), 8.02 (d, J= 5.2 Hz, 1H), 12.85 (bs,1H).	450.0
D71		4-[(1S)-1-[[8-[4-(Trifluoromethyl)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR (400 MHz, DMSO-d6): δ 1.56 (d, J= 6.8 Hz, 3H), 5.45-5.48 (m, 1H), 6.91 (d, J= 6	454.0

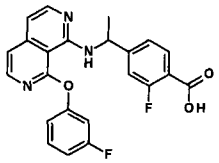
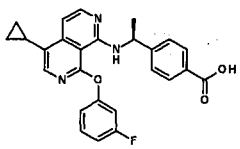
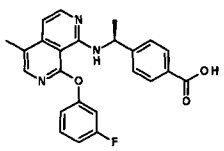
		Hz, 1H), 7.33 (d, *J* = 6 Hz, 1H), 7.56 (d, *J* = 8Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.86-7.89 (m, 4H), 7.98 (d, *J* = 6 Hz, 1H), 8.03 (d, *J* = 5.6 Hz, 1H), 12.80 (bs, 1H).	
D72		4-[(1S)-1-[[8-(4-Chlorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR (400 MHz, DMSO-d6): δ 1.57 (d, *J* = 8 Hz, 3H), 5.43-5.47 (m, 1H), 6.92 (d, 5.2 Hz, 1H), 7.32 (d, *J* = 7.42 Hz, 2H), 7.54-7.57 (m, 4H); 7.88 (d, *J* = 8 Hz, 2H); 7.88 (d, *J* = 8 Hz, 2H); 7.98-8.01 (m, 2H); 12.80 (bs, 1H)	420.0
D73		4-[(1S)-1-[[8-(4-Fluoro-3-methyl-phenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR (400 MHz, DMSO-d6): δ 1.55 (d, J = 6.8 Hz, 3H), 2.28 (s, 3H), 5.43-5.47 (m, 1H), 6.88 (d, J = 5.6 Hz , 1H), 7.21- 7.31 (m, 4H), 7.55 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 7.2 Hz, 1H), 7.88 (d, J = 8 Hz, 2H), 7.96 (d, J = 5.6 Hz, 1H), 8.01 (d, J = 5.6 Hz, 1H), 12.80 (bs, 1H)	418.0

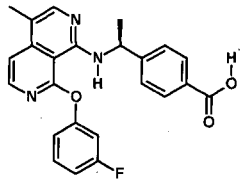
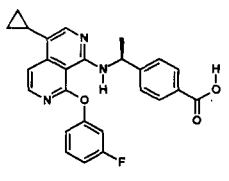
D74		4-[(1S)-1-[[8-(2-Chloro-4-fluoro-phenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR (400 MHz, DMSO-d6): δ 1.57 (d, J = 6.8 Hz, 3H), 5.50-5.54 (m, 1H), 6.91 (d, J = 5.6 Hz, 1H), 7.32 (d, J = 5.2 Hz, 1H), 7.35-7.40 (m, 1H), 7.56 (d, J = 8 Hz, 2H), 7.63-7.69 (m, 2H), 7.8435 (d, J = 6.8 Hz, 1H), 7.88 (d, J = 8.8 Hz, 2H), 7.95 (d, J = 6 Hz, 1H), 8.04 (d, J = 6 Hz, 1H), 12.80 (bs, 1H).	438.0
D75		4-[(1S)-1-[[8-(3-Chloro-4-fluoro-phenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.56 (d, *J* = 6.4 Hz, 3H), 5.44-5.48 (m, 1H), 6.89 (d, *J* = 6.0 Hz, 1H), 7.30 (d, *J* = 6.0 Hz, 1H), 7.41-7.45 (m, 1H), 7.52-7.58 (m, 3H), 7.75-7.78 (m, 2H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.97 (d, *J* = 5.6 Hz, 1H), 8.02 (d, *J* = 6.0 Hz, 1H), 12.80 (bs, 1H).	438.1
D76		4-[(1S)-1-[[8-[3-(Trifluoromethoxy)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.57 (d, *J* = 7.2 Hz, 3H), 5.44-5.48 (m,	470.1

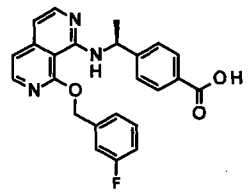
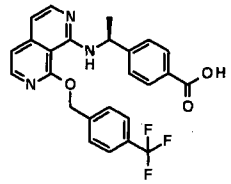
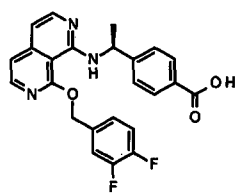
		1H), 6.92 (d, J = 5.6 Hz, 1H), 7.32-7.35 (m, 2H), 7.44 (dd, J = 8.0 & 2.0 Hz, 1H), 7.51 (br s, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.60-7.65 (m, 1H), 7.87 (d, J = 8.0 Hz, 2H), 7.99-8.02 (m, 2H), 12.80 (b s, 1H).	
D77		4-[(1S)-1-[[8-[4-(Trifluoromethoxy)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.58 (d, J = 6.4 Hz, 3H), 5.45-5.48 (m, 1H), 6.92 (d, J = 6.0 Hz, 1H), 7.33 (d, J = 5.6 Hz, 1H), 7.52 (s, 4H), 7.57 (d, J = 8.0 Hz, 2H), 7.88 (d, J = 8.8 Hz, 2H), 7.99-8.02 (m, 2H), 12.82 (bs, 1H).	470.1
D78		4-[1-[[8-(3-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]propyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 0.90 (t, J = 6.8 Hz, 3H), 1.90 (d, J = 6.8 Hz, 2H),5.25-5.29 (m, 1H), 6.88 (d, J = 6 Hz, 1H), 7.19 (td, J = 8.4, 2.8 Hz, 1H), 7.24 (dd, J = 8.2 & 2.2 Hz, 1H), 7.30 (d, J = 5.2 Hz, 1H), 7.38 (dt, J = 10.4 & 2.0 Hz, 1H), 7.52-7.58 (m, 3H), 7.84-7.89 (m, 3H), 7.98 (d, J = 3.6 Hz, 1H), 8.00 (d, J = 3.6 Hz, 1H), 12.70 (bs, 1H).	418.0

D79		6-[1-[[8-(3-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]pyridine-3-carboxylic acid ^{1}H NMR DMSO-d_6: δ 1.55 (d, *J* = 6.4 Hz, 3H), 5.49-5.52 (m, 1H), 6.91 (d, *J* = 6.0 Hz, 1H), 7.16-7.21 (m, 1H),7.25 (d, *J* = 8.0 Hz, 1H), 7.31-7.35 (m, 2H), 7.52-7.60 (m, 2H), 8.00 (d, *J* = 5.6 Hz, 1H), 8.11 (d, *J* = 5.2 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 8.81 (bs, 1H), 8.86 (s, 1H), 13.35 (bs, 1H).	405.1
D80		4-[(1S)-1-[[8-[(5-Fluoro-3-pyridyl)oxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.58 (d, *J* = 6.8 Hz, 3H), 5.47-5.51 (m, 1H), 6.91 (d, *J* = 5.6 Hz, 1H), 7.34 (d, *J* = 5.6 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 6.8 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 6.0 Hz, 1H), 8.03-7.06 (m, 2H), 8.58-8.60 (m, 2H), 12.80 (bs, 1H).	405.2
D81		4-[1-[[8-(3-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]-3-methyl-benzoic acid ^{1}H NMR DMSO-d_6: δ 1.50 (d, *J* = 6.8 Hz, 3H), 2.57 (s, 3H), 5.51-5.55 (m, 1H), 6.87 (d, *J* = 5.6 Hz, 1H), 7.15-7.23 (m,	418.2

		2H), 7.30 (d, J = 5.6 Hz, 1H), 7.34-7.38 (m, 1H), 7.50-7.56 (m, 2H), 7.68 (d, J = 8.0 Hz, 1H), 7.73 (s, 1H), 7.79 (d, J = 6.4 Hz, 1H), 7.98 (d, J = 5.2 Hz, 1H), 8.02 (d, J = 5.6 Hz, 1H), 12.75 (bs, 1H).	
D82		3-chloro-4-[(1S)-1-[[8-(3-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR (400 MHz, DMSO-d6): δ 1.55 (d, J = 6.8 Hz, 3H), 5.62-5.66 (m, 1H), 6.90 (d, J = 5.2 Hz, 1H), 7.19-7.22 (m, 1H), 7.25-7.28 (m, 1H), 7.32 (d, J = 5.2 Hz, 1H), 7.38-7.41 (m, 1H), 7.52-7.59 (m, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.89-7.90 (m, 2H), 7.98-8.02 (m, 2H), 13.2(bs, 1H).	438.0
D83		5-[1-[[8-(3-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]thiophene-2-carboxylic acid ^{1}H NMR (400 MHz, DMSO-d6): δ 1.67 (d, J = 6.8 Hz, 3H), 5.74-5.79 (m, 1H), 6.98 (d, J = 6.0 Hz, 1H), 7.13-7.19 (m, 3H), 7.27-7.35 (m, 2H), 7.48-7.54 (m, 1H), 7.57 (d, J = 4.0 Hz, 1H), 7.76 (d, J = 7.2 Hz, 2H), 7.99 (d, J = 5.2 Hz, 1H), 8.13 (d, J = 5.6 Hz, 1H), 12.9	410.1

