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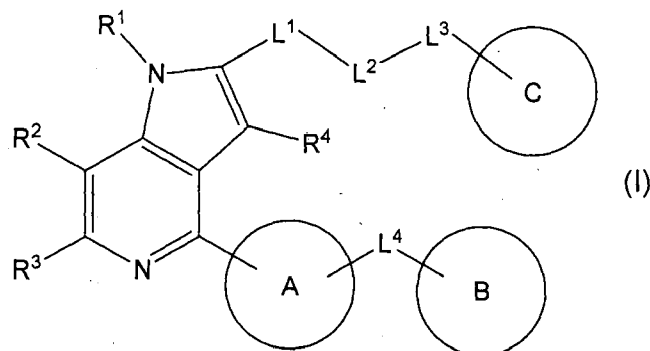
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(54) Title: PYRROLO[3,2-C]PYRIDINE DERIVATIVES AS TLR INHIBITORS



(57) Abstract: The present invention provides a heterocyclic compound having a TLR7, TLR9, TLR7/8, TLR7/9 or TLR7/8/9 inhibitory action, which is useful as an agent for the prophylaxis or treatment of autoimmune diseases, inflammatory diseases and the like, in particular, systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, psoriasis, inflammatory bowel disease and the like. The present invention is a compound represented by the formula (1): wherein each symbol is as described in the specification, or a salt thereof.

DESCRIPTION

PYRROLO[3,2-C]PYRIDINE DERIVATIVES AS TLR INHIBITORS

Technical Field

5 [0001]

The present invention relates to a heterocyclic compound having a Toll-like receptors (TLR)7, TLR9, TLR7/8, TLR7/9 or TLR7/8/9 inhibitory action, which is useful as an agent for the prophylaxis or treatment of TLR7, TLR9, TLR7/8, TLR7/9 or
10 TLR7/8/9 related diseases such as autoimmune diseases, inflammatory diseases and the like, in particular, systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, psoriasis, inflammatory bowel disease and the like.

Background of the Invention

15 [0002]

Toll-Like Receptors (TLRs) are conserved membrane pattern recognition receptors (PRRs) of innate immunity responsible for clearing microbial pathogens. TLRs are expressed in many immune and non-immune cells and detect pattern recognition
20 motifs that recognize microbial products, namely, the pathogen associated molecular patterns (PAMPs, ex: nucleic acids, lipoprotein and polysaccharides) (Kawai et. al., 2011, *Immunity*, 34(5):637-50). In addition to PAMPs, several TLRs also recognize endogenous ligands resulting from cellular
25 insult due to inflammatory response and cell-death, called damage associated molecular patterns (DAMPs) (Abdelsadik et. al, 2011, *Human Immunology*, 72, 1188-1193). Till date, ten functional TLRs (TLR1-10) have been identified in human, of which TLR1, TLR2, TLR4, TLR5 and TLR6, that recognize
30 lipoproteins and lipopolysaccharides are expressed on the plasma membrane and TLR3, TLR7, TLR8 and TLR9 that recognize nucleic acids are expressed in endosomal compartments. While TLR7 and TLR8 both recognize ssRNA, TLR9 recognizes CpG-rich hypomethylated DNA (Table 1).

35 [0003]

Table 1: Summary of Function and Expression of TLR7 and 9

TLR	Cellular Expression	PAMPs (Microbial)	DAMPs (Host)
TLR7	B-cells, pDCs	ssRNA	ssRNA, Antiphospholipid antibodies, cardiac myosin
TLR9	B-cells, pDCs, GI epithelial, Keratinocytes	CpG DNA	DNA, DNA containing immune complexes, IgG- chromatin complexes

[0004]

Engagement of a cognate ligand to TLRs induces

5 conformational changes allowing formation of homo- or heteromeric interactions within TLRs and recruitment of adaptor proteins such as MyD88, TIRAP, TRIF, and TRAM. TLR7 and TLR9 are localized mainly to ER in the steady state but traffic to the endo/lysosomal compartment with the help of

10 UNC93b1 during activation (Kawai T and Akira S, **2007**, *Sem Immunol*, 19, 24). TLR7 and TLR9 activate NF- κ B and IRF7 via MyD88 to induce pro-inflammatory cytokines (TNF α , IL-1 β , IL-6) and type I interferons (IFN α and IFN β) respectively. The activation of NF- κ B during TLR7 and TLR9 signaling is

15 initiated from the endosomes whereas IRF7 activation is initiated from the lysosome-related organelle (LRO) after TLR7 and TLR9 are transported from the endosome to this vesicle. MyD88-dependent IRF7 activation in pDCs is mediated by activation of IRAK1, TRAF6, TRAF3 and IKK α . In conventional

20 DCs and macrophages, TLR7 and TLR9 induce inflammatory responses by activating NF- κ B via MyD88 but fail to activate IRF7 [Kawai et. al., **2011**, *Immunity*, 34(5):637-50].

[0005]

TLR7/9 activation plays a major role in the inter-phase

of innate and adaptive immunity. They not only activate inflammatory cytokines, up-regulate MHC molecules and co-stimulatory signals in antigen-presentation (innate immune response) but also prime and amplify T-, and B-cell effectors function (adaptive immune response) [Hannessy et. al., **2010**, *Nat Rev Drug Discov.*, 9(4):293-307; Koegh et. al., **2011**, *Trends Pharmacol Sci*, 32(7):435-42].

[0006]

There is increasing evidence of role of TLR-7 and 9 in the pathogenesis of various autoimmune diseases including rheumatoid arthritis (RA). Human synovial tissue from RA patients showed the expression of TLR7 and 9 (along with TLR-2/3/4). The expression of TLR7 was significantly up-regulated in RA synovial fibroblasts (RASFs) compared with healthy controls or patients with non-inflammatory arthritis. Stimulation of cultured RASFs with TLR7 ligands resulted in significant up-regulation of chemokines, cytokines, metalloproteinases and type I IFNs. [Roelofs et. al., **2005**, *Arthritis Rheum.* 52(8):2313-22].

[0007]

Recent studies have shown that the development and progression of Systemic Lupus Erythematosus (SLE) are driven by the over-expression of TLR-7, 8 and 9 within B-cells and pDCs [Komatsuda et. al., **2008**, *Clin Exp Immunol.*;152 (3):482-7; Migita et. al., **2007**, *J Rheumatol.*, 34 (3): 493-500]. A knockout of TLR7 in a spontaneous murine model of SLE (MRL-/Mplpr/lpr), showed decreased anti-RNA antibodies, diminished splenic immune activation and suppressed the development of nephritis [Nickerson et. al., **2010**, *J Immunol.*, 15, 184 (4):1840-8; Christensen et. al., **2006**, *Immunity*, 25 (3): 417-28], validating the target in the pathogenesis of this disease.

[0008]

Antagonists of these nucleic acid-recognizing TLRs have primarily been oligonucleotide-based molecules. IMO-3100, an oligonucleotide based antagonist of TLR7 and TLR9 has

demonstrated clinical activity in psoriasis patients. This antagonist has also shown encouraging results in mouse models of lupus, collagen induced arthritis and psoriasis. IMO-8400, a TLR-7/8/9 antagonist has been shown to suppress the
5 production of autoimmune antibodies, improve kidney histopathology and decrease blood urea nitrogen and proteinuria in lupus prone mice.

[0009]

The small molecule anti-malarial drugs like chloroquine,
10 hydroxychloroquine and quinacrine, that are also known to show TLR-7/8/9 antagonism, have been used since the 1950s to treat immune-mediated inflammatory disorders (IMID) such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). However, side effects associated with these drugs and
15 also the suboptimal efficacy has limited the use of these anti-malarials in IMID.

[0010]

There is literature prior art disclosing small molecule TLR-7/8/9, TLR-7/9 and TLR9 antagonists. Coley Pharmaceuticals
20 has disclosed series of 4-aminoquinoline derivatives as inhibitors of immune stimulation involving at least one of TLR9, TLR8, TLR7 and TLR3 (US 7410975). Eisai R & D has disclosed benzoxazole compounds as antimalarials, claiming the compounds being antagonists of TLR9 (WO 2010/036908). In a
25 patent application (WO 2011/115183), Dainippon Pharma has disclosed monocyclic pyrimidine derivatives that are effective in the prophylaxis and/or treatment of disorders associated with signal transmission mediated by Toll-like receptors (TLR). The biological data disclosed in the application substantiate
30 the claimed compounds as TLR9 antagonists. In a very recent patent application by Janus Biotherapeutics (WO 2013/052550), imidazoloquinoline-based compounds have been described as immune system modulators. Two more patent applications from Janus Biotherapeutics (WO 2012/167046 and WO 2012/167053) have
35 described pyrazinopyrimidines and imidazolopyrimidines as

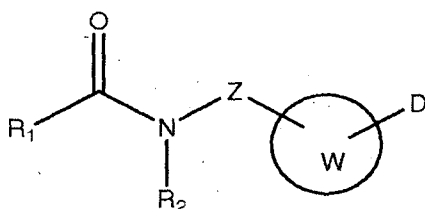
immune system modulators. In all the three patent applications, biological data reveal that the claimed compounds demonstrate TLR9 antagonism.

[0011]

5 Despite several discoveries in this area, there are no safe and efficacious orally administered small molecule TLR-7/8/9 antagonists available in the market. CPG-52364 from Coley Pharma and Pfizer has been discontinued from clinical trials in 2008 for unknown reason. Therefore, there is a
10 strong need for a novel small molecule TLR-7/8/9 antagonist that will be orally available and will have potential clinical utility. These compounds will have medical application in the disease area of inflammation, autoimmune disorder and cell proliferation, rheumatoid arthritis, psoriasis, psoriatic
15 arthritis, systemic lupus erythematosus, Sjögren's Syndrome, multiple sclerosis, inflammatory bowel disease, allergic diseases, infectious diseases affecting immune system, asthma, type 1 diabetes, myasthenia gravis, hematopoietic dysfunction, B-cell malignancies, transplant rejection and graft-versus-
20 host disease.

[0012]

Patent Document 1 discloses a compound represented by the formula:



25 wherein each symbol is as defined in the specification, as a Bruton's tyrosine kinase inhibitor.

Document List

Patent Document

[0013]

30 Patent Document 1: WO 2010/068806

Summary of the Invention

Problems to be Solved by the Invention

[0014]

The present invention aims to provide a compound having a TLR7, TLR9, TLR7/8, TLR7/9 or TLR7/8/9 inhibitory action, which is useful as an agent for the prophylaxis or treatment of autoimmune diseases, inflammatory diseases and the like, in particular, systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, psoriasis, inflammatory bowel disease and the like.

Means of Solving the Problems

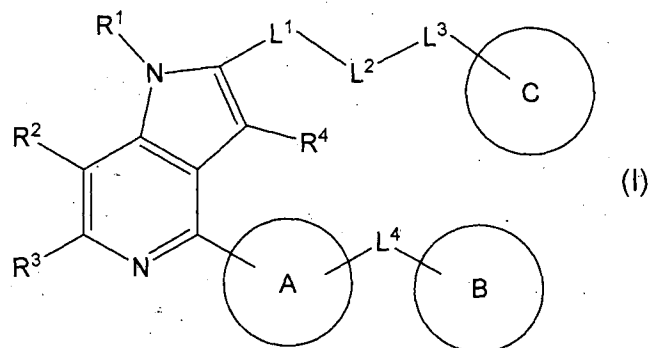
[0015]

The present inventors have conducted intensive studies, and have found that a compound represented by the formula (I) shown below unexpectedly has a TLR7, TLR9, TLR7/8, TLR7/9 or TLR7/8/9 inhibitory action, and therefore, is useful as an agent for the prophylaxis or treatment of autoimmune diseases, inflammatory diseases and the like, in particular, systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, psoriasis, inflammatory bowel disease and the like, and completed the present invention based on these findings.

[0016]

Accordingly, the present invention provides the following:

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



25

wherein

R¹ is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted hydroxy group, an optionally

substituted amino group, an optionally substituted sulfanyl group, or an acyl group,

R^2 , R^3 and R^4 are independently a hydrogen atom or a substituent,

Ring A is an optionally substituted ring,

5 Ring B is an optionally substituted heterocycle,

Ring C is an optionally substituted 3- to 10-membered nitrogen-containing heterocycle,

L^1 is a bond or a divalent hydrocarbon group,

10 L^2 is a bond, -O-, -C(O)-, -NH-C(O)-, -C(O)-NH-, -S-, -SO-, -SO₂-, -SO₂-O-, -O-SO₂- or -CH(CN)-,

L^3 is a bond or a divalent hydrocarbon group, with the proviso that at least one of L^1 , L^2 and L^3 is not a bond, and

L^4 is a bond or a spacer having 1 to 6 atoms,

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

15 [2] The compound or salt of the above-mentioned [1], wherein R^1 is a hydrogen atom, a C₁₋₁₀ alkyl group or a C₃₋₁₀ cycloalkyl group,

R^2 is a hydrogen atom or a C₁₋₁₀ alkyl group,

20 R^3 is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted hydroxy group,

R^4 is a hydrogen atom, a halogen atom or an optionally substituted hydrocarbon group,

Ring A is an optionally substituted C₃₋₁₀ cycloalkane, an optionally substituted C₃₋₁₀ cycloalkene, an optionally substituted C₆₋₁₄ aromatic hydrocarbon or an optionally substituted aromatic heterocycle optionally fused with benzene,

Ring B is an optionally substituted 3- to 10-membered non-aromatic heterocycle,

Ring C is an optionally substituted 5- or 6- membered nitrogen-containing aromatic heterocycle or an optionally substituted 3- to 10-membered nitrogen-containing non-aromatic heterocycle,

30 L^1 and L^3 are independently

(1) a bond,

35 (2) a C₁₋₁₀ alkylene group, or

(3) a C₃₋₈ cycloalkylene group,

L² is a bond or -C(O)-, and

L⁴ is a bond, a straight chain C₁₋₆ alkylene group, -X¹-O-X²-, -X¹-C(O)-X²- or -X¹-NH-C(O)-X²-, wherein X¹ and X² are

5 independently a bond or a straight chain C₁₋₅ alkylene group, and the total atom number is 6 or less.

[3] 4-[2-[4-[4-(4-Isopropylpiperazin-1-yl)phenyl]-6,7-dimethyl-1H-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine or a salt thereof.

10 [4] 4-[2-[4-[4-(4-Isopropylpiperazin-1-yl)phenyl]-1,6-dimethyl-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine or a salt thereof.

[5] 4-[[4-[4-(4-Isopropylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine or a salt thereof.

15 [6] 4-[4-(4-Isopropylpiperazin-1-yl)phenyl]-2-(1-piperidylmethyl)-1H-pyrrolo[3,2-c]pyridine or a salt thereof.

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

[8] The medicament of the above-mentioned [7], which is a TLR7, 20 TLR9, TLR7/8, TLR7/9 or TLR7/8/9 inhibitor.

[9] The medicament of the above-mentioned [7], which is an agent for the prophylaxis or treatment of autoimmune diseases and/or inflammatory diseases.

[10] The medicament of the above-mentioned [9], wherein the 25 autoimmune diseases and/or inflammatory diseases is selected from systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, psoriasis and inflammatory bowel disease.

[11] The compound or salt of the above-mentioned [1] for use in the prophylaxis or treatment of autoimmune diseases and/or 30 inflammatory diseases.

[12] The compound or salt of the above-mentioned [11], wherein the autoimmune diseases and/or inflammatory diseases is selected from systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, psoriasis and inflammatory bowel disease.

35 [13] A method of inhibiting TLR7, TLR9, TLR7/8, TLR7/9 or

TLR7/8/9 in a mammal, which comprises administering an effective amount of the compound or salt of the above-mentioned [1] to the mammal.

[14] A method for the prophylaxis or treatment of autoimmune diseases and/or inflammatory diseases in a mammal, which comprises administering an effective amount of the compound or salt of the above-mentioned [1] to the mammal.

[15] The method of the above-mentioned [14], wherein the autoimmune diseases and/or inflammatory diseases is selected from systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, psoriasis and inflammatory bowel disease.

[16] Use of the compound or salt of the above-mentioned [1] for the production of an agent for the prophylaxis or treatment of autoimmune diseases and/or inflammatory diseases.

[17] Use of the above-mentioned [16], wherein the autoimmune diseases and/or inflammatory diseases is selected from systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, psoriasis and inflammatory bowel disease.