		(bs, 1H).	
D84		2-Fluoro-4-[1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.56 (d, *J* = 7.2 Hz, 3H), 5.38-5.42 (m, 1H), 6.91 (d, *J* = 5.6 Hz, 1H), 7.18 (td, *J* = 8.8, 2.4 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 5.2 Hz, 1H), 7.34-7.39 (m, 3H), 7.50-7.56 (m, 1H), 7.76-7.79 (m, 2H), 7.99 (d, *J* = 5.2 Hz, 1H), 8.02 (d, *J* = 5.6 Hz, 1H), 12.05 (bs, 1H).	422.2
D86		4-[(1S)-1-[[5-Cyclopropyl-8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR (400 MHz, DMSO-*d6*): δ 0.60-0.64 (m, 2H), 0.95 (d, *J* = 8.4 Hz, 2H), 1.55 (d, *J* = 6.8 Hz, 3H), 1.90-2.05 (m, 1H), 5.44-5.49 (m, 1H), 7.15-7.21 (m, 3H), 7.31-7.34 (m, 1H), 7.49-7.56 (m, 3H), 7.80 (s, 1H), 7.83 (d, *J* = 7.2 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 2H), 8.12 (d, *J* = 6.0 Hz, 1H), 12.80 (bs, 1H).	444.1
D87		4-[(1S)-1-[[8-(3-Fluorophenoxy)-5-methyl-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid	418.1

		^{1}H NMR (400 MHz, DMSO-*d6*): δ 1.55 (d, *J* = 6.8 Hz, 3H), 2.32 (s, 3H), 5.44-5.48 (m, 1H), 6.87 (d, *J* = 5.6 Hz, 1H), 7.14-7.21 (m, 2H), 7.31-7.35 (m, 1H), 7.49-7.55 (m, 3H), 7.83-7.88 (m, 4H), 8.09 (d, *J* = 6.0 Hz, 1H), 12.80 (bs, 1H).	
D88		4-[(1S)-1-[[8-(3-Fluorophenoxy)-4-methyl-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR (400 MHz, DMSO-*d6*): δ 1.54 (d, *J* = 6.8 Hz, 3H), 2.26 (s, 3H), 5.40-5.44 (m, 1H), 7.15-7.23 (m, 2H), 7.33-7.38 (m, 2H), 7.51-7.56 (m, 3H), 7.67 (d, *J* = 6.8 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.90 (s, 1H), 8.07 (d, *J* = 5.6 Hz, 1H), 12.80 (bs, 1H).	418.1
D89		4-[(1S)-1-[[4-Cyclopropyl-8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR (400 MHz, DMSO-*d6*): δ 0.52-0.59 (m, 2H), 0.89-0.91 (m, 2H), 1.54 (d, *J* = 6.8 Hz, 3H), 1.89-1.93 (m, 1H), 5.40-5.44 (m, 1H), 7.16-7.24 (m, 2H), 7.34-7.38 (m, 1H), 7.51-7.57 (m, 3H), 7.67 (d, *J* = 5.6 Hz, 1H), 7.72 (d, *J* = 6.8 Hz, 1H), 7.86-7.88 (m, 3H), 8.10 (d, *J* = 5.6 Hz, 1H), 12.80	444.0

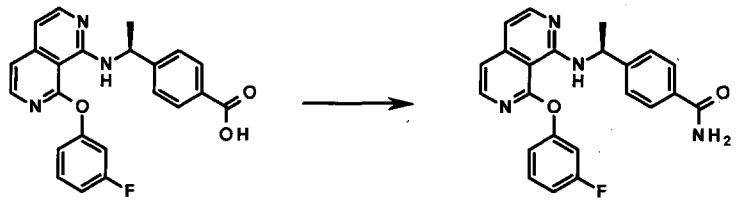
		(bs, 1H).	
D90		4-[(1S)-1-[[8-[(3-Fluorophenyl)methoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.30 (d, J = 6.4 Hz, 3H), 5.31-5.35 (m, 1H), 5.57 (d, J = 3.6 Hz, 2H), 6.80 (dd, J = 15.6, 12 Hz, 1H), 7.18-7.23 (m, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.43-7.49 (m, 3H), 7.78 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 7.2 Hz, 1H), 7.94 (d, J = 5.6 Hz, 1H), 8.08 (d, J = 5.6 Hz, 1H), 12.90 (bs, 1H).	
D91		4-[(1S)-1-[[8-[[4-(Trifluoromethyl)phenyl]methoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.34 (d, J = 7.2 Hz, 3H), 5.34-5.38 (m, 1H), 5.65-5.70 (m, 2H), 6.83 (d, J = 5.6 Hz, 1H), 7.22 (d, J = 5.2 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.75-7.86 (m, 7H), 7.97 (d, J = 5.2 Hz, 1H), 8.09 (d, J = 6.0 Hz, 1H), 12.90 (bs, 1H).	
D92		4-[(1S)-1-[[8-[(3,4-Difluorophenyl)methoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid ^{1}H NMR DMSO-d_6: δ 1.33 (d, J = 6.8 Hz, 3H), 5.32-5.35 (m,	

		1H), 5.55 (dd, J = 16.2, 11.2 Hz, 2H), 6.82 (d, J = 5.2 Hz, 1H), 7.21 (d, J = 5.2 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.47-7.51 (m, 2H), 7.73-7.82 (m, 4H), 7.96 (d, J = 5.2 Hz, 1H), 8.10 (d, J = 5.6 Hz, 1H), 12.70 (bs, 1H).	

[0332]

Example E1: 4-[(1S)-1-[[8-(3-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzamide

[0333]



[0334]

To a solution of 4-[(1S)-1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid (0.5 g, 1.24 mmol, Example D45) in THF (10 ml) were added triethylamine (0.25 g, 2.48 mmol) and ethyl chloroformate (0.13 ml, 1.364 mmol) at 0 °C under argon atmosphere. After 15 min stirring at 0°C, 7N ammonia solution (10 ml) in dioxane was added thereto, and the mixture was stirred for 1 hr. The reaction mixture was concentrated under vacuum, and the obtained residue was purified by silica gel (100-200) column chromatography with 35% ethyl acetate:hexane to give title compound as white solid (430 mg,86%). MS(ESI)m/z: 403.1 (M+1); ^{1}H NMR (400 MHz, DMSO-d6): δ 1.55 (d, J = 6.8 Hz, 3H), 5.41-5.47 (m, 1H), 6.89 (d, J = 5.6 Hz, 1H), 7.15-7.39 (m, 5H), 7.48-7.56 (m, 3H), 7.77-7.82 (m, 3H), 7.89 (bs, 1H), 7.98 (d, J = 6.0 Hz, 1H), 8.02 (d, J = 5.6 Hz, 1H).

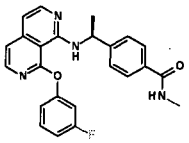
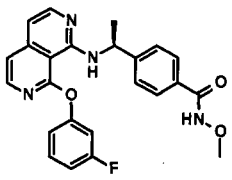
[0335]

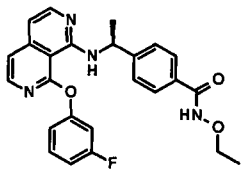
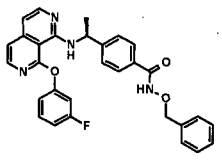
The compounds of Examples E2-E5 were synthesized in a

similar manner to that of Example E1.

[0336]

Table 12

Ex. No.	Structure	IUPAC Name ^{1}H NMR data	MS(ESI)m/z: (M+1)
E2		4-[(1S)-1-[[8-(3-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]-N-methyl-benzamide ^{1}H NMR (400 MHz, DMSO-d6): δ 1.55 (d, *J* = 6.8 Hz, 3H), 2.75 (d, *J* = 4.0 Hz, 3H), 5.41-5.47 (m, 1H), 6.89 (d, *J* = 5 2 Hz, 1H), 7.15-7.24 (m, 2H), 7.30 (d, *J* = 6.0 Hz, 1H), 7.34-7.38 (m, 1H), 7.50-7.57 (m, 3H), 7.73-7.79 (m, 3H), 7.98 (d, *J* = 5.6 Hz, 1H), 8.02(d, *J* = 6.0 Hz, 1H), 8.30-8.39(m, 1H).	404.1
E3		4-[(1S)-1-[[8-(3-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]-N-methoxy-benzamide ^{1}H NMR (400 MHz, DMSO-d6): δ 1.54 (d, *J* = 6.8 Hz, 3H), 3.68 (s, 3H), 5.39-5.45 (m, 1H), 6.89 (d, *J* = 6 Hz, 1H), 7.15-7.24 (m, 2H), 7.31 (d, *J* = 6 Hz, 1H), 7.34-7.38 (m,	417.1

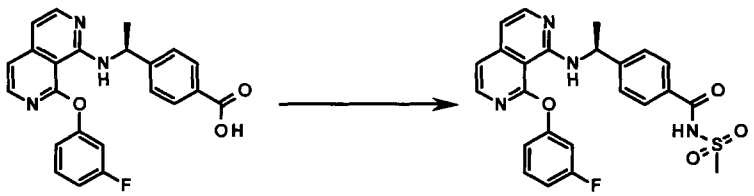
		1H), 7.50-7.56 (m, 3H), 7.67 (d,*J* = 8.4 Hz,2H), 7.77 (d,*J* = 6.8 Hz, 1H), 7.98 (d,*J* = 5.6 Hz, 1H), 8.02 (d, *J* = 6 Hz, 1H), 11.63 (bs , 1H).	
E4		N-Ethoxy-4-[(1S)-1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzamide ^{1}H NMR (400 MHz, DMSO-d6): δ 1.18 (t, 7.2 Hz, 3H), 1.54 (d, *J* = 7.2 Hz, 3H), 3.90 (q, *J* = 7.2 Hz, 2H), 5.39-5.45 (m, 1H), 6.89 (d, *J* = 5.2 Hz, 1H), 7.15-7.23 (m, 2H), 7.31 (d, *J* = 5.2 Hz, 1H), 7.34-7.38 (m, 1H), 7.50-7.56 (m, 3H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.77(d, *J* = 6.8 Hz, 1H), 7.98 (d, *J* = 5.2 Hz, 1H), 8.02 (d, J = 6 Hz, 1H), 11.56 (bs, 1H).	447.1
E5		N-Benzyloxy-4-[(1S)-1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzamide ^{1}H NMR (400 MHz, DMSO-d6): δ 1.54 (d, *J* = 7.2 Hz, 3H), 4.90 (s, 2H), 5.39-5.45 (m, 1H), 6.89 (d, *J* = 6 Hz, 1H), 7.15-7.24 (m, 2H), 7.31 (d, *J* =6.0	509.1

		Hz, 1H), 7.34-7.40 (m, 4H), 7.41-7.45 (m, 2H), 7.50-7.56 (m, 3H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.77 (d, J = 6.8 Hz, 1H), 7.98 (d, *J* = 5.6 Hz, 1H), 8.02 (d, *J* = 5.2 Hz, 1H), 11.65 (bs, 1H).	

[0337]

Example F1: 4-[(1S)-1-[[8-(3-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]-N-methylsulfonyl-benzamide

[0338]



[0339]

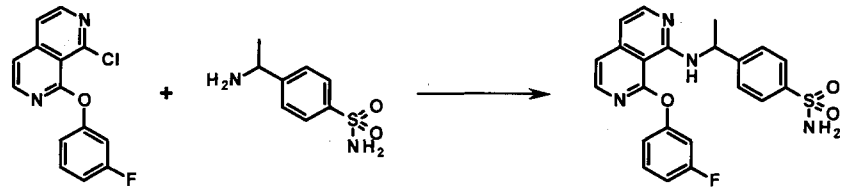
To a mixture of 4-[(1S)-1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid (0.25 g, 0.62 mmol, Example D45), triethylamine (0.3 ml, 1.861 mmol), methanesulfonamide (0.176 g, 1.861 mmol) and 4-N,N-dimethylaminopyridine (0.015 g, 0.124 mmol) in acetonitrile (10 ml) was added 2-methyl-6-nitrobenzoic anhydride (0.256 g, 0.74 mmol) at 0°C under argon atmosphere. After 15 min stirring at 0°C, the mixture was allowed to stirred at room temperature for 3 hr. Water was added thereto, and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL) and dried over sodium sulfate. The organic layer was concentrated under vacuum, and the residue was purified by silica gel (100-200) column chromatography with 20-30% ethyl acetate in hexane as a mobile phase to give the title compound as light yellow solid (0.025 g, 8.5%). MS(ESI)m/z: 481.2 (M+1); ^{1}H NMR (400 MHz, DMSO-*d6*): δ 1.56 (d, *J* = 6.8 Hz, 3H),

2.90 (s, 3H), 5.41-5.47 (m, 1H), 6.80 (bs, 2H), 6.89 (d, J = 5.6 Hz, 1H), 7.15-7.24 (m, 2H), 7.31 (d, 1H), 7.34-7.39 (m, 1H), 7.48-7.58 (m, 3H), 7.79 (d, J=6.4 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 5.6 Hz, 1H), 8.01 (d, J = 5.6 Hz, 1H).

[0340]

Example G1: 4-[1-[[8-(3-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzenesulfonamide

[0341]



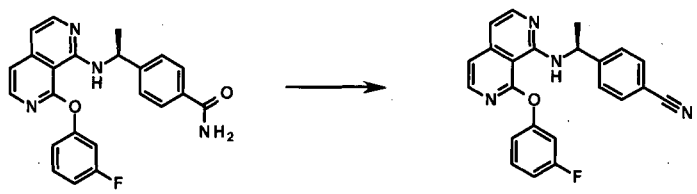
[0342]

The Example G1 was performed in analogous manner to that of Example A1 using 1-chloro-8-(3-fluorophenoxy)-2,7-naphthyridine (0.1 g, 0.37 mmol, Preparation 28) and 4-(1-aminoethyl)benzenesulfonamide (0.087 g, 0.44 mmol; Preparation 76) to give the title compound (0.021 g, 13%). MS(ESI) m/z: 439.0 (M+1); ^{1}H NMR DMSO-d_6: δ 1.56 (d, J = 6.8 Hz, 3H), 5.41-5.42 (m, 1H), 6.89 (d, J = 6 Hz, 1H), 7.17-7.27(m, 4 H), 7.31(d, J = 6 Hz, 1H), 7.38 (dt, J = 10.4, 2.1 Hz, 1H), 7.51-7.57 (m, 1H), 7.62 (d, J = 8 Hz, 2H),7.75 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 2.8 Hz, 1H), 7.99 (d, J = 6 Hz, 1H), 8.01 (d, J = 6 Hz, 1H)

[0343]

Example H1: 4-[(1S)-1-[[8-(3-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzonitrile

[0344]



[0345]

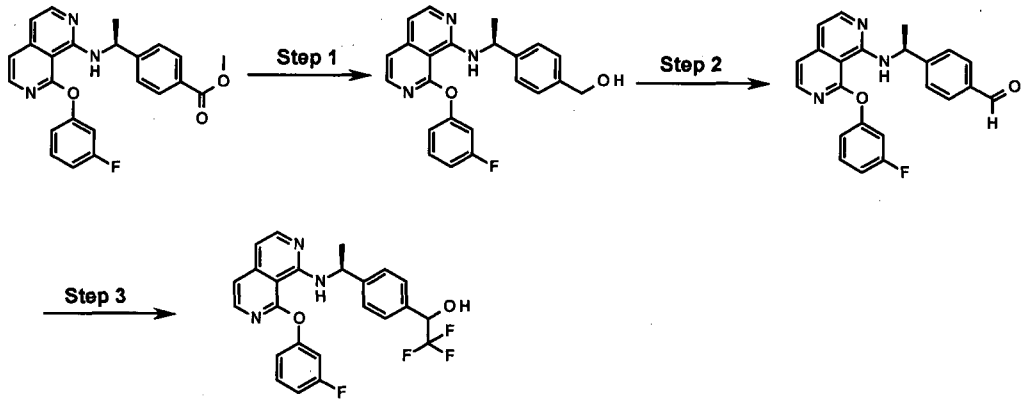
To a solution of 4-[(1S)-1-[[8-(3-fluorophenoxy)-2,7-

naphthyridin-1-yl]amino]ethyl]benzamide (0.4 g~~gm,~~ 0.995 mmol, Example E1) in pyridine (10 ml) were added immidazole (0.135 g, 1.99 mmol) and phosphorus oxychloride (0.61 g, 3.98 mmol) at -20°C under argon atmosphere. The mixture was stirred for 1 hrs at -20°C. Water was added thereto, and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL) and dried over sodium sulfate. The organic layer was concentrated under vacuum, and the residue was purified by silica gel (100-200) column chromatography with 20-30% ethyl acetate in hexane as a mobile phase to give the title compound as light yellow solid (0.33 g, 86%). MS(ESI)m/z: 385.1 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (d, *J* = 6.8 Hz, 3H), 5.47-5.52 (m, 1H), 6.76 (d, *J* = 5.6 Hz, 1H), 7.00-7.06 (m, 3H), 7.11 (d, *J* = 5.2 Hz, 1H), 7.41-7.49 (m, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 6.4 Hz, 1H), 7.96 (d, *J* = 5.6 Hz, 1H), 8.02 (d, *J* = 5.6 Hz, 1H).

[0346]

Example I1: 2,2,2-Trifluoro-1-[4-[(1S)-1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]phenyl]ethanol

[0347]



[0348]

Step 1: [4-[(1S)-1-[[8-(3-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]phenyl]methanol

To a solution of methyl 4-[(1S)-1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoate (1.0 g, 2.39 mmol,

Example A45) in THF (10 ml) was added lithium aluminium hydride (2.4 ml, 2.39 mmol) (1.0 M slution in THF) at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 1 hour and the product formation was confirmed by TLC. The mixture was quenched by aq. sodium sulfate solution, and the obtained solid was removed by filtration, and the filtrate was concentrated to dryness to give the title compound (0.8 g, 86%). MS(EI)m/z: 390.1 (M+1); ^{1}H NMR (400 MHz, , $CDCl_3$): δ 1.61 (d, J = 7.2 Hz, 3H), 4.66 (d, J = 4.4 Hz, 2H), 5.51-5.55 (m, 1H), 6.73 (d, J = 5.6 Hz, 1H), 6.98-7.05 (m, 3H), 7.09 (d, J = 6.0 Hz, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 6.8 Hz, 1H), 7.94 (d, J = 6.0 Hz, 1H), 8.09 (d, J = 6.0 Hz, 1H).

[0349]

Step 2: 4-[(1S)-1-[[8-(3-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzaldehyde

To a solution of [4-[(1S)-1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]phenyl]methanol (0.6 g, 1.54 mmol) in DCM (20 ml) was added Desmartine periodinane (0.98 g, 2.31 mmol) at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 1 hour and the product formation was confirmed by TLC. Then water (25 mL) was added thereto, and the mixture was extracted with dichloromethane (2 x 25 mL). The combined organic layers were washed with brine and dried over sodium sulfate. The organic layer was concentrated under vacuo to give the title compound (0.5 g., 84%) as a crude product, which was used in the next step without further purification. MS(EI)m/z: 388.2 (M+1); ^{1}H NMR (400 MHz, , $CDCl_3$): δ 1.63 (d, J = 6.8 Hz, 3H), 5.53-5.57 (m, 1H), 6.76 (d, J = 5.6 Hz, 1H), 7.02-7.07 (m, 3H), 7.11 (d, J = 5.2 Hz, 1H), 7.42-7.46 (m, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 6.4 Hz, 1H), 7.84 (d, J = 7.6 Hz, 2H), 7.97 (d, J = 5.2 Hz, 1H), 8.05 (d, J = 5.6 Hz, 1H), 9.98 (s, 1H).