Effect of the Invention

[0017]

According to the present invention, the compound having a TLR7, TLR9, TLR7/8, TLR7/9 or TLR7/8/9 inhibitory action, which is useful as an agent for the prophylaxis or treatment of autoimmune diseases, inflammatory diseases and the like, in particular, systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, psoriasis, inflammatory bowel disease and the like, can be provided.

Brief Description of the Drawings

[0018]

Figure 1A shows reduction in anti-dsDNA IgG with Example B6 after 6 weeks of treatment.

Figure 1B shows reduction in anti-dsDNA IgG with Example B6 after 9 weeks of treatment.

Figure 2A shows reduction in anti-dsDNA IgG with Example B11 after 6 weeks of treatment.

[0019]

[Detailed Description of the Invention]

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

5 The "halogen atom" in the present specification means, unless otherwise specified, a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

The "C₁₋₃ alkylenedioxy group" in the present specification means, unless otherwise specified,
10 methylenedioxy, ethylenedioxy or the like.

The "C₁₋₆ alkyl group" in the present specification means, unless otherwise specified, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl,
15 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl or the like.

[0020]

The "C₁₋₆ alkoxy group" in the present specification means, unless otherwise specified, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy or the
20 like.

The "C₁₋₆ alkoxy-carbonyl group" in the present specification means, unless otherwise specified, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl or the like.

25 The "C₁₋₆ alkyl-carbonyl group" in the present specification means, unless otherwise specified, acetyl, propanoyl, butanoyl, isobutanoyl, pentanoyl, isopentanoyl, hexanoyl or the like.

[0021]

30 R¹ is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted hydroxy group, an optionally substituted amino group, an optionally substituted sulfanyl group, or an acyl group.

35 R², R³ and R⁴ are independently a hydrogen atom or a

substituent.

[0022]

Examples of the "substituent" for R², R³ or R⁴ include a "halogen atom", a "cyano group", a "nitro group", an
5 "optionally substituted hydrocarbon group", an "optionally substituted heterocyclic group", an "optionally substituted hydroxy group", an "optionally substituted amino group", an "optionally substituted sulfanyl group", an "acyl group" and the like.

10 [0023]

Examples of the "hydrocarbon group" of the above-mentioned "optionally substituted hydrocarbon group" include a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group, a C₃₋₁₀ cycloalkyl group, a C₃₋₁₀ cycloalkenyl group, a C₄₋₁₀
15 cycloalkadienyl group, a C₆₋₁₄ aryl group, a C₇₋₁₃ aralkyl group, a C₈₋₁₃ arylalkenyl group and the like.

[0024]

Examples of the C₁₋₁₀ alkyl group include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl,
20 pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, heptyl, octyl, nonyl, decyl and the like. Of these, a C₁₋₆ alkyl group is preferable.

[0025]

25 Examples of the C₂₋₁₀ 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, 5-hexenyl, 1-heptenyl, 1-octenyl and the like. Of
30 these, a C₂₋₆ alkenyl group is preferable.

[0026]

Examples of the C₂₋₁₀ alkynyl group include ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexynyl, 2-
35 hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptyne, 1-

octynyl and the like. Of these, a C₂₋₆ alkynyl group is preferable.

[0027]

Examples of the C₃₋₁₀ cycloalkyl group include cyclopropyl, 5 cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like. Of these, a C₃₋₆ cycloalkyl group is preferable.

[0028]

Examples of the C₃₋₁₀ cycloalkenyl group include 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, 3-10 cyclohexen-1-yl and the like. Of these, a C₃₋₆ cycloalkenyl group is preferable.

[0029]

Examples of the C₄₋₁₀ cycloalkadienyl group include 2,4-15 cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl and the like. Of these, a C₄₋₆ cycloalkadienyl group is preferable.

[0030]

The above-mentioned C₃₋₁₀ cycloalkyl group, C₃₋₁₀ cycloalkenyl group and C₄₋₁₀ cycloalkadienyl group are each 20 optionally fused with a benzene ring to form a fused ring group. Examples of the fused ring group include indanyl, dihydronaphthyl, tetrahydronaphthyl, fluorenyl and the like.

[0031]

In addition, the above-mentioned C₃₋₁₀ cycloalkyl group, 25 C₃₋₁₀ cycloalkenyl group and C₄₋₁₀ cycloalkadienyl group may be each a C₇₋₁₀ bridged hydrocarbon group. Examples of the C₇₋₁₀ bridged hydrocarbon group include bicyclo[2.2.1]heptyl (norbornyl), bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, 30 bicyclo[4.3.1]decyl, adamantyl and the like.

[0032]

Moreover, the above-mentioned C₃₋₁₀ cycloalkyl group, C₃₋₁₀ cycloalkenyl group and C₄₋₁₀ cycloalkadienyl group each optionally forms a spiro ring group together with a C₃₋₁₀ 35 cycloalkane, a C₃₋₁₀ cycloalkene or a C₄₋₁₀ cycloalkadiene.

Examples of the C₃₋₁₀ cycloalkane, C₃₋₁₀ cycloalkene and C₄₋₁₀ cycloalkadiene include rings corresponding to the above-mentioned C₃₋₁₀ cycloalkyl group, C₃₋₁₀ cycloalkenyl group and C₄₋₁₀ cycloalkadienyl group. Examples of the spiro ring group
5 include spiro[4.5]decan-8-yl and the like.

[0033]

Examples of the C₆₋₁₄ aryl group include phenyl, naphthyl, anthryl, phenanthryl, acenaphthyl, biphenyl and the like. Of these, a C₆₋₁₂ aryl group is preferable.

10 [0034]

Examples of the C₇₋₁₃ aralkyl group include benzyl, phenethyl, naphthylmethyl, biphenylmethyl and the like.

[0035]

Examples of the C₈₋₁₃ arylalkenyl group include styryl and
15 the like.

[0036]

The C₁₋₁₀ alkyl group, C₂₋₁₀ alkenyl group and C₂₋₁₀ alkynyl group, which are exemplified as the above-mentioned "hydrocarbon group", optionally have 1 to 7 (preferably 1 to
20 3) substituents at substitutable positions.

[0037]

Examples of the substituent include

(1) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclohexyl);
(2) a C₆₋₁₄ aryl group (e.g., phenyl, naphthyl) optionally
25 substituted by 1 to 3 substituents selected from

(a) a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms,
(b) a hydroxy group,
(c) a C₁₋₆ alkoxy group optionally substituted by 1 to 3
30 halogen atoms, and
(d) a halogen atom;

(3) an aromatic heterocyclic group (e.g., thienyl, furyl, pyridyl, pyrazolyl, imidazolyl, tetrazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl) optionally substituted
35 by 1 to 3 substituents selected from

- (a) a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms,
- (b) a hydroxy group,
- (c) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atoms, and
- (d) a halogen atom;
- (4) a non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, piperazinyl, oxetanyl) optionally substituted by 1 to 3 substituents selected from
- (a) a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms,
- (b) a hydroxy group,
- (c) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atoms,
- (d) a halogen atom, and
- (e) an oxo group;
- (5) an amino group optionally mono- or di-substituted by substituent(s) selected from
- (a) a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms,
- (b) a C₁₋₆ alkyl-carbonyl group optionally substituted by 1 to 3 halogen atoms,
- (c) a C₁₋₆ alkoxy-carbonyl group optionally substituted by 1 to 3 halogen atoms,
- (d) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl) optionally substituted by 1 to 3 halogen atoms,
- (e) a carbamoyl group optionally mono- or di-substituted by C₁₋₆ alkyl group(s) optionally substituted by 1 to 3 halogen atoms, and
- (f) an aromatic heterocyclic group (e.g., thienyl, furyl, pyridyl, pyrazolyl, imidazolyl, tetrazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl);
- (6) a C₁₋₆ alkyl-carbonyl group optionally substituted by 1 to 3 halogen atoms;

- (7) a C₁₋₆ alkoxy-carbonyl group optionally substituted by 1 to 3 substituents selected from
- (a) a halogen atom,
 - (b) a C₁₋₆ alkoxy group,
 - 5 (c) a C₆₋₁₄ aryl group (e.g., phenyl), and
 - (d) a heterocyclic group (e.g., tetrahydrofuryl);
- (8) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl, isopropylsulfonyl) optionally substituted by 1 to 3 halogen atoms;
- 10 (9) a carbamoyl group optionally mono- or di-substituted by C₁₋₆ alkyl group(s) optionally substituted by 1 to 3 halogen atoms;
- (10) a thiocarbamoyl group optionally mono- or di-substituted by C₁₋₆ alkyl group(s) optionally substituted by 1 to 3 halogen atoms;
- 15 (11) a sulfamoyl group optionally mono- or di-substituted by C₁₋₆ alkyl group(s) optionally substituted by 1 to 3 halogen atoms;
- (12) a carboxy group;
- (13) a hydroxy group;
- 20 (14) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 substituents selected from
- (a) a halogen atom,
 - (b) a carboxy group,
 - (c) a C₁₋₆ alkoxy group,
 - 25 (d) a C₁₋₆ alkoxy-carbonyl group optionally substituted by 1 to 3 C₆₋₁₄ aryl groups (e.g., phenyl),
 - (e) an amino group optionally mono- or di-substituted by substituent(s) selected from a C₁₋₆ alkyl group and a C₁₋₆ alkoxy-carbonyl group,
 - 30 (f) a heterocyclic group (e.g., tetrahydrofuryl), and
 - (g) a C₃₋₁₀ cycloalkyl group;
- (15) a C₂₋₆ alkenyloxy group (e.g., ethenyloxy) optionally substituted by 1 to 3 halogen atoms;
- (16) a C₇₋₁₃ aralkyloxy group (e.g., benzyloxy);
- 35 (17) a C₆₋₁₄ aryloxy group (e.g., phenyloxy, naphthyloxy);

(18) a C₁₋₆ alkyl-carbonyloxy group (e.g., acetyloxy, tert-butylcarbonyloxy);

(19) a C₆₋₁₄ aryl-carbonyl group (e.g., benzoyl) optionally substituted by 1 to 3 substituents selected from

5 (a) a halogen atom, and

(b) a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms;

(20) a non-aromatic heterocyclylcarbonyl group (e.g., pyrrolidinylcarbonyl, morpholinylcarbonyl) optionally

10 substituted by 1 to 3 C₁₋₆ alkyl groups optionally substituted by 1 to 3 halogen atoms;

(21) a sulfanyl group;

(22) a C₁₋₆ alkylthio group (e.g., methylthio, ethylthio) optionally substituted by 1 to 3 substituents selected from

15 (a) a halogen atom, and

(b) a C₁₋₆ alkoxy-carbonyl group;

(23) a C₇₋₁₃ aralkylthio group (e.g., benzylthio);

(24) a C₆₋₁₄ arylthio group (e.g., phenylthio, naphthylthio);

(25) a cyano group;

20 (26) a nitro group;

(27) a halogen atom;

(28) a C₁₋₃ alkylenedioxy group;

(29) a C₁₋₃ alkyleneoxy group (e.g., methyleneoxy, ethyleneoxy);

(30) an aromatic heterocyclylcarbonyl group (e.g.,
25 pyrazolylcarbonyl, pyrazinylcarbonyl, isoxazolylcarbonyl, pyridylcarbonyl, thiazolylcarbonyl) optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms;

(31) a C₃₋₁₀ cycloalkoxy group (e.g., cyclopropoxy,
30 cyclopentyloxy) optionally substituted by 1 to 3 substituents selected from

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

(b) a C₁₋₆ alkoxy group (e.g., methoxy)

and the like. When the number of the substituents is not less
35 than 2, the respective substituents may be the same or

different.

[0038]

The C₃₋₁₀ cycloalkyl group, C₃₋₁₀ cycloalkenyl group, C₄₋₁₀ cycloalkadienyl group, C₆₋₁₄ aryl group, C₇₋₁₃ aralkyl group and
5 C₈₋₁₃ arylalkenyl group, which are exemplified as the above-mentioned "hydrocarbon group", optionally have 1 to 3 substituents at substitutable positions.

[0039]

Examples of the substituent include

10 (1) the groups exemplified as the substituents for the above-mentioned C₁₋₁₀ alkyl group and the like;

(2) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from

- (a) a halogen atom,
- 15 (b) a carboxy group,
- (c) a hydroxy group,
- (d) a C₁₋₆ alkoxy-carbonyl group,
- (e) a C₁₋₆ alkoxy group, and
- (f) an amino group optionally mono- or di-substituted by C₁₋₆
20 alkyl group(s);

(3) a C₂₋₆ alkenyl group (e.g., ethenyl, 1-propenyl) optionally substituted by 1 to 3 substituents selected from

- (a) a halogen atom,
- (b) a carboxy group,
- 25 (c) a hydroxy group,
- (d) a C₁₋₆ alkoxy-carbonyl group,
- (e) a C₁₋₆ alkoxy group, and
- (f) an amino group optionally mono- or di-substituted by C₁₋₆ alkyl group(s);

30 (4) a C₇₋₁₃ aralkyl group (e.g., benzyl) optionally substituted by 1 to 3 substituents selected from

- (a) a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms,
- (b) a hydroxy group,
- 35 (c) a C₁₋₆ alkoxy group, and

(d) a halogen atom;
and the like. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

5 [0040]

Examples of the "heterocyclic group" of the above-mentioned "optionally substituted heterocyclic group" include an "aromatic heterocyclic group" and a "non-aromatic heterocyclic group".

10 [0041]

Examples of the aromatic heterocyclic group include a 4- to 7-membered (preferably 5- or 6-membered) monocyclic aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atoms, 1 to 4 hetero atoms selected from
15 an oxygen atom, a sulfur atom and a nitrogen atom, and a fused aromatic heterocyclic group. Examples of the fused aromatic heterocyclic group include a group derived from a fused ring wherein a ring corresponding to the 4- to 7-membered monocyclic aromatic heterocyclic group and 1 or 2 rings
20 selected from a 5- or 6-membered aromatic heterocycle containing 1 or 2 nitrogen atoms (e.g., pyrrole, imidazole, pyrazole, pyrazine, pyridine, pyrimidine), a 5-membered aromatic heterocycle containing one sulfur atom (e.g., thiophene) and a benzene ring are fused, and the like.

25 [0042]

Preferable examples of the aromatic heterocyclic group include
monocyclic aromatic heterocyclic groups such as furyl (e.g.,
2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl),
30 pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrazinyl (e.g., 2-pyrazinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-
35 imidazolyl, 5-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-

pyrazolyl, 4-pyrazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (e.g., 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl), thiadiazolyl (e.g., 1,3,4-thiadiazol-2-yl), triazolyl (e.g., 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g., tetrazol-1-yl, tetrazol-5-yl),
10 triazinyl (e.g., 1,2,4-triazin-1-yl, 1,2,4-triazin-3-yl) and the like;

fused aromatic heterocyclic groups such as quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 6-quinolyl), isoquinolyl (e.g., 3-isoquinolyl), quinazolyl (e.g.,
15 2-quinazolyl, 4-quinazolyl), quinoxalyl (e.g., 2-quinoxalyl, 6-quinoxalyl), benzofuranyl (e.g., 2-benzofuranyl, 3-benzofuranyl), benzothienyl (e.g., 2-benzothienyl, 3-benzothienyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzisoxazolyl (e.g., 7-benzisoxazolyl), benzothiazolyl (e.g.,
20 2-benzothiazolyl), benzimidazolyl (e.g., benzimidazol-1-yl, benzimidazol-2-yl, benzimidazol-5-yl), benzotriazolyl (e.g., 1H-1,2,3-benzotriazol-5-yl), indolyl (e.g., indol-1-yl, indol-2-yl, indol-3-yl, indol-5-yl), indazolyl (e.g., 1H-indazol-3-yl), pyrrolopyrazinyl (e.g., 1H-pyrrolo[2,3-b]pyrazin-2-yl,
25 1H-pyrrolo[2,3-b]pyrazin-6-yl), imidazopyridinyl (e.g., 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 2H-imidazo[1,2-a]pyridin-3-yl), thienopyridinyl (e.g., thieno[2,3-b]pyridin-3-yl), imidazopyrazinyl (e.g., 1H-imidazo[4,5-b]pyrazin-2-yl), pyrazolopyridinyl (e.g., 1H-pyrazolo[4,3-c]pyridin-3-yl), pyrazolothienyl (e.g., 2H-pyrazolo[3,4-b]thiophen-2-yl), pyrazolotriazinyl (e.g., pyrazolo[5,1-c][1,2,4]triazin-3-yl), pyridopyridinyl (e.g., pyrido[2,3-b]pyridin-3-yl), thienopyridyl (e.g., thieno[2,3-b]pyridin-3-yl) and the like;

35 and the like.