[0350]

Step 3: 2,2,2-Trifluoro-1-[4-[(1S)-1-[[8-(3-fluorophenoxy)-

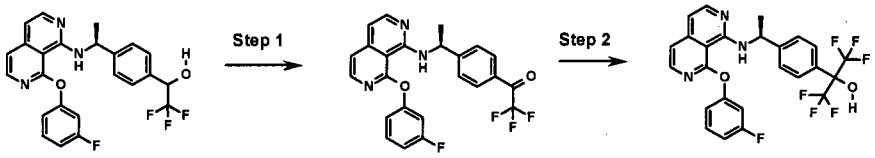
2,7-naphthyridin-1-yl]amino]ethyl]phenyl]ethanol

To a solution of 4-[(1S)-1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzaldehyde (0.1 g, 1.54 mmol) in DMF (5 ml) were added dropwise potassium carbonate (0.1 g, 0.77 mmol) and trifluoromethyltrimethylsilane (2.0 M solution in THF) (1.3 mL, 2.58 mmol) at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 1 hour and the product formation was confirmed by TLC. Then water (25 mL) was added thereto, and the mixture was extracted with ethyl acetate (2 x 15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. The organic layer was concentrated under vacuo, and the obtained crude material was purified by combiflash column chromatography using 5-10% ethyl acetate in hexane as a mobile phase to give the title compound (0.04 g, 34%). MS(EI)m/z: 458.3 (M+1) ^{1}H NMR DMSO-d_6: δ 1.25 (d, J = 6.8 Hz, 3H), 5.09 (bs, 1H), 5.55 (d, J = 6.8 Hz, 1H), 6.01 (d, J = 7.6 Hz, 1H), 6.08 (d, J = 12.4 Hz, 1H), 6.36-6.38 (m, 1H), 6.53 (d, J = 7.2 Hz, 1H), 6.73 (t, J = 5.2 Hz, 1H), 6.88-6.94 (m, 1H), 7.37 (t, J = 6.8 Hz, 1H), 7.43 (d, J = 7.6 Hz, 2H), 7.52 (d, J = 5.2 Hz, 1H), 7.80 (d, J = 7.6 Hz, 2H), 8.62 (d, J = 5.6 Hz, 1H), 11.20 (d, J = 4.8 Hz, 1H).

[0351]

Example I2: 1,1,1,3,3,3-Hexafluoro-2-[4-[(1S)-1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]phenyl]propan-2-ol

[0352]



[0353]

Step 1: 2,2,2-Trifluoro-1-[4-[(1S)-1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]phenyl]ethanone

To a solution of 2,2,2-trifluoro-1-[4-[(1S)-1-[[8-(3-

fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]phenyl]ethanol (0.3 g, 0.65 mmol, Example I1) in DCM (15 mL) was added Desmartine periodinane (0.42 g, 0.98 mmol) at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 1 hour and the product formation was confirmed by TLC. Then water (25 mL) was added thereto, and the mixture was extracted with dichloromethane (2 x 25 mL). The combined organic layers were washed with brine and dried over sodium sulfate. The organic layer was concentrated under vacuo, and the obtained crude material was purified by combiflash column chromatography using 5-10% ethyl acetate in hexane as a mobile phase to give the title compound (0.1 g, 33%). MS(EI)m/z: 456.2 (M+1) ^{1}H NMR DMSO-d_6: δ 1.28 (d, J = 6.8 Hz, 3H), 5.65-5.67 (m, 1H), 6.03 (d, J = 8.0 Hz, 1H), 6.11 (d, J = 13.2 Hz, 1H), 6.39-6.42 (m, 1H), 6.54-6.56 (m, 1H), 6.90-6.95 (m, 1H), 7.38-7.43 (m, 1H), 7.55 (d, J = 5.2 Hz, 1H), 8.03 (d, J = 8.1 Hz, 2H), 8.11 (d, J = 8.0 Hz, 2H), 8.63 (d J = 5.2 Hz, 1H), 11.20 (d, J = 4.8 Hz, 1H).

[0354]

Step 2: 1,1,1,3,3,3-Hexafluoro-2-[4-[(1S)-1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]phenyl]propan-2-ol

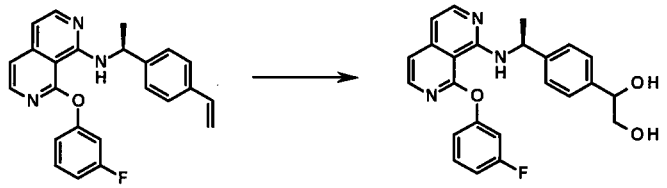
To a solution of 2,2,2-trifluoro-1-[4-[(1S)-1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]phenyl]ethanone (0.1 g, 0.22 mmol) in DMF (10 mL) were added dropwise potassium carbonate (0.09 g, 0.66 mmol) and trifluoromethyltrimethylsilane (2.0 M solution in THF) (1.1 mL, 2.19 mmol) at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 16 hour and the product formation was confirmed by TLC. Then water (25 mL) was added thereto, and the mixture was extracted with ethyl acetate (2 x 15 mL). The combined organic layers were washed with brine and dried over sodium sulfate. The organic layer was concentrated under vacuo and the obtained crude material was purified by LCMS purification method using ACN:formic acid

and water as a mobile phase to give the title compound (0.011 g, 10%). MS(EI)m/z: 526.2 (M+1) ^{1}H NMR DMSO-d_6: δ 1.27 (d, J = 6.4 Hz, 3H), 5.63 (d, J = 6.8 Hz, 1H), 6.01 (d, J = 7.6 Hz, 1H), 6.04 (d, J = 8.4 Hz, 1H), 6.09 (d, J = 12.0 Hz, 1H), 6.37-6.41 (m, 1H), 6.53 (d, J = 6.8 Hz, 1H), 6.90-6.96 (m, 1H), 7.37 (t, J = 6.0 Hz, 1H), 7.51 (d, J = 5.6 Hz, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 8.4 Hz, 2H), 8.61 (d, J = 6.0 Hz, 1H), 11.20 (bs, 1H).

[0355]

Example J1: 1-[4-[(1S)-1-[[8-(3-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]phenyl]ethane-1,2-diol

[0356]



[0357]

To a mixture of 8-(3-fluorophenoxy)-N-[(1S)-1-(4-vinylphenyl)ethyl]-2,7-naphthyridin-1-amine (0.11 g, 0.28 mmol, Example A86) in acetone:hexane (10:1) (11 mL) were added dropwise N-methylmorpholine N-oxide (0.15 g, 1.26 mmol) and osmium tetroxide (0.2 mL) (1.0 g, in 10 mL), and the mixture was stirred at room temperature for 1 hour and the product formation was confirmed by TLC. To the reaction mixture was added water (10 mL), and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water (25 mL), brine (20 mL) and dried over sodium sulfate. The organic layer was concentrated under vacuum, and the residue was purified by combiflash column chromatography using 25-30% ethyl acetate in hexane as a mobile phase to give the title compound (0.03 g., 27%). MS(ESI)m/z: 420.1 (M+1); ^{1}H NMR DMSO-d_6: δ 1.52 (d, J = 6.8 Hz, 3H), 3.85 (t, J = 6.8 Hz, 2H), 5.47-5.49 (m, 1H), 4.65 (t, J = 5.6 Hz, 1H), 5.13 (t, J = 4.4 Hz, 1H), 5.39-5.43 (m, 1H), 6.88 (d, J = 5.6 Hz, 1H), 7.15-7.21 (m, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 5.2

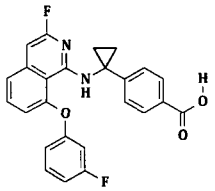
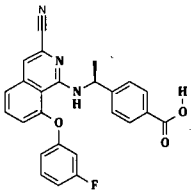
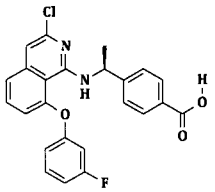
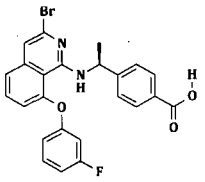
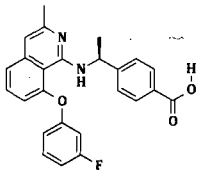
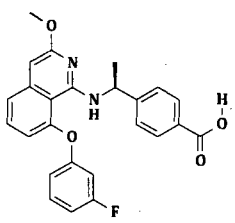
Hz, 1H), 7.33 (bs, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.49-7.54 (m, 1H), 7.74 (d, J = 7.2 Hz, 1H), 7.97 (d, J = 5.2 Hz, 1H), 8.06 (d, J = 5.2 Hz, 1H).

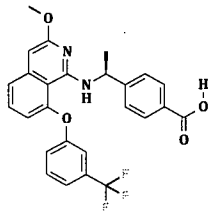
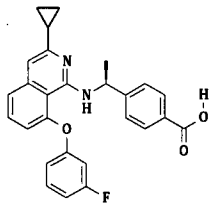
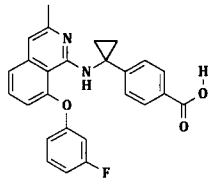
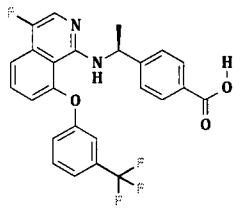
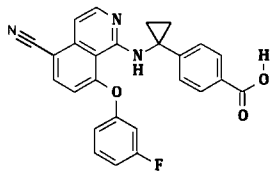
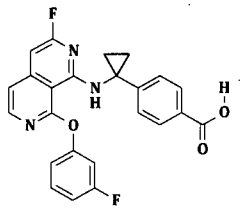
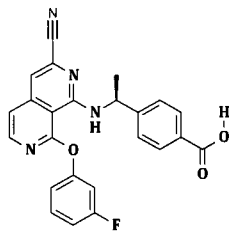
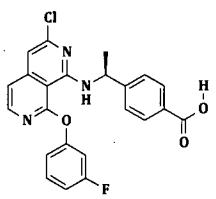
[0358]

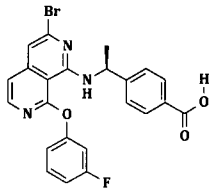
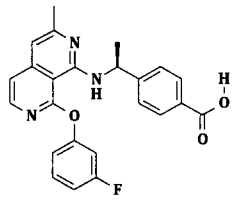
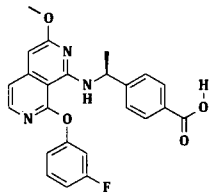
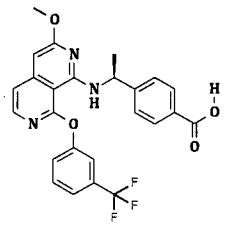
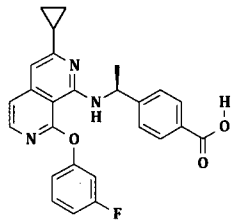
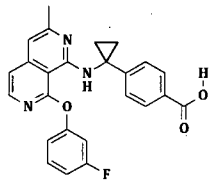
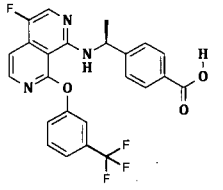
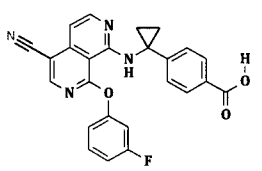
The following compounds as shown in Table 13 can also be prepared according to Schemes 1-11 or in the same manner as in the above-mentioned Examples.

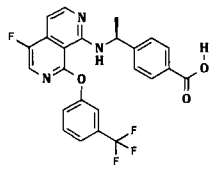
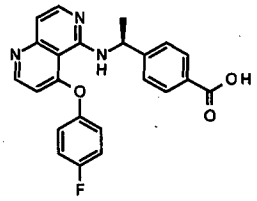
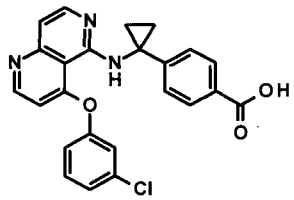
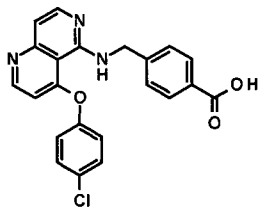
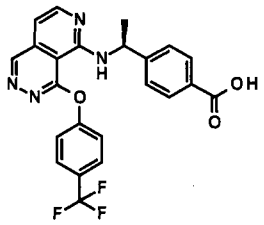
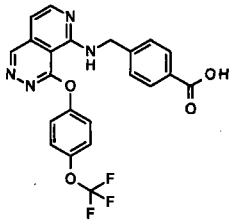
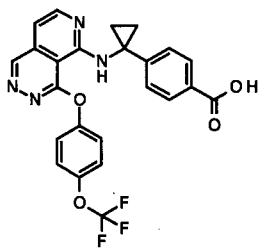
[0359]

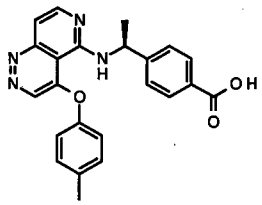
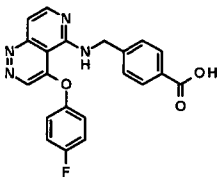
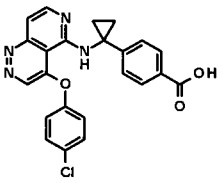
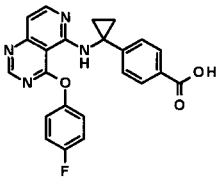
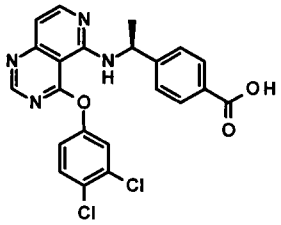
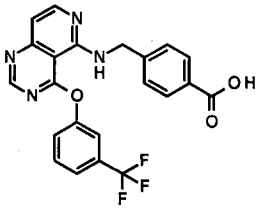
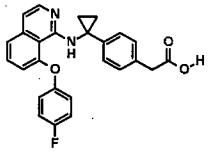
Table 13

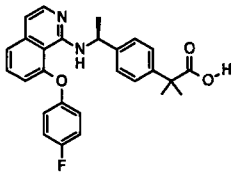
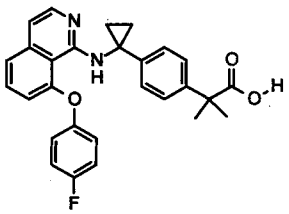
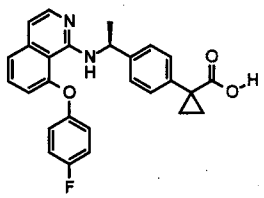
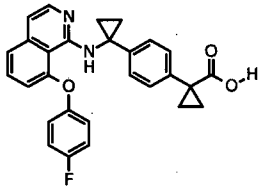
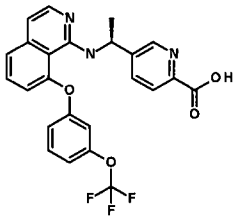
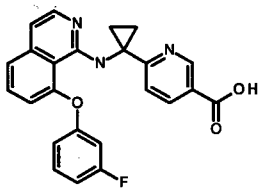
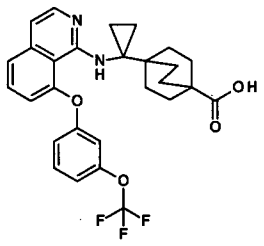
Structure	IUPAC NAME
	4-[1-[[3-fluoro-8-(3-fluorophenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoic acid
	4-[(1S)-1-[[3-cyano-8-(3-fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid
	4-[(1S)-1-[[3-chloro-8-(3-fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid
	4-[(1S)-1-[[3-bromo-8-(3-fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid
	4-[(1S)-1-[[8-(3-fluorophenoxy)-3-methyl-1-isoquinolyl]amino]ethyl]benzoic acid
	4-[(1S)-1-[[8-(3-fluorophenoxy)-3-methoxy-1-isoquinolyl]amino]ethyl]benzoic acid

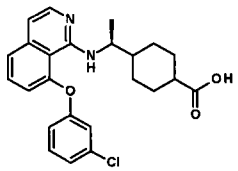
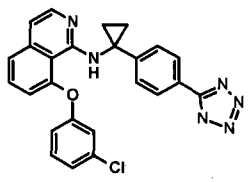
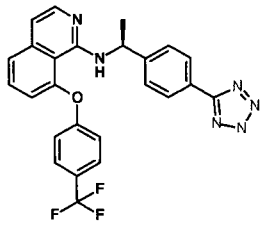
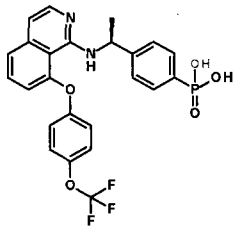
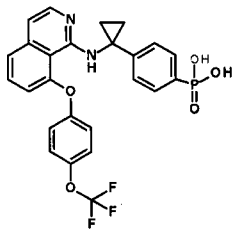
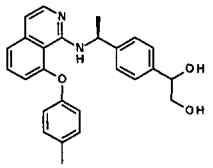
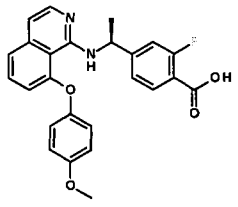
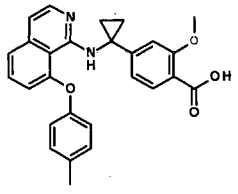
	4-[(1S)-1-[[3-methoxy-8-[3-(trifluoromethyl)phenoxy]-1-isoquinolyl]amino]ethyl]benzoic acid
	4-[(1S)-1-[[3-cyclopropyl-8-(3-fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid
	4-[1-[[8-(3-fluorophenoxy)-3-methyl-1-isoquinolyl]amino]cyclopropyl]benzoic acid
	4-[(1S)-1-[[4-fluoro-8-[3-(trifluoromethyl)phenoxy]-1-isoquinolyl]amino]ethyl]benzoic acid
	4-[1-[[5-cyano-8-(3-fluorophenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoic acid
	4-[1-[[3-fluoro-8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]cyclopropyl]benzoic acid
	4-[(1S)-1-[[3-cyano-8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid
	4-[(1S)-1-[[3-chloro-8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid

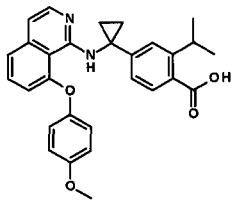
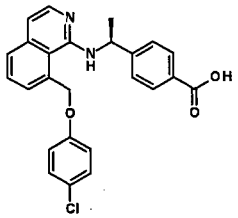
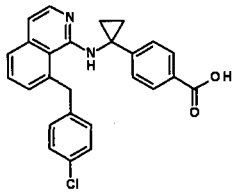
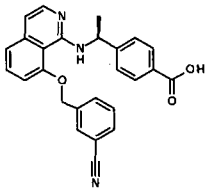
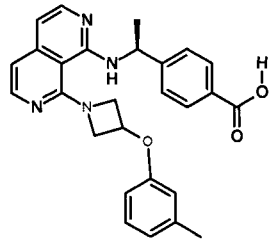
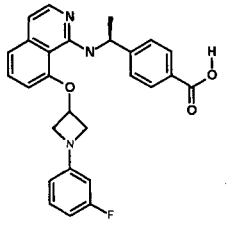
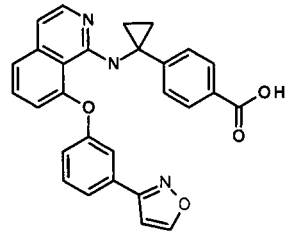
	4-[(1S)-1-[[3-bromo-8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid
	4-[(1S)-1-[[8-(3-fluorophenoxy)-3-methyl-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid
	4-[(1S)-1-[[8-(3-fluorophenoxy)-3-methoxy-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid
	4-[(1S)-1-[[3-methoxy-8-[3-(trifluoromethyl)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid
	4-[(1S)-1-[[3-cyclopropyl-8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid
	4-[1-[[8-(3-fluorophenoxy)-3-methyl-2,7-naphthyridin-1-yl]amino]cyclopropyl]benzoic acid
	4-[(1S)-1-[[4-fluoro-8-[3-(trifluoromethyl)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid
	4-[1-[[5-cyano-8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]cyclopropyl]benzoic acid