[0043]

Examples of the non-aromatic heterocyclic group include a 4- to 7-membered (preferably 5- or 6-membered) monocyclic non-aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atoms, 1 to 4 hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and a fused aromatic heterocyclic group. Examples of the fused aromatic heterocyclic group include a group derived from a fused ring wherein a ring corresponding to the 4- to 7-membered monocyclic non-aromatic heterocyclic group and 1 or 2 rings selected from a 5- or 6-membered aromatic heterocycle containing 1 or 2 nitrogen atoms (e.g., pyrrole, imidazole, pyrazole, pyrazine, pyridine, pyrimidine), a 5-membered aromatic heterocycle containing one sulfur atom (e.g., thiophene) and a benzene ring are fused, a group wherein the above-mentioned group is partially saturated, and the like.

[0044]

Preferable examples of the non-aromatic heterocyclic group include

monocyclic non-aromatic heterocyclic groups such as azetidiny (e.g., 1-azetidiny, 2-azetidiny, 3-azetidiny), pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl), piperidyl (e.g., piperidino, 2-piperidyl, 3-piperidyl, 4-piperidyl), morpholinyl (e.g., morpholino), thiomorpholinyl (e.g., thiomorpholino), 1-oxidothiomorpholine, 1,1-dioxidothiomorpholine, piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl, 3-piperazinyl), hexamethyleniminyl (e.g., hexamethylenimin-1-yl), oxazolidinyl (e.g., oxazolidin-2-yl), thiazolidinyl (e.g., thiazolidin-2-yl), imidazolidinyl (e.g., imidazolidin-2-yl, imidazolidin-3-yl), oxazolinyl (e.g., oxazolin-2-yl), thiazolinyl (e.g., thiazolin-2-yl), imidazolinyl (e.g., imidazolin-2-yl, imidazolin-3-yl), dioxolyl (e.g., 1,3-dioxol-4-yl), dioxolanyl (e.g., 1,3-dioxolan-4-yl), dihydrooxadiazolyl (e.g., 4,5-dihydro-1,2,4-oxadiazol-3-yl), pyranyl (e.g., 4-pyranyl), tetrahydropyranyl

(e.g., 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl), thiopyranyl (e.g., 4-thiopyranyl), tetrahydrothiopyranyl (e.g., 2-tetrahydrothiopyranyl, 3-tetrahydrothiopyranyl, 4-tetrahydrothiopyranyl),
5 tetrahydrofuryl (e.g., tetrahydrofuran-3-yl, tetrahydrofuran-2-yl), pyrazolidinyl (e.g., pyrazolidin-1-yl, pyrazolidin-3-yl), pyrazolinyl (e.g., pyrazolin-1-yl), tetrahydropyrimidinyl (e.g., tetrahydropyrimidin-1-yl), dihydrotriazolyl (e.g., 2,3-dihydro-1H-1,2,3-triazol-1-yl), tetrahydrotriazolyl (e.g.,
10 2,3,4,5-tetrahydro-1H-1,2,3-triazol-1-yl) and the like;
fused non-aromatic heterocyclic groups such as dihydroindolyl (e.g., 2,3-dihydro-1H-indol-1-yl), dihydroisoindolyl (e.g., 1,3-dihydro-2H-isoindol-2-yl), dihydrobenzofuranyl (e.g., 2,3-dihydro-1-benzofuran-5-yl),
15 dihydrobenzodioxinyl (e.g., 2,3-dihydro-1,4-benzodioxinyl), dihydrobenzodioxepinyl (e.g., 3,4-dihydro-2H-1,5-benzodioxepinyl), tetrahydrobenzofuranyl (e.g., 4,5,6,7-tetrahydro-1-benzofuran-3-yl), chromenyl (e.g., 4H-chromen-2-yl, 2H-chromen-3-yl), dihydrochromenyl (e.g., 3,4-dihydro-2H-chromen-2-yl), dihydroquinolinyl (e.g., 1,2-dihydroquinolin-4-yl), tetrahydroquinolinyl (e.g., 1,2,3,4-tetrahydroquinolin-4-yl), dihydroisoquinolinyl (e.g., 1,2-dihydroisoquinolin-4-yl), tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydroisoquinolin-4-yl), dihydrophthalazinyl (e.g., 1,4-dihydrophthalazin-4-yl)
20 and the like;
and the like.

[0045]

The above-mentioned non-aromatic heterocyclic group may be bridged. Examples of the bridged non-aromatic heterocyclic
30 group include 3-azabicyclo[2.2.1]heptane, 3-azabicyclo[3.3.1]nonane, 6-azabicyclo[3.1.1]heptane and the like.

Moreover, the above-mentioned non-aromatic heterocyclic group optionally forms a spiro ring group together with a C₃₋₁₀
35 cycloalkane, a C₃₋₁₀ cycloalkene, a C₄₋₁₀ cycloalkadiene or a

non-aromatic heterocycle. Examples of the C₃₋₁₀ cycloalkane, C₃₋₁₀ cycloalkene, C₄₋₁₀ cycloalkadiene and non-aromatic heterocycle include rings corresponding to the above-mentioned C₃₋₁₀ cycloalkyl group, C₃₋₁₀ cycloalkenyl group, C₄₋₁₀ cycloalkadienyl group and non-aromatic heterocyclic group. Examples of the spiro ring group include 6-azaspiro[3.3]heptane, 7-azaspiro[3.5]nonane and the like.

[0046]

The "heterocyclic group" of the "optionally substituted heterocyclic group" optionally has 1 to 3 substituents at substitutable positions. Examples of the substituent include those similar to the substituents that the C₃₋₁₀ cycloalkyl group and the like exemplified as the "hydrocarbon group" of the above-mentioned "optionally substituted hydrocarbon group" optionally has. When the heterocyclic group is a "non-aromatic heterocyclic group", the substituent further includes an oxo group. When the number of the substituents is not less than 2, the respective substituents may be the same or different.

[0047]

Examples of the above-mentioned "optionally substituted hydroxy group" include a hydroxy group optionally substituted by a substituent selected from a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₃₋₁₀ cycloalkenyl group, a C₆₋₁₄ aryl group, a C₇₋₁₃ aralkyl group, a C₈₋₁₃ arylalkenyl group, a C₁₋₆ alkyl-carbonyl group, a heterocyclic group and the like, each of which is optionally substituted.

[0048]

Examples of the C₁₋₁₀ alkyl group, C₂₋₁₀ alkenyl group, C₃₋₁₀ cycloalkyl group, C₃₋₁₀ cycloalkenyl group, C₆₋₁₄ aryl group, C₇₋₁₃ aralkyl group and C₈₋₁₃ arylalkenyl group include those exemplified as the "hydrocarbon group" of the above-mentioned "optionally substituted hydrocarbon group".

[0049]

Examples of the heterocyclic group include those similar to the "aromatic heterocyclic group" and "non-aromatic

heterocyclic group" exemplified as the "heterocyclic group" of the above-mentioned "optionally substituted heterocyclic group".

[0050]

5 The above-mentioned C₁₋₁₀ alkyl group, C₂₋₁₀ alkenyl group, C₃₋₁₀ cycloalkyl group, C₃₋₁₀ cycloalkenyl group, C₆₋₁₄ aryl group, C₇₋₁₃ aralkyl group, C₈₋₁₃ arylalkenyl group, C₁₋₆ alkyl-carbonyl group and heterocyclic group optionally have 1 to 3 substituents at substitutable positions. When the number of
10 the substituents is not less than 2, the respective substituents may be the same or different.

[0051]

 Examples of the substituent for the C₁₋₁₀ alkyl group, C₂₋₁₀ alkenyl group and C₁₋₆ alkyl-carbonyl group include those
15 similar to the substituent that the C₁₋₁₀ alkyl group and the like exemplified as the "hydrocarbon group" of the above-mentioned "optionally substituted hydrocarbon group" optionally has.

[0052]

20 Examples of the substituent for the C₃₋₁₀ cycloalkyl group, C₃₋₁₀ cycloalkenyl group, C₆₋₁₄ aryl group, C₇₋₁₃ aralkyl group and C₈₋₁₃ arylalkenyl group include those similar to the substituent that the C₃₋₁₀ cycloalkyl group and the like exemplified as the "hydrocarbon group" of the above-mentioned "optionally
25 substituted hydrocarbon group" optionally has. Examples of the substituent for the heterocyclic group include those similar to the substituent that the "heterocyclic group" of the above-mentioned "optionally substituted heterocyclic group" optionally has.

30 [0053]

 Examples of the above-mentioned "optionally substituted sulfanyl group" include a sulfanyl group optionally substituted by a substituent selected from a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₃₋₁₀
35 cycloalkenyl group, a C₆₋₁₄ aryl group, a C₇₋₁₃ aralkyl group, a

C₈₋₁₃ arylalkenyl group, a C₁₋₆ alkyl-carbonyl group, a heterocyclic group and the like, each of which is optionally substituted.

[0054]

5 Examples of the substituent include those exemplified as the substituents of the above-mentioned "optionally substituted hydroxy group".

[0055]

10 Examples of the above-mentioned "optionally substituted amino group" include an amino group optionally mono- or di-substituted by substituent(s) selected from a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₃₋₁₀ cycloalkenyl group, a C₆₋₁₄ aryl group, a C₇₋₁₃ aralkyl group, a C₈₋₁₃ arylalkenyl group and a heterocyclic group, each of which
15 is optionally substituted; an acyl group and the like.

[0056]

20 Examples of the C₁₋₁₀ alkyl group, C₂₋₁₀ alkenyl group, C₃₋₁₀ cycloalkyl group, C₃₋₁₀ cycloalkenyl group, C₆₋₁₄ aryl group, C₇₋₁₃ aralkyl group and C₈₋₁₃ arylalkenyl group include those exemplified as the "hydrocarbon group" of the above-mentioned "optionally substituted hydrocarbon group".

[0057]

25 Examples of the heterocyclic group include those similar to the "aromatic heterocyclic group" and "non-aromatic heterocyclic group" exemplified as the "heterocyclic group" of the above-mentioned "optionally substituted heterocyclic group". Of these, a 5- to 7-membered monocyclic aromatic heterocyclic group is preferable.

[0058]

30 The C₁₋₁₀ alkyl group, C₂₋₁₀ alkenyl group, C₃₋₁₀ cycloalkyl group, C₃₋₁₀ cycloalkenyl group, C₆₋₁₄ aryl group, C₇₋₁₃ aralkyl group, C₈₋₁₃ arylalkenyl group and heterocyclic group optionally have 1 to 3 substituents at substitutable positions. When the number of the substituents is not less than 2, the respective
35 substituents may be the same or different.

[0059]

Examples of the substituent for the C₁₋₁₀ alkyl group and C₂₋₁₀ alkenyl group include those similar to the substituent that the C₁₋₁₀ alkyl group and the like exemplified as the "hydrocarbon group" of the above-mentioned "optionally substituted hydrocarbon group" optionally has.

[0060]

Examples of the substituent for the C₃₋₁₀ cycloalkyl group, C₃₋₁₀ cycloalkenyl group, C₆₋₁₄ aryl group, C₇₋₁₃ aralkyl group and C₈₋₁₃ arylalkenyl group include those similar to the substituent that the C₃₋₁₀ cycloalkyl group and the like exemplified as the "hydrocarbon group" of the above-mentioned "optionally substituted hydrocarbon group" optionally has. Examples of the substituent for the heterocyclic group include those similar to the substituent that the "heterocyclic group" of the above-mentioned "optionally substituted heterocyclic group" optionally has.

[0061]

Examples of the "acyl group" exemplified as the substituent for the "optionally substituted amino group" include those similar to the "acyl group" below, which is exemplified as the "substituent" for R².

[0062]

Examples of the "acyl group" exemplified as the "substituent" for R² include a group represented by the formula: -COR^A, -CO-OR^A, -SO₃R^A, -S(O)₂R^A, -SOR^A, -CO-NR^AR^B, -CS-NR^AR^B or -S(O)₂NR^AR^B wherein R^A is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, and R^A and R^B are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group, or R^A and R^B form, together with the adjacent nitrogen atom, an optionally substituted nitrogen-containing heterocycle, and the like.

[0063]

Examples of the "optionally substituted hydrocarbon group" and "optionally substituted heterocyclic group" for R^A , $R^{A'}$ or R^B include those similar to the "optionally substituted hydrocarbon group" and "optionally substituted heterocyclic group", which are exemplified as the "substituent" for R^2 .
[0064]

Examples of the "nitrogen-containing heterocycle" of the "optionally substituted nitrogen-containing heterocycle" formed by $R^{A'}$ and R^B together with the adjacent nitrogen atom include a 5- to 7-membered nitrogen-containing heterocycle containing, as a ring-constituting atom besides carbon atoms, at least one nitrogen atom and optionally further containing one or two hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom. Preferable examples of the nitrogen-containing heterocycle include pyrrolidine, imidazolidine, pyrazolidine, piperidine, piperazine, morpholine, thiomorpholine and the like.
[0065]

The nitrogen-containing heterocycle optionally has 1 to 5 (preferably 1 or 2) substituents at substitutable positions. Examples of the substituent include those similar to the substituent that the "heterocyclic group" of the "optionally substituted heterocyclic group", which is exemplified as the "substituent" for R^2 , optionally has. When the number of the substituents is not less than 2, the respective substituents may be the same or different.
[0066]

Preferable examples of the "acyl group" include

- (1) a formyl group;
- (2) a carboxy group;
- (3) a C_{1-6} alkyl-carbonyl group (e.g., acetyl) optionally substituted by 1 to 3 halogen atoms;
- (4) a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl) optionally substituted by 1 to 3 halogen atoms;

(5) a C₃₋₁₀ cycloalkyl-carbonyl group (e.g., cyclopropylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl);

(6) a C₆₋₁₄ aryl-carbonyl group (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl) optionally substituted by 1 to 3 halogen atoms;

5 (7) a carbamoyl group optionally mono- or di-substituted by substituent(s) selected from

(a) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a C₁₋₆ alkoxy group, a C₁₋₆ alkoxy-carbonyl group and a carboxy group, and

10 (b) an amino group optionally mono- or di-substituted by C₁₋₆ alkoxy-carbonyl group(s);

(8) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl, isopropylsulfonyl) optionally substituted by 1 to 3 halogen atoms;

15 (9) a C₆₋₁₄ arylsulfonyl group (e.g., benzenesulfonyl);

(10) a sulfamoyl group;

(11) a thiocarbamoyl group;

(12) an aromatic heterocyclylcarbonyl group (e.g., furylcarbonyl, thienylcarbonyl) optionally substituted by 1 to

20 3 substituents selected from a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms;

(13) a non-aromatic heterocyclylcarbonyl group (e.g., tetrahydrofurylcarbonyl, pyrrolidinylcarbonyl) optionally substituted by 1 to 3 substituents selected from a C₁₋₆ alkyl

25 group optionally substituted by 1 to 3 halogen atoms; and the like.

[0067]

R¹ is preferably a hydrogen atom, an optionally substituted C₁₋₁₀ alkyl group (preferably an optionally substituted C₁₋₆ alkyl group (e.g. methyl)) or an optionally substituted C₃₋₁₀ cycloalkyl group (preferably an optionally substituted C₃₋₆ cycloalkyl group (e.g., cyclopropyl)).

R¹ is more preferably a hydrogen atom, a C₁₋₁₀ alkyl group (preferably a C₁₋₆ alkyl group (e.g. methyl)) or a C₃₋₁₀ cycloalkyl group (preferably a C₃₋₆ cycloalkyl group (e.g.,

35

cyclopropyl)).

R^1 is still more preferably a hydrogen atom or a C_{1-10} alkyl group (preferably a C_{1-6} alkyl group (e.g. methyl)).

In another embodiment, R^1 is still more preferably a
5 hydrogen atom.

[0068]

R^2 is preferably a hydrogen atom, a halogen atom or an optionally substituted C_{1-10} alkyl group (preferably an optionally substituted C_{1-6} alkyl group (e.g. methyl)).

10 R^2 is more preferably a hydrogen atom or an optionally substituted C_{1-10} alkyl group (preferably an optionally substituted C_{1-6} alkyl group (e.g. methyl)).