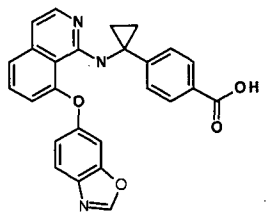
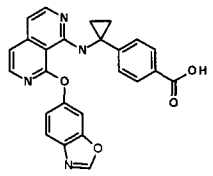
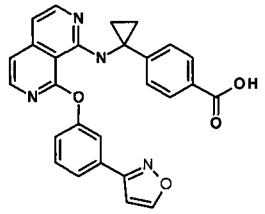
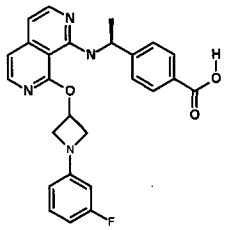
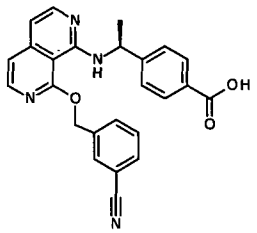
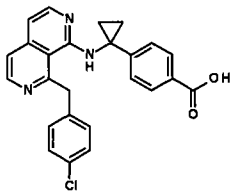
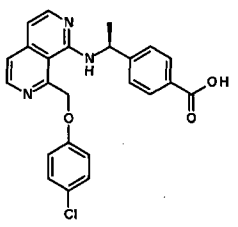
	4-[(1S)-1-[[5-fluoro-8-[3-(trifluoromethyl)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid
	4-[(1S)-1-[[4-(4-fluorophenoxy)-1,6-naphthyridin-5-yl]amino]ethyl]benzoic acid
	4-[1-[[4-(3-chlorophenoxy)-1,6-naphthyridin-5-yl]amino]cyclopropyl]benzoic acid
	4-[[[4-(4-chlorophenoxy)-1,6-naphthyridin-5-yl]amino]methyl]benzoic acid
	4-[(1S)-1-[[4-[4-(trifluoromethyl)phenoxy]pyrido[3,4-d]pyridazin-5-yl]amino]ethyl]benzoic acid
	4-[[[4-[4-(trifluoromethoxy)phenoxy]pyrido[3,4-d]pyridazin-5-yl]amino]methyl]benzoic acid
	4-[1-[[4-[4-(trifluoromethoxy)phenoxy]pyrido[3,4-d]pyridazin-5-yl]amino]cyclopropyl]benzoic acid

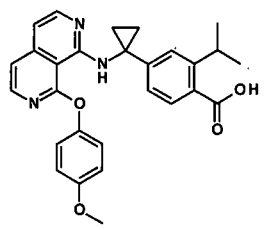
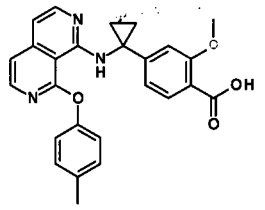
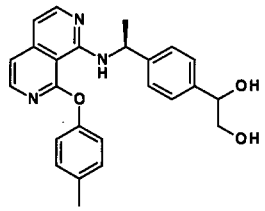
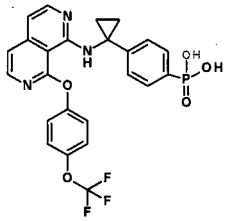
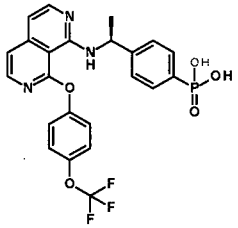
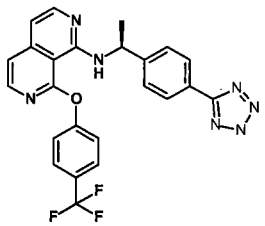
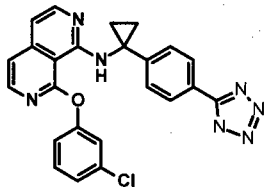
	4-[(1S)-1-[[4-(4-methylphenoxy)pyrido[4,3-c]pyridazin-5-yl]amino]ethyl]benzoic acid
	4-[[[4-(4-fluorophenoxy)pyrido[4,3-c]pyridazin-5-yl]amino]methyl]benzoic acid
	4-[1-[[4-(4-chlorophenoxy)pyrido[4,3-c]pyridazin-5-yl]amino]cyclopropyl]benzoic acid
	4-[1-[[4-(4-fluorophenoxy)pyrido[4,3-d]pyrimidin-5-yl]amino]cyclopropyl]benzoic acid
	4-[(1S)-1-[[4-(3,4-dichlorophenoxy)pyrido[4,3-d]pyrimidin-5-yl]amino]ethyl]benzoic acid
	4-[[[4-[3-(trifluoromethyl)phenoxy]pyrido[4,3-d]pyrimidin-5-yl]amino]methyl]benzoic acid
	2-[4-[1-[[8-(4-fluorophenoxy)-1-isoquinolyl]amino]cyclopropyl]phenyl]acetic acid
	2-[4-[(1S)-1-[[8-(4-fluorophenoxy)-1-isoquinolyl]amino]ethyl]phenyl]-2-

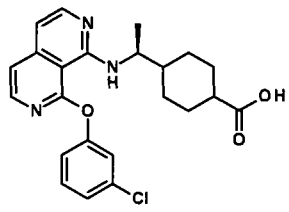
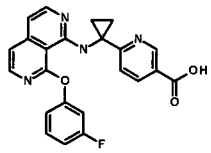
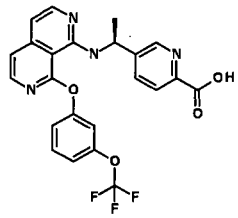
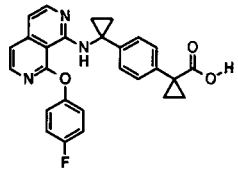
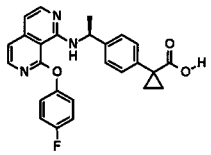
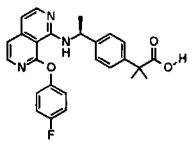
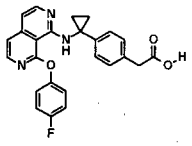
	methylpropanoic acid
	2-[4-[1-[[8-(4-fluorophenoxy)-1-isoquinolyl]amino]cyclopropyl]phenyl]-2-methylpropanoic acid
	1-[4-[(1S)-1-[[8-(4-fluorophenoxy)-1-isoquinolyl]amino]ethyl]phenyl]cyclopropanecarboxylic acid
	1-[4-[1-[[8-(4-fluorophenoxy)-1-isoquinolyl]amino]cyclopropyl]phenyl]cyclopropanecarboxylic acid
	5-[(1S)-1-[[8-[3-(trifluoromethoxy)phenoxy]-1-isoquinolyl]amino]ethyl]pyridine-2-carboxylic acid
	6-[1-[[8-(3-fluorophenoxy)-1-isoquinolyl]amino]cyclopropyl]pyridine-3-carboxylic acid
	4-[1-[[8-[3-(trifluoromethoxy)phenoxy]-1-isoquinolyl]amino]cyclopropyl]bicyclo[2.2.2]octane-1-carboxylic acid

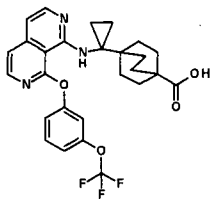
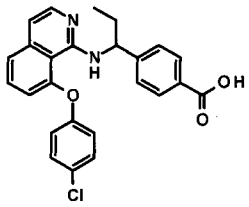
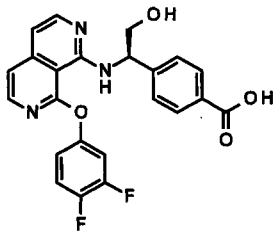
	4-[(1S)-1-[[8-(3-chlorophenoxy)-1-isoquinolyl]amino]ethyl]cyclohexanecarboxylic acid
	8-(3-chlorophenoxy)-N-[1-[4-(1H-tetrazol-5-yl)phenyl]cyclopropyl]isoquinolin-1-amine
	N-[(1S)-1-[4-(2H-tetrazol-5-yl)phenyl]ethyl]-8-[4-(trifluoromethyl)phenoxy]isoquinolin-1-amine
	[4-[(1S)-1-[[8-[4-(trifluoromethoxy)phenoxy]-1-isoquinolyl]amino]ethyl]phenyl]phosphonic acid
	[4-[1-[[8-[4-(trifluoromethoxy)phenoxy]-1-isoquinolyl]amino]cyclopropyl]phenyl]phosphonic acid
	1-[4-[(1S)-1-[[8-(4-methylphenoxy)-1-isoquinolyl]amino]ethyl]phenyl]ethane-1,2-diol
	2-fluoro-4-[(1S)-1-[[8-(4-methoxyphenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid
	2-methoxy-4-[1-[[8-(4-methylphenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoic acid

	2-isopropyl-4-[1-[[8-(4-methoxyphenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoic acid
	4-[(1S)-1-[[8-[(4-chlorophenoxy)methyl]-1-isoquinolyl]amino]ethyl]benzoic acid
	4-[1-[[8-[(4-chlorophenyl)methyl]-1-isoquinolyl]amino]cyclopropyl]benzoic acid
	4-[(1S)-1-[[8-[(3-cyanophenyl)methoxy]-1-isoquinolyl]amino]ethyl]benzoic acid
	4-[(1S)-1-[[8-[3-(3-methylphenoxy)azetidin-1-yl]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid
	4-[(1S)-1-[[8-[1-(3-fluorophenyl)azetidin-3-yl]oxy-1-isoquinolyl]amino]ethyl]benzoic acid
	4-[1-[[8-(3-(isoxazol-3-yl)phenoxy)-1-isoquinolyl]amino]cyclopropyl]benzoic acid

	4-[1-[[8-(1,3-benzoxazol-6-yloxy)-1-isoquinolyl]amino]cyclopropyl]benzoic acid
	4-[1-[[8-(1,3-benzoxazol-6-yloxy)-2,7-naphthyridin-1-yl]amino]cyclopropyl]benzoic acid
	4-[1-[[8-(3-(isoxazol-3-yl)phenoxy)-2,7-naphthyridin-1-yl]amino]cyclopropyl]benzoic acid
	4-[(1S)-1-[[8-[1-(3-fluorophenyl)azetidin-3-yl]oxy-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid
	4-[(1S)-1-[[8-[(3-cyanophenyl)methoxy]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid
	4-[1-[[8-[(4-chlorophenyl)methyl]-2,7-naphthyridin-1-yl]amino]cyclopropyl]benzoic acid
	4-[(1S)-1-[[8-[(4-chlorophenoxy)methyl]-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid

	2-isopropyl-4-[1-[[8-(4-methoxyphenoxy)-2,7-naphthyridin-1-yl]amino]cyclopropyl]benzoic acid
	2-methoxy-4-[1-[[8-(4-methylphenoxy)-2,7-naphthyridin-1-yl]amino]cyclopropyl]benzoic acid
	1-[4-[(1S)-1-[[8-(4-methylphenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]phenyl]ethane-1,2-diol
	[4-[1-[[8-[4-(trifluoromethoxy)phenoxy]-2,7-naphthyridin-1-yl]amino]cyclopropyl]phenyl]phosphonic acid
	[4-[(1S)-1-[[8-[4-(trifluoromethoxy)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]phenyl]phosphonic acid
	N-[(1S)-1-[4-(2H-tetrazol-5-yl)phenyl]ethyl]-8-[4-(trifluoromethyl)phenoxy]-2,7-naphthyridin-1-amine
	8-(3-chlorophenoxy)-N-[1-[4-(1H-tetrazol-5-yl)phenyl]cyclopropyl]-2,7-naphthyridin-1-amine

	4-[(1S)-1-[[8-(3-chlorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]cyclohexanecarboxylic acid
	6-[1-[[8-(3-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]cyclopropyl]pyridine-3-carboxylic acid
	5-[(1S)-1-[[8-[3-(trifluoromethoxy)phenoxy]-2,7-naphthyridin-1-yl]amino]ethyl]pyridine-2-carboxylic acid
	1-[4-[1-[[8-(4-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]cyclopropyl]phenyl]cyclopropanecarboxylic acid
	1-[4-[(1S)-1-[[8-(4-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]phenyl]cyclopropanecarboxylic acid
	2-[4-[(1S)-1-[[8-(4-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]phenyl]-2-methylpropanoic acid
	2-[4-[1-[[8-(4-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]cyclopropyl]phenyl]acetic acid

	4-[1-[[8-[3-(trifluoromethoxy)phenoxy]-2,7-naphthyridin-1-yl]amino]cyclopropyl]bicyclo[2.2.2]octane-1-carboxylic acid
	4-[1-[[8-(4-chlorophenoxy)-1-isoquinolyl]amino]propyl]benzoic acid
	4-[(1R)-1-[[8-(3,4-difluorophenoxy)-2,7-naphthyridin-1-yl]amino]-2-hydroxy-ethyl]benzoic acid

[0360]

Formulation Example 1 (production of capsule)

1) compound of Example 1	30 mg
2) fine powder cellulose	10 mg
3) lactose	19 mg
4) magnesium stearate	1 mg
Total	60 mg

1), 2), 3) and 4) are mixed and filled in a gelatin capsule.

[0361]

Formulation Example 2 (production of tablet)

1) compound of Example 1	30 g
2) lactose	50 g
3) cornstarch	15 g
4) calcium carboxymethylcellulose	44 g
5) magnesium stearate	1 g
1000 tablets total	140 g

The total amount of 1), 2) and 3) and 4) (30 g) is kneaded with water, vacuum dried, and sieved. The sieved

powder is mixed with 4) (14 g) and 5) (1 g), and the mixture is punched by a tableting machine, whereby 1000 tablets containing 30 mg of the compound of Example 1 per tablet are obtained.

[0362]

Experimental Example 1

Membrane preparation:

The full-length coding sequences for human EP1 (NM_000955), human EP2 (NM_000956), human EP3 (NM_198717) and human EP4 (NM_000958) were cloned into pcDNA3.1(+) vector (Life Technologies, CA, USA). In order to prepare overexpressed EP 1-4 membrane in Freestyle293 cells (Life Technologies, CA, USA), the pcDNA3.1(+) vector encoding a cDNA of the relevant gene was transiently transfected into FreeStyle293 cells using 293Fectin (Life Technologies, CA, USA) according to the manufacturer instruction manual. After 2 days, cultured cells were centrifuged (1,000 × g, 10 min, 4°C) and pellets homogenized by a probe sonicator (Sonics vibracell, Sonics and Materials Inc., USA; 31% Amp, 5sec pulse, 1min interval, 4 cycles) in ice-cold 50 mM Tris-HCl buffer (pH 7.5 at 25°C) containing 0.5 mM EDTA, 250 mM Sucrose and 10 mM $MgCl_2$. Cell homogenates were centrifuged (890 × g, 10 min, 4°C), and the supernatant was recovered. Total membrane fractions were isolated by ultracentrifugation (140,000 × g, 60 min, 4°C). Pellets were re-suspended in the same buffer, and stored at -80°C until use. The protein concentration in homogenate was determined with the BCA Protein Assay Kit (Pierce Biotechnology, Inc., IL, USA) according to the manufacturer protocol.

[0363]

Primary *in vitro* binding assay:

The binding affinity of the compounds was evaluated using a competitive radioligand binding assay which measured the specific binding of [3H] PGE2 to the human EP4 receptor. Briefly, varying concentrations of NCEs were incubated with

cell membrane fractions generated HEK293F cells transiently transfected with human EP4 receptor as described above. Each reaction consisted of 10 µg membrane protein and NCE in 50 mM Tris.Hcl, pH-6.0 by NaOH, 10 mM $MgCl_2$ and 0.5 mM EDTA assay buffer. Radioligand, [3H] PGE2 (American Radiochemicals Inc. Specific Activity 180 Ci/mmol), at a final of 1 nM was added to each reaction where the final assay volume was 200 µL and concentration of DMSO was adjusted to 1%. Appropriate controls included total binding in the assay (vehicle control) and control for non-specific binding. Non-specific binding was evaluated by incubating the hEP4 protein with 10 µM unlabeled PGE2 under the same assay conditions as NCEs. The reaction was incubated at room temperature for 2 hours and terminated by harvesting the reaction contents to a PEI coated GF/C filter plate(PerkinElmer). The plate was washed four times with cold 50mM Tris-HCl, pH-7.5 wash buffer and dried at 50°C for 2 hours or at 37°C overnight. [3H] PGE2 bound to the protein was quantified by the addition of 25 µL of Microscint PS (PerkinElmer) and plate was read on MicroBeta2 liquid Scintillation and luminescence counter (PerkinElmer). Data was analyzed using GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA) where non-specific binding was normalized to 0% specific binding of [3]PGE2 and vehicle control (DMSO) was normalized to 100% specific binding of [3]PGE2. Binding affinity of NCEs, Ki, was generated using One site - Fit Ki equation in GraphPad Prism 5.

[0364]

Functional Assay:

The functional assay for hEP4 activation and inhibition was carried out via the quantitative determination of agonist, PGE2, induced cAMP response using HTRF in a competitive immunoassay (Cisbio dynamic 2 kit). NCEs at varying concentrations were evaluated for inhibition of PGE2 induced increase in cAMP. Briefly, C6 glioma cells overexpressing hEP4 (Takeda) were cultured in DMEM (low glucose, pyruvate), 10%

FBS (Gibco) and PenStep. The cells were harvested on the day of the assay, washed with HBSS + 10 mM HEPES (pH 7.4) + 0.1% BSA buffer and pre-incubated with varying concentrations of NCE. Each reaction contained 7000 cells and NCEs in HBSS + 10 mM HEPES + 0.1% BSA assay buffer along with PDE inhibitors IBMX and Ro 20-1724 (final concentration of each inhibitor 200 mM). Following 15 min pre-incubation, the cells were treated with EC80 concentration of agonist PGE2 for 30 min to induce cAMP. Final volume of the assay was 6 µL and DMSO concentration was maintained at 1%. The reaction was terminated with the addition of cAMP labeled with the dye d2 in lysis buffer according to manufacturers' protocol. This was followed by the addition of the anti-cAMP antibody labeled with Cryptate according to the manufacturers' protocol. The reaction was incubated at room temperature in dark for 45 min and the plate was evaluated for fluorescence at 665 nm (FRET) and 620 nm (cryptate emission) on a Flexstation III microplate reader (Molecular Devices, Sunnyvale, CA) Ex max: 313 nm; Em1: 620 nm ; Em2: 665 nm. Data was analyzed using GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA) where cells treated with agonist (EC_{80}) was normalized to 0% inhibition of hEP4 and cells treated with buffer (no agonist) was normalized to 100% inhibition of hEP4. IC_{50} of NCEs was generated using non-linear regression - Log(inhibitor) vs. response equation in GraphPad Prism 5.