R^2 is further more preferably a hydrogen atom or a C_{1-10} alkyl group (preferably a C_{1-6} alkyl group (e.g. methyl)).

15 R^2 is still more preferably a hydrogen atom.

[0069]

R^3 is preferably a hydrogen atom, a halogen atom, an optionally substituted C_{1-10} alkyl group (preferably an optionally substituted C_{1-6} alkyl group (e.g. methyl)), an
20 optionally substituted C_{3-10} cycloalkyl group (preferably an optionally substituted C_{3-6} cycloalkyl group (e.g., cyclopropyl, cyclobutyl)) or an optionally substituted C_{1-10} alkoxy group (preferably an optionally substituted C_{1-6} alkoxy group (e.g. ethoxy)).

25 In another embodiment, R^3 is preferably a hydrogen atom, an optionally substituted hydrocarbon group [preferably an optionally substituted C_{1-10} alkyl group (preferably an optionally substituted C_{1-6} alkyl group (e.g. methyl)), an optionally substituted C_{3-10} cycloalkyl group (preferably an
30 optionally substituted C_{3-6} cycloalkyl group (e.g., cyclopropyl, cyclobutyl))], or an optionally substituted hydroxy group [preferably an optionally substituted C_{1-10} alkoxy group (preferably an optionally substituted C_{1-6} alkoxy group (e.g. ethoxy))].

35 [0070]

R^3 is more preferably a hydrogen atom, an optionally substituted C_{1-10} alkyl group (preferably an optionally substituted C_{1-6} alkyl group (e.g. methyl)), an optionally substituted C_{3-10} cycloalkyl group (preferably an optionally substituted C_{3-6} cycloalkyl group (e.g., cyclopropyl, cyclobutyl)) or an optionally substituted C_{1-10} alkoxy group (preferably an optionally substituted C_{1-6} alkoxy group (e.g. ethoxy)).

R^3 is further more preferably

- (1) a hydrogen atom,
- (2) a C_{1-10} alkyl group (preferably a C_{1-6} alkyl group (e.g. methyl)) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (3) a C_{3-10} cycloalkyl group (preferably a C_{3-6} cycloalkyl group (e.g., cyclopropyl, cyclobutyl)), or
- (4) a C_{1-10} alkoxy group (preferably a C_{1-6} alkoxy group (e.g. ethoxy)) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom).

[0071]

R^3 is still more preferably

- (1) a hydrogen atom,
- (2) a C_{1-10} alkyl group (preferably a C_{1-6} alkyl group (e.g. methyl)) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), or
- (3) a C_{3-10} cycloalkyl group (preferably a C_{3-6} cycloalkyl group (e.g., cyclopropyl)).

In another embodiment, R^3 is still more preferably a hydrogen atom or a C_{1-10} alkyl group (preferably a C_{1-6} alkyl group (e.g. methyl)).

[0072]

R^4 is preferably a hydrogen atom, a halogen atom (e.g., a chlorine atom), or an optionally substituted hydrocarbon group [preferably an optionally substituted C_{1-10} alkyl group (preferably an optionally substituted C_{1-6} alkyl group (e.g. methyl)), or an optionally substituted C_{3-10} cycloalkyl group

(preferably an optionally substituted C₃₋₆ cycloalkyl group (e.g., cyclopropyl))].

R⁴ is more preferably a hydrogen atom, a halogen atom (e.g., a chlorine atom), an optionally substituted C₁₋₁₀ alkyl group (preferably an optionally substituted C₁₋₆ alkyl group (e.g. methyl)), or an optionally substituted C₃₋₁₀ cycloalkyl group (preferably an optionally substituted C₃₋₆ cycloalkyl group (e.g., cyclopropyl)).

R⁴ is further more preferably a hydrogen atom, a halogen atom (e.g., a chlorine atom), a C₁₋₆ alkyl group (e.g. methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), or a C₃₋₆ cycloalkyl group (e.g., cyclopropyl).

R⁴ is still more preferably a hydrogen atom or a halogen atom (e.g., a chlorine atom).

In another embodiment, R⁴ is still more preferably a hydrogen atom.

[0073]

Ring A is an optionally substituted ring.

Examples of the "ring" of the "optionally substituted ring" for Ring A include a C₆₋₁₄ aromatic hydrocarbon, a C₃₋₁₀ cycloalkane, a C₃₋₁₀ cycloalkene, a C₄₋₁₀ cycloalkadiene, an aromatic heterocycle and a non-aromatic heterocycle.

Examples of the C₆₋₁₄ aromatic hydrocarbon, C₃₋₁₀ cycloalkane, C₃₋₁₀ cycloalkene and C₄₋₁₀ cycloalkadiene include rings corresponding to the above-mentioned C₆₋₁₄ aryl group, C₃₋₁₀ cycloalkyl group, C₃₋₁₀ cycloalkenyl group and C₄₋₁₀ cycloalkadienyl group exemplified as the "hydrocarbon group" of the "optionally substituted hydrocarbon group", which is exemplified as the "substituent" for R², R³ or R⁴.

Examples of the aromatic heterocycle and non-aromatic heterocycle include rings corresponding to the above-mentioned aromatic heterocyclic group and non-aromatic heterocyclic group exemplified as the "heterocyclic group" of the "optionally substituted heterocyclic group", which is exemplified as the "substituent" for R², R³ or R⁴.

The "ring" of the "optionally substituted ring" for Ring A optionally has 1 to 3 substituents at substitutable positions. Examples of the substituent include those similar to the substituents that the "heterocyclic group" of the
5 "optionally substituted heterocyclic group", which is exemplified as the "substituent" for R^2 , R^3 or R^4 , optionally has. When the number of the substituents is not less than 2, respective substituents may be the same or different.

[0074]

10 Ring A is preferably an optionally substituted C_{6-14} aromatic hydrocarbon (preferably an optionally substituted C_{6-12} aromatic hydrocarbon (e.g., benzene)) or an optionally substituted aromatic heterocycle optionally fused with benzene (preferably an optionally substituted 5- or 6-membered
15 aromatic heterocycle optionally fused with benzene (e.g., pyridine, pyrazole, indole, thiazole)).

Ring A is more preferably

(1) a C_{6-14} aromatic hydrocarbon (preferably a C_{6-12} aromatic hydrocarbon (e.g., benzene)) optionally substituted by 1 to 3
20 substituents selected from a halogen atom (e.g., a fluorine atom) and a cyano group, or
(2) an aromatic heterocycle (preferably a 5- or 6-membered aromatic heterocycle optionally fused with benzene (e.g., pyridine, pyrazole, indole, thiazole)).

25 Ring A is still more preferably a C_{6-14} aromatic hydrocarbon (preferably a C_{6-12} aromatic hydrocarbon (e.g., benzene)).

[0075]

In another embodiment, Ring A is preferably an optionally
30 substituted C_{3-10} cycloalkane (preferably an optionally substituted C_{3-6} cycloalkane (e.g., cyclohexane)), an optionally substituted C_{3-10} cycloalkene (preferably an optionally substituted C_{3-6} cycloalkene (e.g., cyclohexene)), an optionally substituted C_{6-14} aromatic hydrocarbon (preferably an optionally
35 substituted C_{6-12} aromatic hydrocarbon (e.g., benzene)) or an

optionally substituted aromatic heterocycle optionally fused with benzene (preferably an optionally substituted 5- or 6-membered aromatic heterocycle optionally fused with benzene (e.g., pyridine, pyrazole, indole, thiazole)).

5 In this embodiment, Ring A is more preferably

(1) a C₃₋₁₀ cycloalkane (preferably a C₃₋₆ cycloalkane (e.g., cyclohexane)),

(2) a C₃₋₁₀ cycloalkene (preferably a C₃₋₆ cycloalkene (e.g., cyclohexene)),

10 (3) a C₆₋₁₄ aromatic hydrocarbon (preferably a C₆₋₁₂ aromatic hydrocarbon (e.g., benzene)) optionally substituted by 1 to 3 substituents selected from

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

(ii) a C₁₋₆ alkyl group (e.g. methyl) optionally substituted
15 by 1 to 3 halogen atoms (e.g., a fluorine atom),

(iii) a C₁₋₆ alkoxy group (e.g. methoxy), and

(iv) a cyano group, or

(4) an aromatic heterocycle optionally fused with benzene (preferably a 5- or 6-membered aromatic heterocycle optionally
20 fused with benzene (e.g., pyridine, pyrazole, indole, thiazole)).

In this embodiment, Ring A is still more preferably

(1) a C₃₋₁₀ cycloalkane (preferably a C₃₋₆ cycloalkane (e.g., cyclohexane)),

25 (2) a C₃₋₁₀ cycloalkene (preferably a C₃₋₆ cycloalkene (e.g., cyclohexene)),

(3) a C₆₋₁₄ aromatic hydrocarbon (preferably a C₆₋₁₂ aromatic hydrocarbon (e.g., benzene)) optionally substituted by 1 to 3 substituents selected from

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

(ii) a C₁₋₆ alkyl group (e.g. methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and

(iii) a C₁₋₆ alkoxy group (e.g. methoxy), or

(4) an aromatic heterocycle optionally fused with benzene
35 (preferably a 5- or 6-membered aromatic heterocycle optionally

fused with benzene (e.g., pyridine, pyrazole, thiazole)).

[0076]

Ring B is an optionally substituted heterocycle.

Examples of the "heterocycle" of the "optionally substituted heterocycle" for Ring B include an aromatic heterocycle and a non-aromatic heterocycle.

Examples of the aromatic heterocycle and non-aromatic heterocycle include rings corresponding to the above-mentioned aromatic heterocyclic group and non-aromatic heterocyclic group exemplified as the "heterocyclic group" of the "optionally substituted heterocyclic group", which is exemplified as the "substituent" for R^2 , R^3 or R^4 .

The "heterocycle" of the "optionally substituted heterocycle" for Ring B optionally has 1 to 3 substituents at substitutable positions. Examples of the substituent include those similar to the substituents that the "heterocyclic group" of the "optionally substituted heterocyclic group", which is exemplified as the "substituent" for R^2 , R^3 or R^4 , optionally has. When the number of the substituents is not less than 2, respective substituents may be the same or different.

[0077]

Ring B is preferably an optionally substituted 3- to 10-membered non-aromatic heterocycle (e.g. azetidine, pyrrolidine, piperidine, piperazine, tetrahydropyridine, morpholine, 1,1-dioxidothiomorpholine, oxetane, 3-azabicyclo[2.2.1]heptane, 3-azabicyclo[3.3.1]nonane, 7-azaspiro[3.5]nonane).

Ring B is more preferably a 3- to 10-membered non-aromatic heterocycle (e.g. azetidine, pyrrolidine, piperidine, piperazine, tetrahydropyridine, morpholine, 1,1-dioxidothiomorpholine, oxetane, 3-azabicyclo[2.2.1]heptane, 3-azabicyclo[3.3.1]nonane, 7-azaspiro[3.5]nonane) optionally substituted by 1 to 3 substituents selected from

- (1) a halogen atom (e.g., a fluorine atom),
- (2) a hydroxy group,
- (3) a carboxy group,

- (4) a C₁₋₆ alkyl group (e.g. methyl, ethyl, isopropyl) optionally substituted by 1 to 3 hydroxy groups,
(5) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),
(6) a C₁₋₆ alkoxy-carbonyl group (e.g. methoxycarbonyl, tert-butoxycarbonyl), and
(7) a non-aromatic heterocyclic group (preferably a 3- to 10-membered non-aromatic heterocyclic group (e.g., oxetanyl)).

Ring B is still more preferably a 5- or 6-membered non-aromatic heterocycle (e.g. piperidine, piperazine) optionally substituted by 1 to 3 substituents selected from

- (1) a hydroxy group,
(2) a carboxy group,
(3) a C₁₋₆ alkyl group (e.g. methyl, ethyl, isopropyl), and
(4) a C₁₋₆ alkoxy-carbonyl group (e.g. methoxycarbonyl, tert-butoxycarbonyl).

[0078]

In another embodiment, Ring B is more preferably a 3- to 10-membered non-aromatic heterocycle (e.g. azetidine, pyrrolidine, piperidine, piperazine, tetrahydropyridine, morpholine, 1,1-dioxidothiomorpholine, oxetane, 3-azabicyclo[2.2.1]heptane, 3-azabicyclo[3.3.1]nonane, 7-azaspiro[3.5]nonane) optionally substituted by 1 to 3 substituents selected from

- (1) a halogen atom (e.g., a fluorine atom),
(2) a hydroxy group,
(3) a carboxy group,
(4) a C₁₋₆ alkyl group (e.g. methyl, ethyl, isopropyl) optionally substituted by 1 to 3 substituents selected from
(i) a hydroxy group,
(ii) a halogen atom (e.g., a fluorine atom), and
(iii) an aromatic heterocyclic group (preferably a 5- or 6-membered aromatic heterocyclic group (e.g., oxazolyl)),
(5) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),
(6) a C₁₋₆ alkoxy-carbonyl group (e.g. methoxycarbonyl,

ethoxycarbonyl, tert-butoxycarbonyl), and

(7) a non-aromatic heterocyclic group (preferably a 3- to 10-membered non-aromatic heterocyclic group (e.g., oxetanyl)).

5 In this embodiment, Ring B is still more preferably a 3- to 10-membered non-aromatic heterocycle (e.g. piperidine, piperazine, tetrahydropyridine, morpholine) optionally substituted by 1 to 3 substituents selected from

(1) a hydroxy group,

10 (2) a carboxy group,

(3) a C₁₋₆ alkyl group (e.g. methyl, ethyl, isopropyl)

optionally substituted by 1 to 3 substituents selected from

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

(ii) an aromatic heterocyclic group (preferably a 5- or

15 6-membered aromatic heterocyclic group (e.g., oxazolyl)),

(4) a C₁₋₆ alkoxy-carbonyl group (e.g. methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl), and

(5) a non-aromatic heterocyclic group (preferably a 3- to 10-membered non-aromatic heterocyclic group (e.g.,

20 oxetanyl)).

[0079]

Ring C is an optionally substituted 3- to 10-membered nitrogen-containing heterocycle.

Examples of the "3- to 10-membered nitrogen-containing
25 heterocycle" of the "optionally substituted 3- to 10-membered nitrogen-containing heterocycle" for Ring C include a 3- to 10-membered nitrogen-containing heterocycle, from among rings corresponding to the above-mentioned aromatic heterocyclic group and non-aromatic heterocyclic group exemplified as the
30 "heterocyclic group" of the "optionally substituted heterocyclic group", which is exemplified as the "substituent" for R², R³ or R⁴.

Specific examples thereof include azetidine, pyrrolidine, imidazolidine, pyrazolidine, piperidine, piperazine,
35 morpholine, thiomorpholine, 1-oxidothiomorpholine, 1,1-

dioxidothiomorpholine, 3-azabicyclo[2.2.1]heptane, 3-azabicyclo[3.3.1]nonane, 6-azabicyclo[3.1.1]heptane, 6-azaspiro[3.3]heptane, 7-azaspiro[3.5]nonane and the like.
[0080]

5 The "3- to 10-membered nitrogen-containing heterocycle" of the "optionally substituted 3- to 10-membered nitrogen-containing heterocycle" for Ring C optionally has 1 to 3 substituents at substitutable positions. Examples of the substituent include those similar to the substituents that the
10 "heterocyclic group" of the "optionally substituted heterocyclic group", which is exemplified as the "substituent" for R^2 , R^3 or R^4 , optionally has. When the number of the substituents is not less than 2, respective substituents may be the same or different.

15 [0081]

Ring C is preferably an optionally substituted 3- to 10-membered nitrogen-containing non-aromatic heterocycle (e.g., morpholine, azetidine, pyrrolidine, piperidine, 6-azaspiro[3.3]heptane, 7-azaspiro[3.5]nonane, 6-
20 azabicyclo[3.1.1]heptane, 3-azabicyclo[2.2.1]heptane).

Ring C is more preferably a 3- to 10-membered nitrogen-containing non-aromatic heterocycle (e.g., morpholine, azetidine, pyrrolidine, piperidine, 6-azaspiro[3.3]heptane, 7-azaspiro[3.5]nonane, 6-azabicyclo[3.1.1]heptane, 3-
25 azabicyclo[2.2.1]heptane) optionally substituted by 1 to 3 substituents selected from

- (1) a halogen atom (e.g., a fluorine atom),
- (2) a hydroxyl group,
- (3) a C_{1-6} alkyl group (e.g. methyl),
- 30 (4) a carboxy group, and
- (5) a C_{1-6} alkoxy-carbonyl group (e.g. methoxycarbonyl).

Ring C is still more preferably a 5- or 6-membered nitrogen-containing non-aromatic heterocycle (e.g., morpholine).

35 [0082]

In another embodiment, Ring C is preferably an optionally substituted 5- or 6-membered nitrogen-containing aromatic heterocycle (e.g., pyrazole) or an optionally substituted 3- to 10-membered nitrogen-containing non-aromatic heterocycle (e.g., morpholine, azetidine, pyrrolidine, piperidine, 6-azaspiro[3.3]heptane, 7-azaspiro[3.5]nonane, 6-azabicyclo[3.1.1]heptane, 3-azabicyclo[2.2.1]heptane).

In this embodiment, Ring C is more preferably

- (1) a 5- or 6-membered nitrogen-containing aromatic heterocycle (e.g., pyrazole), or
 - (2) a 3- to 10-membered nitrogen-containing non-aromatic heterocycle (e.g., morpholine, azetidine, pyrrolidine, piperidine, 6-azaspiro[3.3]heptane, 7-azaspiro[3.5]nonane, 6-azabicyclo[3.1.1]heptane, 3-azabicyclo[2.2.1]heptane)
- optionally substituted by 1 to 3 substituents selected from
- (1) a halogen atom (e.g., a fluorine atom),
 - (2) a hydroxyl group,
 - (3) a C₁₋₆ alkyl group (e.g. methyl),
 - (4) a carboxy group, and
 - (5) a C₁₋₆ alkoxy-carbonyl group (e.g. methoxycarbonyl).

In this embodiment, Ring C is still more preferably

- (1) a 5- or 6-membered nitrogen-containing aromatic heterocycle (e.g., pyrazole), or
 - (2) a 3- to 10-membered nitrogen-containing non-aromatic heterocycle (e.g., morpholine, azetidine, pyrrolidine, piperidine, 7-azaspiro[3.5]nonane) optionally substituted by 1 to 3 substituents selected from
- (1) a halogen atom (e.g., a fluorine atom),
 - (2) a hydroxyl group,
 - (3) a C₁₋₆ alkyl group (e.g. methyl),
 - (4) a carboxy group, and
 - (5) a C₁₋₆ alkoxy-carbonyl group (e.g. methoxycarbonyl).

[0083]

L¹ is a bond or a divalent hydrocarbon group.

L³ is a bond or a divalent hydrocarbon group.

Examples of the "divalent hydrocarbon group" for L¹ or L³ include a divalent chain hydrocarbon group, a divalent cyclic hydrocarbon group, a divalent chain-cyclic hydrocarbon group and the like, specifically,

- 5 (1) a C₁₋₁₀ alkylene group (preferably a C₁₋₆ alkylene group (e.g., -CH₂-, -(CH₂)₂-, -(CH₂)₃-, -(CH₂)₄-, -(CH₂)₅-, -(CH₂)₆-, -CHCH₃-, -C(CH₃)₂-, -(CH(CH₃))₂-, -(CH₂)₂C(CH₃)₂-, -(CH₂)₃C(CH₃)₂-));
 - (2) a C₂₋₁₀ alkenylene group (preferably a C₂₋₆ alkenylene group
10 (e.g., -CH=CH-, -CH₂-CH=CH-, -CH=CH-CH₂-, -CH=CH-CH₂-CH₂-, -C(CH₃)₂-CH=CH-, -CH₂-CH=CH-CH₂-, -CH₂-CH₂-CH=CH-, -CH=CH-CH=CH-, -CH=CH-CH₂-CH₂-CH₂-));
 - (3) a C₂₋₁₀ alkynylene group (preferably a C₂₋₆ alkynylene group (e.g., -C≡C-, -CH₂-C≡C-, -CH₂-C≡C-CH₂-CH₂-));
 - 15 (4) a C₃₋₈ cycloalkylene group (preferably a C₃₋₆ cycloalkylene group (e.g., 1,1-cyclopropylene, 1,2-cyclopropylene, 1,3-cyclobutylene, 1,3-cyclopentylene, 1,3-cyclohexylene, 1,4-cyclohexylene, 1,4-cycloheptylene, 1,5-cyclooctylene));
 - (5) a C₆₋₁₄ arylene group (preferably a C₆₋₁₂ arylene group (e.g.,
20 phenylene (e.g., 1,2-phenylene, 1,3-phenylene, 1,4-phenylene), naphthylene (e.g., 1,2-naphthylene, 1,3-naphthylene, 1,4-naphthylene, 1,5-naphthylene, 1,6-naphthylene, 1,7-naphthylene, 1,8-naphthylene, 2,3-naphthylene, 2,6-naphthylene, 2,7-naphthylene), biphenylene (e.g., 2,2'-biphenylene, 3,3'-
25 biphenylene, 4,4'-biphenylene) and the like. The C₆₋₁₄ arylene may be saturated partially, and examples of the partially saturated C₆₋₁₄ arylene include tetrahydronaphthylene and the like));
 - (6) a combination of any two selected from the above-mentioned
30 (1) to (5) (e.g., methylene-phenylene, phenylene-methylene, ethylene-phenylene, phenylene-ethylene, methylene-cyclohexylene, cyclohexylene-methylene, methylene-naphthylene, naphthylene-methylene);
- and the like.

35 [0084]

L^1 and L^3 are preferably independently

- (1) a bond,
- (2) a C_{1-10} alkylene group (preferably a C_{1-6} alkylene group, more preferably a C_{1-3} alkylene group (e.g., $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-C(CH_3)_2-$)), or
- (3) a C_{3-8} cycloalkylene group (preferably a C_{3-6} cycloalkylene group (e.g., 1,1-cyclopropylene)).

L^1 and L^3 are more preferably independently

- (1) a bond, or
- (2) a C_{1-6} alkylene group, (preferably a C_{1-3} alkylene group (e.g., $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$)).

In another embodiment, L^1 and L^3 are more preferably independently

- (1) a bond, or
- (2) a C_{1-6} alkylene group, (preferably a C_{1-3} alkylene group (e.g., $-CH_2-$, $-(CH_2)_2-$)).

[0085]

L^2 is a bond, $-O-$, $-C(O)-$, $-NH-C(O)-$, $-C(O)-NH-$, $-S-$, $-SO-$, $-SO_2-$, $-SO_2-O-$, $-O-SO_2-$ or $-CH(CN)-$.

[0086]

L^2 is preferably a bond or $-C(O)-$.

L^2 is more preferably a bond.

[0087]

$L^1-L^2-L^3$ is preferably

- (1) a C_{1-10} alkylene group (preferably a C_{1-6} alkylene group, more preferably a C_{1-3} alkylene group (e.g., $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-C(CH_3)_2-$)),
- (2) a C_{3-8} cycloalkylene group (preferably a C_{3-6} cycloalkylene group (e.g., 1,1-cyclopropylene)), or
- (3) $-C(O)-$.

$L^1-L^2-L^3$ is more preferably

- (1) a C_{1-10} alkylene group (preferably a C_{1-6} alkylene group, more preferably a C_{1-3} alkylene group (e.g., $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$)), or
- (2) $-C(O)-$.

In another embodiment, $L^1-L^2-L^3$ is more preferably a C_{1-6} alkylene group (preferably a C_{1-3} alkylene group (e.g., $-CH_2-$, $-(CH_2)_2-$)).

[0088]

5 L^4 is a bond or a spacer having 1 to 6 atoms.

The "spacer having 1 to 6 atoms" for L^4 is a straight chain connecting Ring A and Ring B, and the atom number is counted such that the number of atoms will be minimum. The straight chain consists of 1 to 6 atoms selected from a carbon
10 atom and a hetero atom (e.g., O, S, N etc.), and may be saturated or unsaturated. In addition, S may be oxidized.

Examples of the "spacer having 1 to 6 atoms" include a straight chain C_{1-6} alkylene group, $-X^1-NH-X^2-$, $-X^1-O-X^2-$, $-X^1-S-X^2-$, $-X^1-C(O)-X^2-$, $-X^1-NH-C(O)-X^2-$, $-X^1-C(O)-NH-X^2-$, $-X^1-NH-C(O)-$
15 $O-X^2-$, $-X^1-O-C(O)-NH-X^2-$, $-X^1-SO-X^2-$, $-X^1-SO_2-X^2-$, $-X^1-SO_2-O-X^2-$ and $-X^1-O-SO_2-X^2-$ [wherein X^1 and X^2 are independently a bond or a straight chain C_{1-5} alkylene group, and the total atom number is 6 or less] and the like.

Examples of the "straight chain C_{1-6} alkylene group"
20 include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2CH_2-$ and $-CH_2CH_2CH_2CH_2CH_2CH_2-$. Of these, a straight chain C_{1-3} alkylene group is preferable.

Examples of the "straight chain C_{1-5} alkylene group" for X^1 or X^2 include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$ and $-$
25 $CH_2CH_2CH_2CH_2CH_2-$. Of these, a straight chain C_{1-3} alkylene group is preferable.

The "spacer having 1 to 6 atoms" optionally has substituent(s) (preferably 1 to 3 substituents) at substitutable position(s) (optionally at the carbon atom and
30 nitrogen atom constituting the main chain). Examples of the substituent include those similar to the substituents that the "heterocyclic group" of the "optionally substituted heterocyclic group", which is exemplified as the "substituent" for R^2 , R^3 or R^4 , optionally has. When the number of the
35 substituents is not less than 2, respective substituents may

be the same or different.

[0089]

L^4 is preferably a bond, a straight chain C_{1-6} alkylene group (preferably a straight chain C_{1-3} alkylene group (e.g., -CH₂-, -CH₂CH₂-)), -X¹-O-X²-, -X¹-C(O)-X²- or -X¹-NH-C(O)-X²- [wherein X¹ and X² are independently a bond or a straight chain C_{1-5} alkylene group, and the total atom number is 6 or less].

L^4 is more preferably a bond, a straight chain C_{1-6} alkylene group (preferably a straight chain C_{1-3} alkylene group (e.g., -CH₂-, -CH₂CH₂-)), -O-, -C(O)- or -NH-C(O)-.

L^4 is still more preferably a bond, a straight chain C_{1-6} alkylene group (preferably a straight chain C_{1-3} alkylene group (e.g., -CH₂-)), -O- or -C(O)-.

In another embodiment, L^4 is still more preferably a bond.

[0090]

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

[0091]

[Compound A-1]

Compound (I) wherein

R^1 is a hydrogen atom, an optionally substituted C_{1-10} alkyl group (preferably an optionally substituted C_{1-6} alkyl group (e.g. methyl)) or an optionally substituted C_{3-10} cycloalkyl group (preferably an optionally substituted C_{3-6} cycloalkyl group (e.g., cyclopropyl));

R^2 is a hydrogen atom or an optionally substituted C_{1-10} alkyl group (preferably an optionally substituted C_{1-6} alkyl group (e.g. methyl));

R^3 is a hydrogen atom, an optionally substituted C_{1-10} alkyl group (preferably an optionally substituted C_{1-6} alkyl group (e.g. methyl)), an optionally substituted C_{3-10} cycloalkyl group (preferably an optionally substituted C_{3-6} cycloalkyl group (e.g., cyclopropyl, cyclobutyl)) or an optionally substituted C_{1-10} alkoxy group (preferably an optionally substituted C_{1-6} alkoxy group (e.g. ethoxy));

R^4 is a hydrogen atom, a halogen atom (e.g., a chlorine atom), an optionally substituted C_{1-10} alkyl group (preferably an optionally substituted C_{1-6} alkyl group (e.g. methyl)), or an optionally substituted C_{3-10} cycloalkyl group (preferably an optionally substituted C_{3-6} cycloalkyl group (e.g., cyclopropyl));

Ring A is an optionally substituted C_{6-14} aromatic hydrocarbon (preferably an optionally substituted C_{6-12} aromatic hydrocarbon (e.g., benzene)) or an optionally substituted aromatic heterocycle optionally fused with benzene (preferably an optionally substituted 5- or 6-membered aromatic heterocycle optionally fused with benzene (e.g., pyridine, pyrazole, indole, thiazole));

Ring B is an optionally substituted 3- to 10-membered non-aromatic heterocycle (e.g. azetidine, pyrrolidine, piperidine, piperazine, tetrahydropyridine, morpholine, 1,1-dioxidothiomorpholine, oxetane, 3-azabicyclo[2.2.1]heptane, 3-azabicyclo[3.3.1]nonane, 7-azaspiro[3.5]nonane);

Ring C is an optionally substituted 3- to 10-membered nitrogen-containing non-aromatic heterocycle (e.g., morpholine, azetidine, pyrrolidine, piperidine, 6-azaspiro[3.3]heptane, 7-azaspiro[3.5]nonane, 6-azabicyclo[3.1.1]heptane, 3-azabicyclo[2.2.1]heptane);

L^1 and L^3 are independently

- (1) a bond,
(2) a C_{1-10} alkylene group (preferably a C_{1-6} alkylene group, more preferably a C_{1-3} alkylene group (e.g., $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-C(CH_3)_2-$)), or
(3) a C_{3-8} cycloalkylene group (preferably a C_{3-6} cycloalkylene group (e.g., 1,1-cyclopropylene));

L^2 is a bond or $-C(O)-$;

[preferably, $L^1-L^2-L^3$ is

- (1) a C_{1-10} alkylene group (preferably a C_{1-6} alkylene group, more preferably a C_{1-3} alkylene group (e.g., $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-C(CH_3)_2-$)),

(2) a C₃₋₈ cycloalkylene group (preferably a C₃₋₆ cycloalkylene group (e.g., 1,1-cyclopropylene)), or

(3) -C(O)-]; and

L⁴ is a bond, a straight chain C₁₋₆ alkylene group (preferably a straight chain C₁₋₃ alkylene group (e.g., -CH₂-, -CH₂CH₂-)), -X¹-O-X²-, -X¹-C(O)-X²- or -X¹-NH-C(O)-X²- [wherein X¹ and X² are independently a bond or a straight chain C₁₋₅ alkylene group, and the total atom number is 6 or less].

[0092]

10 [Compound B-1]

Compound (I) wherein

R¹ is a hydrogen atom, a C₁₋₁₀ alkyl group (preferably a C₁₋₆ alkyl group (e.g. methyl)) or a C₃₋₁₀ cycloalkyl group (preferably a C₃₋₆ cycloalkyl group (e.g., cyclopropyl));

15 R² is a hydrogen atom or a C₁₋₁₀ alkyl group (preferably a C₁₋₆ alkyl group (e.g. methyl));

R³ is

- (1) a hydrogen atom,
- (2) a C₁₋₁₀ alkyl group (preferably a C₁₋₆ alkyl group (e.g. methyl)) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (3) a C₃₋₁₀ cycloalkyl group (preferably a C₃₋₆ cycloalkyl group (e.g., cyclopropyl, cyclobutyl)), or
- (4) a C₁₋₁₀ alkoxy group (preferably a C₁₋₆ alkoxy group (e.g. ethoxy)) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom);

R⁴ is a hydrogen atom, a halogen atom (e.g., a chlorine atom), a C₁₋₆ alkyl group (e.g. methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), or a C₃₋₆ cycloalkyl group (e.g., cyclopropyl);

30 Ring A is

- (1) a C₆₋₁₄ aromatic hydrocarbon (preferably a C₆₋₁₂ aromatic hydrocarbon (e.g., benzene)) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., a fluorine atom) and a cyano group, or

(2) an aromatic heterocycle (preferably a 5- or 6-membered aromatic heterocycle optionally fused with benzene (e.g., pyridine, pyrazole, indole, thiazole));

Ring B is a 3- to 10-membered non-aromatic heterocycle (e.g. azetidine, pyrrolidine, piperidine, piperazine, tetrahydropyridine, morpholine, 1,1-dioxidothiomorpholine, oxetane, 3-azabicyclo[2.2.1]heptane, 3-azabicyclo[3.3.1]nonane, 7-azaspiro[3.5]nonane) optionally substituted by 1 to 3 substituents selected from

- (1) a halogen atom (e.g., a fluorine atom),
- (2) a hydroxy group,
- (3) a carboxy group,
- (4) a C₁₋₆ alkyl group (e.g. methyl, ethyl, isopropyl) optionally substituted by 1 to 3 hydroxy groups,
- (5) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),
- (6) a C₁₋₆ alkoxy-carbonyl group (e.g. methoxycarbonyl, tert-butoxycarbonyl), and
- (7) a non-aromatic heterocyclic group (preferably a 3- to 10-membered non-aromatic heterocyclic group (e.g., oxetanyl));

Ring C is a 3- to 10-membered nitrogen-containing non-aromatic heterocycle (e.g., morpholine, azetidine, pyrrolidine, piperidine, 6-azaspiro[3.3]heptane, 7-azaspiro[3.5]nonane, 6-azabicyclo[3.1.1]heptane, 3-azabicyclo[2.2.1]heptane) optionally substituted by 1 to 3 substituents selected from

- (1) a halogen atom (e.g., a fluorine atom),
- (2) a hydroxyl group,
- (3) a C₁₋₆ alkyl group (e.g. methyl),
- (4) a carboxy group, and
- (5) a C₁₋₆ alkoxy-carbonyl group (e.g. methoxycarbonyl);

L¹ and L³ are independently

- (1) a bond,
- (2) a C₁₋₁₀ alkylene group (preferably a C₁₋₆ alkylene group, more preferably a C₁₋₃ alkylene group (e.g., -CH₂-, -(CH₂)₂-, -(CH₂)₃-, -C(CH₃)₂-)), or

(3) a C₃₋₈ cycloalkylene group (preferably a C₃₋₆ cycloalkylene group (e.g., 1,1-cyclopropylene));

L² is a bond or -C(O)-;

[preferably, L¹-L²-L³ is

5 (1) a C₁₋₁₀ alkylene group (preferably a C₁₋₆ alkylene group, more preferably a C₁₋₃ alkylene group (e.g., -CH₂-, -(CH₂)₂-, -(CH₂)₃-, -C(CH₃)₂-)),

(2) a C₃₋₈ cycloalkylene group (preferably a C₃₋₆ cycloalkylene group (e.g., 1,1-cyclopropylene)), or

10 (3) -C(O)-]; and

L⁴ is a bond, a straight chain C₁₋₆ alkylene group (preferably a straight chain C₁₋₃ alkylene group (e.g., -CH₂-, -CH₂CH₂-)), -O-, -C(O)- or -NH-C(O)-.