[0365]

Table 14: Potency of compound in hEP4 radioligand binding assay and cell based assay (cAMP) at 1 µM

Compound	% Inhibition at 1 µM*	
	hEP4 radioligand binding assay	hEP4 cell based assay (cAMP)
Example D1	99	94
Example D2	67	NA
Example D3	79	NA
Example D4	92	78

Example D5	93	85
Example D6	52	62
Example D7	17	49
Example D8	94	88
Example D9	99	93
Example D10	100	95
Example D11	86	NA
Example D12	97	65
Example D13	98	84
Example D14	100	101
Example D15	91	44
Example D16	80	NA
Example D17	83	NA
Example D18	31	NA
Example D19	94	NA
Example D20	92	NA
Example D21	54	NA
Example D22	39	NA
Example D23	97	NA
Example D26	95	101
Example D27	98	110
Example D28	92	NA
Example D29	36	NA
Example D30	93	60
Example D31	87	83
Example D32	100	NA
Example D33	103	95
Example D34	104	92
Example D35	101	86
Example D36	98	76
Example D37	99	86
Example D38	NA	103
Example D39	NA	86
Example D40	97	94

Example D41	96	93
Example D42	100	103
Example D43	96	84
Example D44	77	89
Example D45	99	94
Example D46	83	93
Example D47	NA	83
Example D48	93	102
Example D49	83	89
Example D50	97	106
Example D51	98	99
Example D52	91	97
Example D53	100	98
Example D54	83	60
Example D55	90	55
Example D56	94	91
Example D57	95	91
Example D58	95	92
Example D59	92	86
Example D60	96	89
Example D61	94	91
Example D62	98	90
Example D63	96	82
Example D64	90 at 3 μM	83
Example D65	97	86
Example D66	50 at 3 μM	8
Example D67	91	46
Example D68	91	57
Example D69	92	93
Example D70	91 at 3 μM	25
Example D71	94 at 3 μM	42
Example D72	93	70
Example D73	96	92
Example D74	95	97

Example D75	96	93
Example D76	97	98
Example D77	87	7.8
Example D78	80	NA
Example D79	77	90
Example D80	72	81
Example D81	83	NA
Example D82	92	51
Example D83	82	NA
Example D84	97	81
Example D86	67	79
Example D87	99	100
Example D88	98	96
Example D89	95	68
Example D90	91 at 3 μM	80
Example D91	81 at 3 μM	23
Example D92	93 at 3 μM	77
Example E1	68	NA
Example E2	66	NA
Example E3	57	NA
Example E4	67	NA
Example E5	72	NA
Example F1	60	NA
Example G1	33	NA
Example H1	73	NA
Example I1	No inhibition	NA
Example I2	7	NA
Example J1	48	NA

NA: not available

Industrial Applicability

[0366]

Compound (I) has a superior EP4 receptor antagonistic action, which is useful as an agent for the prophylaxis or treatment of EP4 receptor associated diseases (e.g.,

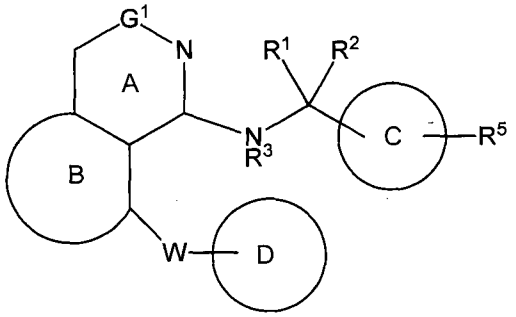
rheumatoid arthritis, aortic aneurysm (e.g. abdominal aortic aneurysm, thoracic aortic aneurysm, thoracoabdominal aortic aneurysm etc.), endometriosis, ankylosing spondylitis, inflammatory breast cancer etc.) and the like.

[0367]

This application is based on patent application No. 2249/DEL/2014 filed on August 7, 2014 in India, the contents of which are encompassed in full herein.

CLAIMS

1. A compound represented by the formula (I):



(I)

wherein

Ring A is an optionally further substituted pyridine or an optionally further substituted pyridazine,

G^1 is N or CR^4,

R^4 is a hydrogen atom or a substituent,

Ring B is an optionally substituted 6-membered aromatic ring,

R^1 and R^2 are each independently a hydrogen atom or an optionally substituted C_{1-6} alkyl group, or R^1 and R^2 are joined together to form a cycloalkane or a heterocycle, each of which is optionally substituted,

R^3 is a hydrogen atom or a substituent,

Ring C is an optionally further substituted ring,

R^5 is a substituent,

Ring D is an optionally substituted ring, and

W is a bond, or a spacer in which the number of atoms in the main chain is 1 to 4,

or a salt thereof.

2. The compound or salt according to claim 1, wherein

Ring A is pyridine optionally further having one substituent, on the carbon atom adjacent to G^1, selected from

(1) a halogen atom,

(2) an optionally halogenated C_{1-6} alkyl group, and

(3) a C_{3-10} cycloalkyl group,

G^1 is CR^4,

R^4 is a hydrogen atom,

Ring B is a 6-membered aromatic ring optionally having 1 to 3 substituents selected from

(1) a halogen atom,

(2) an optionally halogenated C_{1-6} alkyl group,

(3) an optionally halogenated C_{1-6} alkoxy group, and

(4) a C_{3-10} cycloalkyl group,

R^1 and R^2 are each independently a hydrogen atom or a C_{1-6} alkyl group, or R^1 and R^2 are joined together to form a cycloalkane,

R^3 is a hydrogen atom,

Ring C is a C_{6-14} aromatic hydrocarbon ring or a 5- or 6-membered monocyclic aromatic heterocycle, each optionally having 1 to 3 substituents, in addition to R^5, selected from

(1) a halogen atom, and

(2) an optionally halogenated C_{1-6} alkyl group,

R^5 is

(1) a carboxy group,

(2) a C_{1-6} alkoxy-carbonyl group,

(3) a cyano group,

(4) a C_{1-6} alkyl group optionally having 1 to 3 substituents selected from

(a) a halogen atom,

(b) a hydroxy group, and

(c) a carboxy group,

(5) a carbamoyl group optionally having 1 or 2 substituents selected from

(a) a C_{1-6} alkyl group,

(b) a C_{1-6} alkoxy group,

(c) a C_{7-16} aralkyloxy group, and

(d) a C_{1-6} alkylsulfonyl group, or

(6) a sulfamoyl group,

Ring D is a C_{6-14} aromatic hydrocarbon ring or a 5- or 6-membered monocyclic aromatic heterocycle, each optionally having 1 to 3 substituents selected from

(1) a halogen atom,

(2) a cyano group,

(3) an optionally halogenated C_{1-6} alkyl group, and

(4) an optionally halogenated C_{1-6} alkoxy group, and

W is -O- or -O-CH_2- (wherein the left bond is bonded to Ring B, and the right bond is bonded to Ring D).

3. 4-[(1S)-1-[[8-(3-Fluorophenoxy)-1-isoquinolyl]amino]ethyl]benzoic acid or a salt thereof.

4. 4-[(1S)-1-[[5-Chloro-8-(4-fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid or a salt thereof.

5. 4-[(1S)-1-[[8-(3-Fluorophenoxy)-2,7-naphthyridin-1-yl]amino]ethyl]benzoic acid or a salt thereof.

6. A medicament comprising the compound or salt of claim 1.

7. The medicament of claim 6, which is an EP4 receptor antagonist.

8. The medicament of claim 6, which is an agent for the prophylaxis or treatment of EP4 receptor associated diseases.

9. The medicament of claim 6, which is an agent for the prophylaxis or treatment of rheumatoid arthritis, aortic aneurysm, endometriosis, ankylosing spondylitis or inflammatory breast cancer.

10. The compound or salt of claim 1 for use in the prophylaxis or treatment of EP4 receptor associated diseases.

11. The compound or salt of claim 10, wherein the EP4 receptor associated diseases is selected from rheumatoid arthritis, aortic aneurysm, endometriosis, ankylosing spondylitis and inflammatory breast cancer.

12. A method of inhibiting EP4 in a mammal, which comprises administering an effective amount of the compound or salt of claim 1 to the mammal.

13. A method for the prophylaxis or treatment of EP4 receptor associated diseases in a mammal, which comprises administering an effective amount of the compound or salt of claim 1 to the mammal.

14. The method of claim 13, wherein the EP4 receptor associated diseases is selected from rheumatoid arthritis, aortic aneurysm, endometriosis, ankylosing spondylitis and inflammatory breast cancer.

15. Use of the compound or salt of claim 1 for the production of an agent for the prophylaxis or treatment of EP4 receptor associated diseases.

16. Use of claim 15, wherein the EP4 receptor associated diseases is selected from rheumatoid arthritis, aortic aneurysm, endometriosis, ankylosing spondylitis and inflammatory breast cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2015/072884

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D217/20 C07D401/12 C07D471/04 A61K31/4375 A61K31/444
A61K31/472 A61K31/4725 A61K31/502 A61P19/02 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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2014/143608 A1 (SQUIBB BRISTOL MYERS CO [US]) 18 September 2014 (2014-09-18) Paragraph bridging pp.98 and 99; claim 1; examples 19,31,32,36-40	1,6-9
X,P	WO 2014/143609 A1 (SQUIBB BRISTOL MYERS CO [US]) 18 September 2014 (2014-09-18) Paragraph bridging pp.136 and 137; claim 1; examples 22,27,43,50,54,59,72,74	1,6-9
A	WO 2005/021508 A1 (PFIZER [US]; YAMAGISHI TATSUYA [JP]; OKUMURA YOSHIYUKI [JP]; NUKUI SEI) 10 March 2005 (2005-03-10) Page 1, line 29 - page 2, line 2; page 2, lines 19-27; claim 1; example 144	1-16

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[X] Further documents are listed in the continuation of Box C.

[X] 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

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"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	Date of mailing of the international search report
30 September 2015	19/10/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Cooper, Simon

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2015/072884

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 03/066630 A2 (AMGEN INC [US]; NORMAN MARK [GB]; WANG HUI-LING [US]; RZASA ROBERT [US) 14 August 2003 (2003-08-14) Page 40, lines 27-29; page 43, lines 27-32; claim 1	1-16

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/JP2015/072884

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