[0093]

15 [Compound C-1]

Compound (I) wherein

R¹ is a hydrogen atom;

R² is a hydrogen atom;

R³ is a hydrogen atom or a C₁₋₁₀ alkyl group (preferably a
20 C₁₋₆ alkyl group (e.g. methyl));

R⁴ is a hydrogen atom;

Ring A is a C₆₋₁₄ aromatic hydrocarbon (preferably a C₆₋₁₂ aromatic hydrocarbon (e.g., benzene));

Ring B is a 5- or 6-membered non-aromatic heterocycle
25 (e.g. piperidine, piperazine) optionally substituted by 1 to 3 substituents selected from

(1) a hydroxy group,

(2) a carboxy group,

(3) a C₁₋₆ alkyl group (e.g. methyl, ethyl, isopropyl), and

30 (4) a C₁₋₆ alkoxy-carbonyl group (e.g. methoxycarbonyl, tert-butoxycarbonyl);

Ring C is a 5- or 6-membered nitrogen-containing non-aromatic heterocycle (e.g., morpholine);

L¹ and L³ are independently

35 (1) a bond, or

(2) a C₁₋₆ alkylene group, (preferably a C₁₋₃ alkylene group (e.g., -CH₂-, -(CH₂)₂-));

L² is a bond;

[preferably, L¹-L²-L³ is a C₁₋₆ alkylene group (preferably a C₁₋₃ alkylene group (e.g., -CH₂-, -(CH₂)₂-))]; and

L⁴ is a bond.

[0094]

[Compound A-2]

Compound (I) wherein

10 R¹ is a hydrogen atom, an optionally substituted C₁₋₁₀ alkyl group (preferably an optionally substituted C₁₋₆ alkyl group (e.g. methyl)) or an optionally substituted C₃₋₁₀ cycloalkyl group (preferably an optionally substituted C₃₋₆ cycloalkyl group (e.g., cyclopropyl));

15 R² is a hydrogen atom or an optionally substituted C₁₋₁₀ alkyl group (preferably an optionally substituted C₁₋₆ alkyl group (e.g. methyl));

R³ is a hydrogen atom, an optionally substituted C₁₋₁₀ alkyl group (preferably an optionally substituted C₁₋₆ alkyl group (e.g. methyl)), an optionally substituted C₃₋₁₀ cycloalkyl group (preferably an optionally substituted C₃₋₆ cycloalkyl group (e.g., cyclopropyl, cyclobutyl)) or an optionally substituted C₁₋₁₀ alkoxy group (preferably an optionally substituted C₁₋₆ alkoxy group (e.g. ethoxy));

25 R⁴ is a hydrogen atom, a halogen atom (e.g., a chlorine atom), an optionally substituted C₁₋₁₀ alkyl group (preferably an optionally substituted C₁₋₆ alkyl group (e.g. methyl)), or an optionally substituted C₃₋₁₀ cycloalkyl group (preferably an optionally substituted C₃₋₆ cycloalkyl group (e.g., cyclopropyl));

30 Ring A is an optionally substituted C₃₋₁₀ cycloalkane (preferably an optionally substituted C₃₋₆ cycloalkane (e.g., cyclohexane)), an optionally substituted C₃₋₁₀ cycloalkene (preferably an optionally substituted C₃₋₆ cycloalkene (e.g., cyclohexene)), an optionally substituted C₆₋₁₄ aromatic

hydrocarbon (preferably an optionally substituted C₆₋₁₂ aromatic hydrocarbon (e.g., benzene)) or an optionally substituted aromatic heterocycle optionally fused with benzene (preferably an optionally substituted 5- or 6-membered aromatic
5 heterocycle optionally fused with benzene (e.g., pyridine, pyrazole, indole, thiazole));

Ring B is an optionally substituted 3- to 10-membered non-aromatic heterocycle (e.g. azetidine, pyrrolidine, piperidine, piperazine, tetrahydropyridine, morpholine, 1,1-
10 dioxidothiomorpholine, oxetane, 3-azabicyclo[2.2.1]heptane, 3-azabicyclo[3.3.1]nonane, 7-azaspiro[3.5]nonane);

Ring C is an optionally substituted 5- or 6-membered nitrogen-containing aromatic heterocycle (e.g., pyrazole) or an optionally substituted 3- to 10-membered nitrogen-
15 containing non-aromatic heterocycle (e.g., morpholine, azetidine, pyrrolidine, piperidine, 6-azaspiro[3.3]heptane, 7-azaspiro[3.5]nonane, 6-azabicyclo[3.1.1]heptane, 3-azabicyclo[2.2.1]heptane);

L¹ and L³ are independently

- 20 (1) a bond,
(2) a C₁₋₁₀ alkylene group (preferably a C₁₋₆ alkylene group, more preferably a C₁₋₃ alkylene group (e.g., -CH₂-, -(CH₂)₂-, -(CH₂)₃-, -C(CH₃)₂-)), or
(3) a C₃₋₈ cycloalkylene group (preferably a C₃₋₆ cycloalkylene
25 group (e.g., 1,1-cyclopropylene));

L² is a bond or -C(O)-;

[preferably, L¹-L²-L³ is

- (1) a C₁₋₁₀ alkylene group (preferably a C₁₋₆ alkylene group, more preferably a C₁₋₃ alkylene group (e.g., -CH₂-, -(CH₂)₂-,
30 (CH₂)₃-, -C(CH₃)₂-)),
(2) a C₃₋₈ cycloalkylene group (preferably a C₃₋₆ cycloalkylene group (e.g., 1,1-cyclopropylene)), or
(3) -C(O)-]; and

L⁴ is a bond, a straight chain C₁₋₆ alkylene group
35 (preferably a straight chain C₁₋₃ alkylene group (e.g., -CH₂-, -

CH₂CH₂-)), -X¹-O-X²-, -X¹-C(O)-X²- or -X¹-NH-C(O)-X²- [wherein X¹ and X² are independently a bond or a straight chain C₁₋₅ alkylene group, and the total atom number is 6 or less].

[0095]

5 [Compound B-2]

Compound (I) wherein

R¹ is a hydrogen atom, a C₁₋₁₀ alkyl group (preferably a C₁₋₆ alkyl group (e.g. methyl)) or a C₃₋₁₀ cycloalkyl group (preferably a C₃₋₆ cycloalkyl group (e.g., cyclopropyl));

10 R² is a hydrogen atom or a C₁₋₁₀ alkyl group (preferably a C₁₋₆ alkyl group (e.g. methyl));

R³ is

- (1) a hydrogen atom,
- (2) a C₁₋₁₀ alkyl group (preferably a C₁₋₆ alkyl group (e.g. methyl)) optionally substituted by 1 to 3 halogen atoms (e.g.,
15 a fluorine atom),
- (3) a C₃₋₁₀ cycloalkyl group (preferably a C₃₋₆ cycloalkyl group (e.g., cyclopropyl, cyclobutyl)), or
- (4) a C₁₋₁₀ alkoxy group (preferably a C₁₋₆ alkoxy group (e.g. ethoxy)) optionally substituted by 1 to 3 halogen atoms (e.g.,
20 a fluorine atom);

R⁴ is a hydrogen atom, a halogen atom (e.g., a chlorine atom), a C₁₋₆ alkyl group (e.g. methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), or a C₃₋₆
25 cycloalkyl group (e.g., cyclopropyl);

Ring A is

- (1) a C₃₋₁₀ cycloalkane (preferably a C₃₋₆ cycloalkane (e.g., cyclohexane)),
- (2) a C₃₋₁₀ cycloalkene (preferably a C₃₋₆ cycloalkene (e.g.,
30 cyclohexene)),
- (3) a C₆₋₁₄ aromatic hydrocarbon (preferably a C₆₋₁₂ aromatic hydrocarbon (e.g., benzene)) optionally substituted by 1 to 3 substituents selected from

- (i) a halogen atom (e.g., a fluorine atom),
- 35 (ii) a C₁₋₆ alkyl group (e.g. methyl) optionally substituted

by 1 to 3 halogen atoms (e.g., a fluorine atom),

(iii) a C₁₋₆ alkoxy group (e.g. methoxy), and

(iv) a cyano group, or

(4) an aromatic heterocycle optionally fused with benzene
5 (preferably a 5- or 6-membered aromatic heterocycle optionally
fused with benzene (e.g., pyridine, pyrazole, indole,
thiazole));

Ring B is a 3- to 10-membered non-aromatic heterocycle
(e.g. azetidine, pyrrolidine, piperidine, piperazine,
10 tetrahydropyridine, morpholine, 1,1-dioxidothiomorpholine,
oxetane, 3-azabicyclo[2.2.1]heptane, 3-azabicyclo[3.3.1]nonane,
7-azaspiro[3.5]nonane) optionally substituted by 1 to 3
substituents selected from

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

15 (2) a hydroxy group,

(3) a carboxy group,

(4) a C₁₋₆ alkyl group (e.g. methyl, ethyl, isopropyl)

optionally substituted by 1 to 3 substituents selected from

(i) a hydroxy group,

20 (ii) a halogen atom (e.g., a fluorine atom), and

(iii) an aromatic heterocyclic group (preferably a 5- or
6-membered aromatic heterocyclic group (e.g., oxazolyl)),

(5) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),

(6) a C₁₋₆ alkoxy-carbonyl group (e.g. methoxycarbonyl,
25 ethoxycarbonyl, tert-butoxycarbonyl), and

(7) a non-aromatic heterocyclic group (preferably a 3- to
10-membered non-aromatic heterocyclic group (e.g.,
oxetanyl));

Ring C is

30 (1) a 5- or 6-membered nitrogen-containing aromatic
heterocycle (e.g., pyrazole), or

(2) a 3- to 10-membered nitrogen-containing non-aromatic
heterocycle (e.g., morpholine, azetidine, pyrrolidine,
piperidine, 6-azaspiro[3.3]heptane, 7-azaspiro[3.5]nonane, 6-
35 azabicyclo[3.1.1]heptane, 3-azabicyclo[2.2.1]heptane)

optionally substituted by 1 to 3 substituents selected from

- (1) a halogen atom (e.g., a fluorine atom),
- (2) a hydroxyl group,
- (3) a C₁₋₆ alkyl group (e.g. methyl),
- 5 (4) a carboxy group, and
- (5) a C₁₋₆ alkoxy-carbonyl group (e.g. methoxycarbonyl));

L¹ and L³ are independently

- (1) a bond,
- (2) a C₁₋₁₀ alkylene group (preferably a C₁₋₆ alkylene group,
- 10 more preferably a C₁₋₃ alkylene group (e.g., -CH₂-, -(CH₂)₂-, -(CH₂)₃-, -C(CH₃)₂-)), or
- (3) a C₃₋₈ cycloalkylene group (preferably a C₃₋₆ cycloalkylene group (e.g., 1,1-cyclopropylene));

L² is a bond or -C(O)-;

15 [preferably, L¹-L²-L³ is

- (1) a C₁₋₁₀ alkylene group (preferably a C₁₋₆ alkylene group, more preferably a C₁₋₃ alkylene group (e.g., -CH₂-, -(CH₂)₂-, -(CH₂)₃-, -C(CH₃)₂-)),
- (2) a C₃₋₈ cycloalkylene group (preferably a C₃₋₆ cycloalkylene
- 20 group (e.g., 1,1-cyclopropylene)), or
- (3) -C(O)-]; and

L⁴ is a bond, a straight chain C₁₋₆ alkylene group (preferably a straight chain C₁₋₃ alkylene group (e.g., -CH₂-, -CH₂CH₂-)), -O-, -C(O)- or -NH-C(O)-.

25 [0096]

[Compound C-2]

Compound (I) wherein

R¹ is a hydrogen atom or a C₁₋₁₀ alkyl group (preferably a C₁₋₆ alkyl group (e.g. methyl));

30 R² is a hydrogen atom or a C₁₋₁₀ alkyl group (preferably a C₁₋₆ alkyl group (e.g. methyl));

R³ is

- (1) a hydrogen atom,
- (2) a C₁₋₁₀ alkyl group (preferably a C₁₋₆ alkyl group (e.g. methyl)) optionally substituted by 1 to 3 halogen atoms (e.g.,
- 35 methyl))

a fluorine atom), or

(3) a C₃₋₁₀ cycloalkyl group (preferably a C₃₋₆ cycloalkyl group (e.g., cyclopropyl));

R⁴ is a hydrogen atom or a halogen atom (e.g., a chlorine atom);

Ring A is

(1) a C₃₋₁₀ cycloalkane (preferably a C₃₋₆ cycloalkane (e.g., cyclohexane)),

(2) a C₃₋₁₀ cycloalkene (preferably a C₃₋₆ cycloalkene (e.g., cyclohexene)),

(3) a C₆₋₁₄ aromatic hydrocarbon (preferably a C₆₋₁₂ aromatic hydrocarbon (e.g., benzene)) optionally substituted by 1 to 3 substituents selected from

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

(ii) a C₁₋₆ alkyl group (e.g. methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and

(iii) a C₁₋₆ alkoxy group (e.g. methoxy), or

(4) an aromatic heterocycle optionally fused with benzene (preferably a 5- or 6-membered aromatic heterocycle optionally fused with benzene (e.g., pyridine, pyrazole, thiazole));

Ring B is a 3- to 10-membered non-aromatic heterocycle (e.g. piperidine, piperazine, tetrahydropyridine, morpholine) optionally substituted by 1 to 3 substituents selected from

(1) a hydroxy group,

(2) a carboxy group,

(3) a C₁₋₆ alkyl group (e.g. methyl, ethyl, isopropyl) optionally substituted by 1 to 3 substituents selected from

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

(ii) an aromatic heterocyclic group (preferably a 5- or 6-membered aromatic heterocyclic group (e.g., oxazolyl)),

(4) a C₁₋₆ alkoxy-carbonyl group (e.g. methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl), and

(5) a non-aromatic heterocyclic group (preferably a 3- to 10-membered non-aromatic heterocyclic group (e.g., oxetanyl));

Ring C is

(1) a 5- or 6-membered nitrogen-containing aromatic heterocycle (e.g., pyrazole), or

(2) a 3- to 10-membered nitrogen-containing non-aromatic heterocycle (e.g., morpholine, azetidine, pyrrolidine, piperidine, 7-azaspiro[3.5]nonane) optionally substituted by 1 to 3 substituents selected from

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

(2) a hydroxyl group,

(3) a C₁₋₆ alkyl group (e.g. methyl),

(4) a carboxy group, and

(5) a C₁₋₆ alkoxy-carbonyl group (e.g. methoxycarbonyl);

L¹ and L³ are independently

(1) a bond, or

(2) a C₁₋₆ alkylene group, (preferably a C₁₋₃ alkylene group (e.g., -CH₂-, -(CH₂)₂-, -(CH₂)₃-));

L² is a bond or -C(O)-;

[preferably, L¹-L²-L³ is

(1) a C₁₋₁₀ alkylene group (preferably a C₁₋₆ alkylene group, more preferably a C₁₋₃ alkylene group (e.g., -CH₂-, -(CH₂)₂-, -(CH₂)₃-), or

(2) -C(O)-]; and

L⁴ is a bond, a straight chain C₁₋₆ alkylene group (preferably a straight chain C₁₋₃ alkylene group (e.g., -CH₂-)), -O- or -C(O)-.

[0097]

[Compound D-2]

Compound (I) wherein

R¹ is a hydrogen atom, a C₁₋₁₀ alkyl group (preferably a C₁₋₆ alkyl group (e.g. methyl)) or a C₃₋₁₀ cycloalkyl group (preferably a C₃₋₆ cycloalkyl group (e.g., cyclopropyl));

R² is a hydrogen atom or a C₁₋₁₀ alkyl group (preferably a C₁₋₆ alkyl group (e.g. methyl));

R³ is a hydrogen atom, an optionally substituted hydrocarbon group [preferably an optionally substituted C₁₋₁₀

alkyl group (preferably an optionally substituted C₁₋₆ alkyl group (e.g. methyl)), an optionally substituted C₃₋₁₀ cycloalkyl group (preferably an optionally substituted C₃₋₆ cycloalkyl group (e.g., cyclopropyl, cyclobutyl)), or an optionally substituted hydroxy group [preferably an optionally substituted C₁₋₁₀ alkoxy group (preferably an optionally substituted C₁₋₆ alkoxy group (e.g. ethoxy))];

R⁴ is a hydrogen atom, a halogen atom (e.g., a chlorine atom), or an optionally substituted hydrocarbon group [preferably an optionally substituted C₁₋₁₀ alkyl group (preferably an optionally substituted C₁₋₆ alkyl group (e.g. methyl)), or an optionally substituted C₃₋₁₀ cycloalkyl group (preferably an optionally substituted C₃₋₆ cycloalkyl group (e.g., cyclopropyl))];

Ring A is an optionally substituted C₃₋₁₀ cycloalkane (preferably an optionally substituted C₃₋₆ cycloalkane (e.g., cyclohexane)), an optionally substituted C₃₋₁₀ cycloalkene (preferably an optionally substituted C₃₋₆ cycloalkene (e.g., cyclohexene)), an optionally substituted C₆₋₁₄ aromatic hydrocarbon (preferably an optionally substituted C₆₋₁₂ aromatic hydrocarbon (e.g., benzene)) or an optionally substituted aromatic heterocycle optionally fused with benzene (preferably an optionally substituted 5- or 6-membered aromatic heterocycle optionally fused with benzene (e.g., pyridine, pyrazole, indole, thiazole));

Ring B is an optionally substituted 3- to 10-membered non-aromatic heterocycle (e.g. azetidine, pyrrolidine, piperidine, piperazine, tetrahydropyridine, morpholine, 1,1-dioxidothiomorpholine, oxetane, 3-azabicyclo[2.2.1]heptane, 3-azabicyclo[3.3.1]nonane, 7-azaspiro[3.5]nonane);

Ring C is an optionally substituted 5- or 6-membered nitrogen-containing aromatic heterocycle (e.g., pyrazole) or an optionally substituted 3- to 10-membered nitrogen-containing non-aromatic heterocycle (e.g., morpholine, azetidine, pyrrolidine, piperidine, 6-azaspiro[3.3]heptane, 7-

azaspiro[3.5]nonane, 6-azabicyclo[3.1.1]heptane, 3-azabicyclo[2.2.1]heptane);

L^1 and L^3 are independently

(1) a bond,

5 (2) a C_{1-10} alkylene group (preferably a C_{1-6} alkylene group, more preferably a C_{1-3} alkylene group (e.g., $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-C(CH_3)_2-$)), or

(3) a C_{3-8} cycloalkylene group (preferably a C_{3-6} cycloalkylene group (e.g., 1,1-cyclopropylene));

10 L^2 is a bond or $-C(O)-$;

[preferably, $L^1-L^2-L^3$ is

(1) a C_{1-10} alkylene group (preferably a C_{1-6} alkylene group, more preferably a C_{1-3} alkylene group (e.g., $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-C(CH_3)_2-$)),

15 (2) a C_{3-8} cycloalkylene group (preferably a C_{3-6} cycloalkylene group (e.g., 1,1-cyclopropylene)), or

(3) $-C(O)-$]; and

L^4 is a bond, a straight chain C_{1-6} alkylene group (preferably a straight chain C_{1-3} alkylene group (e.g., $-CH_2-$, $-CH_2CH_2-$)), $-X^1-O-X^2-$, $-X^1-C(O)-X^2-$ or $-X^1-NH-C(O)-X^2-$ [wherein X^1 and X^2 are independently a bond or a straight chain C_{1-5} alkylene group, and the total atom number is 6 or less].

[0098]

Examples of the salt of the compound represented by the
25 formula (I) include metal salts, ammonium salts, salts with an organic base, salt with an inorganic acid, salts with an organic acid, salts with a basic or acidic amino acid, and the like.

[0099]

30 Preferable examples of the metal salt include alkaline 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; aluminum salt, and the like.

[0100]

35 Preferable examples of the salt with an organic base

include salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like.

5 [0101]

Preferable examples of the salt with an inorganic acid include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like.

[0102]

10 Preferable examples of the salt with an 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
15 acid and the like.

[0103]

Preferable examples of the salt with a basic amino acid include salts with arginine, lysine, ornithine and the like. Preferable examples of the salt with an acidic amino acid
20 include salt with aspartic acid, glutamic acid and the like.

[0104]

Among the above-mentioned salts, pharmaceutically acceptable salts are preferable.

[0105]

25 Compound (I) may be in the form of a prodrug. The prodrug of compound (I) means a compound which is converted to compound (I) with a reaction due to an enzyme, gastric acid and the like under the physiological condition in the living body, that is, a compound which is converted to compound (I)
30 by enzymatic oxidation, reduction, hydrolysis and the like; a compound which is converted to compound (I) by hydrolysis and the like due to gastric acid, and the like.

[0106]

Examples of the prodrug of compound (I) include a
35 compound obtained by subjecting an amino group in compound (I)

to an acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting an amino group in compound (I) to an eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, 5 tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation or tert-butylation); a compound obtained by subjecting a hydroxy group in compound (I) to an acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting a hydroxy group in compound (I) 10 to an acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation or dimethylaminomethylcarbonylation); a compound obtained by subjecting a carboxyl group in compound (I) to an esterification or amidation (e.g., a compound obtained by 15 subjecting a carboxyl group in compound (I) to a C₁₋₆ alkyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo- 20 1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification or methylamidation) and the like. Among them, a compound esterified by C₁₋₆ alkyl (e.g., methyl, ethyl, tert-butyl and the like) are preferably used. These compounds can be produced from compound (I) 25 according to a method known per se.

[0107]

The prodrug of compound (I) may also be one which is converted into compound (I) under a physiological condition, such as those described in IYAKUHIN no KAIHATSU (Development 30 of Pharmaceuticals), Vol.7, Design of Molecules, p.163-198, 1990, Published by HIROKAWA SHOTEN.

[0108]

Each symbol of the compound in the following Schemes is as defined above, unless otherwise specified. Each compound 35 described in the following Schemes may be in the form of a

salt as long as it does not inhibit the reaction. Examples of the salt include those similar to the salt of compound (I).

[0109]

The compound obtained in each step can be used directly for the next reaction as the reaction mixture or as a crude product, or can also be isolated according to a conventional method from the reaction mixture, and can also be easily purified according to a separation means (e.g., recrystallization, distillation, chromatography etc.).

10 [0110]

The production methods of the compound of the present invention are described in the following.

Compound (I) can be produced according to a method known per se, for example, the production method shown in Scheme 1, 4 or 7, or a method analogous thereto.

In each of the following production methods, each starting compound used for the production of compound (I) may be in the form of a salt. Examples of the salt include those similar to the salt of compound (I).

20 [0111]

Each starting compound to be used for the production of compound (I) can be used directly for the next reaction as the reaction mixture or as a crude product, or can also be isolated according to a conventional method from the reaction mixture, and can also be purified according to a separation means (e.g., extraction, concentration, neutralization, filtration, distillation, recrystallization, chromatography etc.). Examples of the solvent used for the above-mentioned recrystallization include water, alcohols, ethers, hydrocarbons, amides, halogenated hydrocarbons, nitriles, ketones, esters, sulfoxides, organic acids and the like. These solvents may be used alone, or two or more kinds of solvents may be mixed at a suitable ratio, for example, 1:1 - 1:10. In addition, the compounds in the Schemes may be commercially available, or can be produced according to a method known per

se or a method analogous thereto.

[0112]

When compound (I) and intermediate for the production of compound (I) have a convertible functional group (e.g., a
5 carboxyl group, an amino group, a hydroxy group, a carbonyl group, a sulfanyl group, a C₁₋₆ alkoxy-carbonyl group, a C₆₋₁₄ aryloxy-carbonyl group, a C₇₋₁₆ aralkyloxy-carbonyl group, a sulfo group, a halogen atom, an optionally halogenated C₁₋₆ alkylsulfonyloxy group, a cyano group, an aminocarbonyl group,
10 a boryl group etc.), various compounds can be produced by converting such functional group according to a method known per se or a method analogous thereto.

Carboxyl group can be converted, for example, by reactions such as esterification, reduction, amidation,
15 conversion reaction to optionally protected amino group and the like.

Amino group can be converted, for example, by reactions such as amidation, sulfonylation, nitrosation, alkylation, arylation, imidation and the like.

20 Hydroxy group can be converted, for example, by reactions such as esterification, carbamoylation, sulfonylation, alkylation, fluorination, arylation, oxidation, halogenation and the like.

Carbonyl group can be converted, for example, by
25 reactions such as reduction, oxidation, fluorination, imination (including oximation, hydrazonation), (thio)ketalization, alkylidenation, thiocarbonylation and the like.

Sulfanyl group can be converted, for example, by
30 reactions such as alkylation, oxidation and the like.

C₁₋₆ alkoxy-carbonyl group, C₆₋₁₄ aryloxy-carbonyl group and C₇₋₁₆ aralkyloxy-carbonyl group can be converted, for example, by reactions such as reduction, hydrolysis and the like.

35 Sulfo group can be converted, for example, by reactions

such as sulfonamidation, reduction and the like.

Halogen atom can be converted, for example, by various nucleophilic substitution reactions, various coupling reactions and the like.

5 Optionally halogenated C₁₋₆ alkylsulfonyloxy group can be converted, for example, by various nucleophilic substitution reactions, various coupling reactions and the like.

Cyano group can be converted, for example, by reactions such as reduction, hydrolysis and the like.

10 Aminocarbonyl group can be converted, for example, by reactions such as dehydration, reduction and the like.

Boryl group can be converted, for example, by oxidation, various coupling reactions and the like.

In each of the above-mentioned reactions, when the
15 compound is obtained in a free form, it may be converted to a salt according to a conventional method. When it is obtained as a salt, it may be converted to a free form or other salt according to a conventional method.

The conversion of these functional group can be carried
20 out according to a method known per se, for example, the method described in Comprehensive Organic Transformations, Second Edition, Wiley-VCH, Richard C. Larock, or the like.
[0113]

In each reaction in the production method of compound (I)
25 and each reaction of the synthesis of the starting materials, when the starting compound has an amino group, a carboxyl group, a hydroxy group, a carbonyl group or a sulfanyl group as a substituent, a protecting group generally used in peptide chemistry and the like may be introduced into these
30 substituents. By removing the protecting group as necessary after the reaction, the object compound can be obtained.

Examples of the amino-protecting group include a formyl group; and a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, ethylcarbonyl etc.), a phenylcarbonyl group, a C₁₋₆ alkyl-
35 oxycarbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl,

tert-butoxycarbonyl (Boc) etc.), an allyloxycarbonyl (Alloc) group, a phenyloxycarbonyl group, a fluorenylmethoxycarbonyl (Fmoc) group, a C₇₋₁₀ aralkyl-carbonyl group (e.g., benzylcarbonyl etc.), a C₇₋₁₀ aralkyl-oxycarbonyl group (e.g., benzyloxycarbonyl (Z) etc.), a C₇₋₁₀ aralkyl group (e.g., benzyl etc.), a 2-(trimethylsilyl)ethoxymethyl (SEM) group, a trityl group, a phthaloyl group, an N,N-dimethylaminomethylene group, an allyl group and the like, each of which optionally has substituent(s), and the like. As these substituents, a phenyl group, a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom etc.), a C₁₋₆ alkyl-carbonyl group (e.g., methylcarbonyl, ethylcarbonyl, butylcarbonyl etc.), a nitro group and the like are used, and the number of the substituents is about 1 to 3.

Examples of the carboxyl-protecting group include a C₁₋₆ alkyl group (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl etc.), an allyl group, a benzyl group, a phenyl group, a trityl group, a trialkylsilyl group and the like, each of which optionally has substituent(s). As these substituents, a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom etc.), a formyl group, a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, ethylcarbonyl, butylcarbonyl etc.), a nitro group and the like are used, and the number of the substituents is about 1 to 3.

Examples of the hydroxyl-protecting group include a C₁₋₆ alkyl group (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl etc.), a C₇₋₁₀ aralkyl group (e.g., benzyl etc.), a formyl group, a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, ethylcarbonyl etc.), a benzoyl group, a C₇₋₁₀ aralkyl-carbonyl group (e.g., benzylcarbonyl etc.), a tetrahydropyranyl group, a furanyl group, a silyl group and the like, each of which optionally has substituent(s). As these substituents, a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom etc.), a C₁₋₆ alkyl group (e.g., methyl, ethyl, n-propyl etc.), a phenyl group, a C₇₋₁₀ aralkyl

group (e.g., benzyl etc.), a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy, n-propoxy etc.), a nitro group and the like are used, and the number of the substituents is about 1 to 4.

Examples of the protected carbonyl group include cyclic
5 acetal (e.g., 1,3-dioxane), noncyclic acetal (e.g., di-C₁₋₆ alkylacetal) and the like.

Examples of the sulfanyl-protecting group include a C₁₋₆ alkyl group, a phenyl group, a trityl group, a C₇₋₁₀ aralkyl group (e.g., benzyl), a C₁₋₆ alkyl-carbonyl group, a benzoyl
10 group, a C₇₋₁₀ aralkyl-carbonyl group (e.g., benzylcarbonyl), a C₁₋₆ alkoxy-carbonyl group, a C₆₋₁₄ aryloxy-carbonyl group (e.g., phenyloxy-carbonyl), a C₇₋₁₄ aralkyloxy-carbonyl group (e.g., benzyloxy-carbonyl, 9-fluorenylmethoxycarbonyl), a 2-tetrahydropyranyl group, a C₁₋₆ alkylamino-carbonyl group (e.g.,
15 methylaminocarbonyl, ethylaminocarbonyl) and the like. These protecting groups are optionally substituted by 1 to 3 substituents selected from a halogen atom, a C₁₋₆ alkyl group, a C₁₋₆ alkoxy group and a nitro group.

These protecting groups can be introduced and removed by
20 a method known per se, for example, the method described in Greene's Protective Groups in Organic Synthesis, 4th Edition, Wiley-Interscience, Theodora W. Greene, Peter G. M. Wuts or the like. Specifically, a method using acid, base, ultraviolet rays, hydrazine, phenylhydrazine, sodium N-
25 methylthiocarbamate, tetrabutylammonium fluoride, palladium acetate, trialkylsilyl halide (e.g., trimethylsilyl iodide, trimethylsilyl bromide) and the like, a reduction method, and the like can be employed.

[0114]

30 When compound (I) is present as a configurational isomer, a diastereomer, a conformer and the like, each can be isolated by a known means. When compound (I) has an optical isomer, racemates can be resolved by a general optical resolution means, whereby an optically active forms ((+) form, (-) form)
35 can be obtained.

[0115]

When compound (I) has an optical isomer, a stereoisomer, a positional isomer, a rotamer or a tautomer, these are also encompassed in compound (I), and can be obtained as a single
5 product according to synthesis and separation methods known per se.

For example, the method of optical resolution may be a method known per se, such as a fractional recrystallization method, a chiral column method, a diastereomer method etc.

10 1) Fractional recrystallization method

A method wherein a salt of a racemate with an optically active compound (e.g., (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine
15 etc.) is formed, which is separated by a fractional recrystallization method, and if desired, a neutralization step to give a free optical isomer.

2) Chiral column method

A method wherein a racemate or a salt thereof is applied
20 to a column(a chiral column) for separation of an optical isomer to allow separation. In the case of a liquid chromatography, for example, a mixture of the optical isomers is applied to a chiral column such as ENANTIO-OVM (manufactured by Tosoh Corporation), CHIRAL series (manufactured by Daicel Chemical Industries, Ltd.)
25 and the like, and developed with water, various buffers (e.g., phosphate buffer, etc.) and organic solvents (e.g., ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, etc.) as an eluent, solely or in admixture to separate the optical isomer. In the case of a gas chromatography,
30 for example, a chiral column such as CP-Chirasil-DeX CB (manufactured by GL Sciences Inc.) and the like is used to allow separation.

3) Diastereomer method

A method wherein a racemic mixture is prepared into a
35 diastereomeric mixture by chemical reaction with an optically

active reagent, which is made into a single substance by a typical separation means (e.g., a fractional recrystallization method, a chromatography method etc.) and the like, and is subjected to a chemical treatment such as hydrolysis and the like to separate an optically active reagent moiety, whereby an optical isomer is obtained. For example, when compound (I) contains hydroxy group, or primary or secondary amino group within a molecule, the compound and an optically active organic acid (e.g., MTPA [α -methoxy- α -

10 (trifluoromethyl)phenylacetic acid],
(-)-menthoxyacetic acid etc.) and the like are subjected to condensation reaction to give diastereomers of the ester compound or the amide compound, respectively. When compound (I) has a carboxyl group, the compound and an optically active

15 amine or an optically active alcohol reagent are subjected to condensation reaction to give diastereomers of the amide compound or the ester compound, respectively. The separated diastereomer is converted to an optical isomer of the original compound by acid hydrolysis or base hydrolysis.

20 [0116]

The solvent, acid and base recited in the production methods of the compound of the present invention are explained in the following.

Examples of the "solvent" include "alcohols", "ethers",

25 "hydrocarbons", "amides", "halogenated hydrocarbons",
"nitriles", "ketones", "esters", "sulfoxides", "water" and the like.

Examples of the "alcohols" include methanol, ethanol, 1-propanol, 2-propanol, tert-butyl alcohol and the like.

30 Examples of the "ethers" include diethyl ether,
diisopropyl ether, diphenyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, tert-butyl methyl ether and the like.

Examples of the "hydrocarbons" include benzene, toluene,

35 cyclohexane, hexane, petroleum ether and the like.

Examples of the "amides" include N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, hexamethylphosphoric triamide and the like.

Examples of the "halogenated hydrocarbons" include
5 dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, chlorobenzene, benzotrifluoride and the like.

Examples of the "nitriles" include acetonitrile, propionitrile and the like.

Examples of the "ketones" include acetone, ethyl methyl
10 ketone and the like.

Examples of the "esters" include ethyl acetate, tert-butyl acetate and the like.

Examples of the "sulfoxides" include dimethyl sulfoxide and the like.

15 Examples of the "acid" include "organic acids", "mineral acids", "Lewis acids" and the like.

Examples of the "organic acids" include formic acid, acetic acid, propionic acid, trifluoroacetic acid, citric acid, methanesulfonic acid, p-toluenesulfonic acid and the like.

20 Examples of the "mineral acids" include hydrochloric acid, sulfuric acid and the like.

Examples of the "Lewis acids" include boron trichloride, boron tribromide and the like.

Examples of the "base" include "inorganic bases", "basic
25 salts", "aromatic amines", "tertiary amines", "alkali metal hydrides", "alkali metals", "metal amides", "alkyl metals", "aryl metals", "metal alkoxides" and the like.

Examples of the "inorganic bases" include sodium hydroxide, potassium hydroxide, lithium hydroxide, barium
30 hydroxide and the like.

Examples of the "basic salts" include sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, sodium acetate, ammonium acetate and the like.

Examples of the "aromatic amines" include pyridine, 2,6-
35 lutidine and the like.

Examples of the "tertiary amines" include triethylamine, tripropylamine, tributylamine, N,N-diisopropylethylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, 1,8-diazabicyclo[5,4,0]undec-7-ene and the like.

Examples of the "alkali metal hydrides" include sodium hydride, potassium hydride and the like.

Examples of the "alkali metals" include sodium, lithium, potassium and the like.

Examples of the "metal amides" include sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide and the like.

Examples of the "alkyl metals" include butyllithium, sec-butyllithium, tert-butyllithium and the like.

Examples of the "aryl metals" include phenyllithium and the like.

Examples of the "metal alkoxides" include sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide and the like.

[0117]

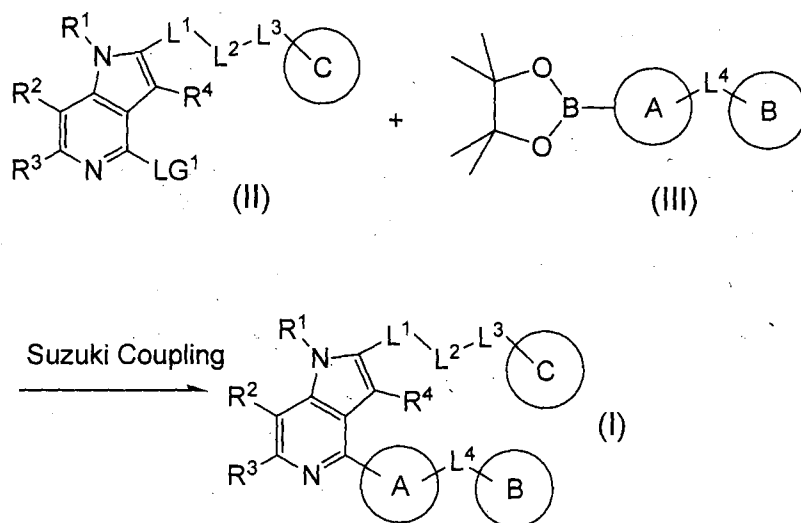
Compound (I) can be produced, for example, according to the method shown in the following Scheme 1, 4 or 7 or a method analogous thereto.

[0118]

Compound (I) can be prepared by subjecting intermediates (II) and (III) to Suzuki coupling as shown in Scheme 1.

[0119]

Scheme 1: Preparation of compound (I)



[0120]

wherein LG¹ is a leaving group selected from a halogen atom, trifluoromethanesulfonyloxy and the like, and the other symbols are as defined above.

[0121]

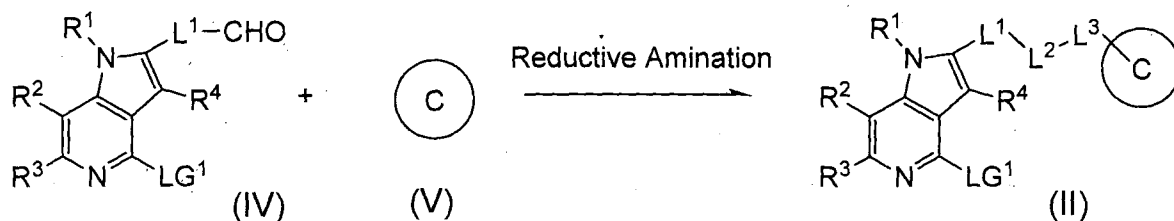
The Suzuki coupling can be carried out according to the method described in *Chemical Reviews* 95 (7): 2457-2483, for example, by reacting intermediate (II) with intermediate (III) in the presence of a catalysis and a base, in a solvent.

Examples of the catalysis include palladium(0) complexes such as tetrakis(triphenylphosphine)palladium, 1,1-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex and the like.

15 [0122]

Intermediate (II) wherein L¹-L²-L³ is -CH₂- or -CH₂CH₂- can be prepared by subjecting intermediates (IV) and (V) to reductive amination as shown in Scheme 2.

[0123]

20 **Scheme 2:** Preparation of intermediate (II)

[0124]

wherein L^1 in intermediate (IV) is either absent or is $-CH_2$, and the other symbols are as defined above.

[0125]

5 The reductive amination can be carried out according to the method described in *Organic Reactions*, 1, 59, 2002, for example, by reacting intermediate (IV) with intermediate (V) in the presence of a reducing agent, in a solvent.

Examples of the reducing agent include sodium
10 cyanoborohydride ($NaBH_3CN$), sodium triacetoxyborohydride ($NaBH(OCOCH_3)_3$) and the like.

[0126]

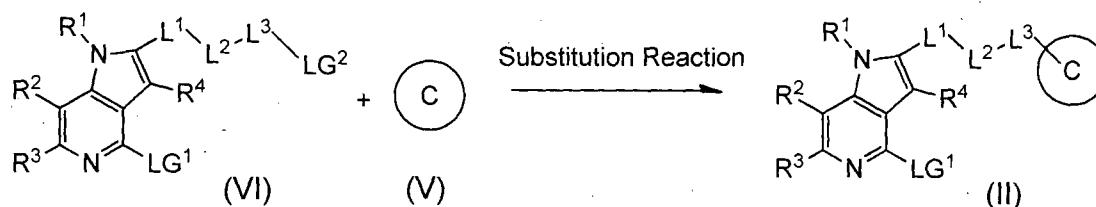
Intermediate (IV) and intermediate (V) may be commercially available, or can also be produced according to a
15 method known per se or a method analogous thereto.

[0127]

Alternatively, intermediate (II) can also be prepared by subjecting intermediates (VI) and (V) to substitution reaction as shown in Scheme 3.

20 [0128]

Scheme 3: Preparation of intermediate (II)



[0129]

wherein LG^2 is a leaving group selected from a chlorine atom, a
25 bromine atom, methanesulfonyloxy, trifluoromethanesulfonyloxy and the like, and the other symbols are as defined above.

[0130]

The substitution reaction can be carried out according to the method described in *J. March, Advanced Organic Chemistry*,
30 4th ed., Wiley, New York, 1992, for example, by reacting intermediate (VI) with intermediate (V) in the presence of a base, in a solvent.

[0131]

Intermediate (VI) may be commercially available, or can also be produced according to a method known per se or a method analogous thereto.

5 [0132]

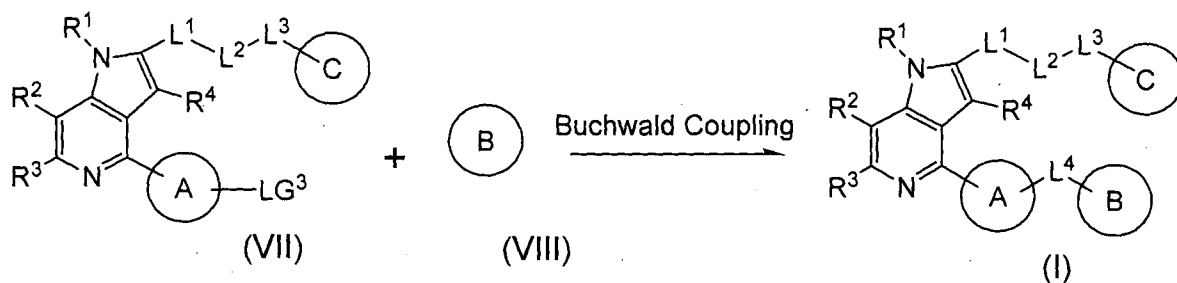
Intermediate (III) may be commercially available, or can also be produced according to a method known per se or a method analogous thereto.

[0133]

10 Compound (I) wherein L^4 is a bond can also be prepared by subjecting intermediates (VII) and (VIII) to Buchwald coupling as shown in Scheme 4.

[0134]

Scheme 4: Preparation of compound (I)



15

[0135]

wherein LG^3 is a halogen atom, and the other symbols are as defined above.

20 [0136]

The Buchwald coupling can be carried out according to the method described in *Chem. Sci.* 2: 27-50, 2011, for example, by reacting intermediate (VII) with intermediate (VIII) in the presence of a palladium compound, a ligand and a base, in a
25 solvent.

Examples of the palladium compound include tris(dibenzylideneacetone)dipalladium(0) and the like.

Examples of the ligand include (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) and the like.

30 Intermediate (VIII) may be commercially available, or can

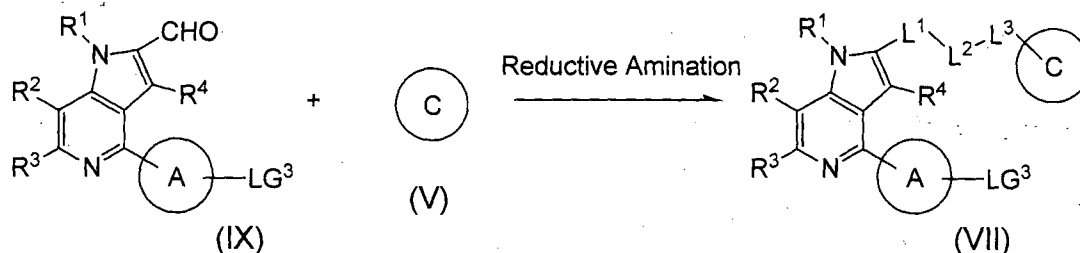
also be produced according to a method known per se or a method analogous thereto.

[0137]

Intermediate (VII) wherein $L^1-L^2-L^3$ is $-CH_2-$ can be prepared by subjecting intermediates (IX) and (V) to reductive amination as shown in Scheme 5.

[0138]

Scheme 5: Preparation of intermediate (VII)



10 [0139]

wherein each symbol is as defined above.

[0140]

The reductive amination can be carried out in the same manner as in Scheme 2.

15 [0141]

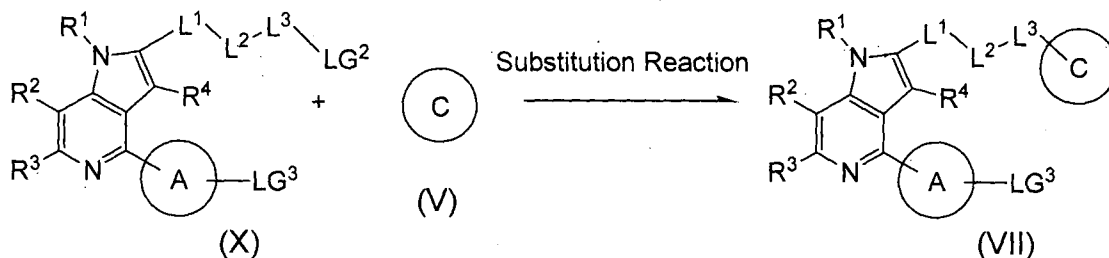
Intermediate (IX) may be commercially available, or can also be produced according to a method known per se or a method analogous thereto.

[0142]

20 Alternatively, intermediate (VII) can also be prepared by subjecting intermediates (X) and (V) to substitution reaction as shown in Scheme 6.

[0143]

Scheme 6: Preparation of intermediate (VII)



25

[0144]

wherein each symbol is as defined above.

[0145]

The substitution reaction can be carried out in the same manner as in Scheme 3.

[0146]

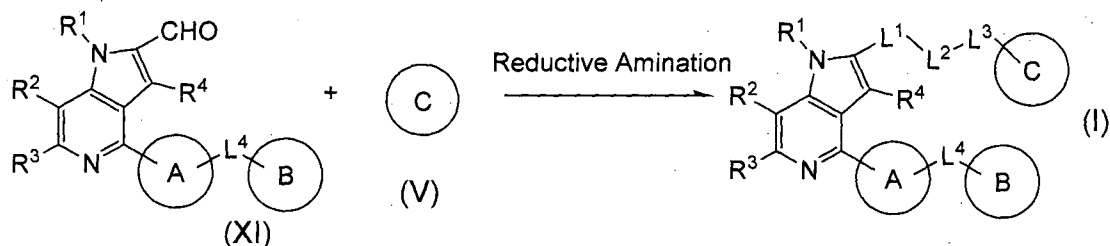
Intermediate (X) may be commercially available, or can also be produced according to a method known per se or a method analogous thereto.

[0147]

Compound (I) wherein $L^1-L^2-L^3$ is $-CH_2-$ can also be prepared by subjecting intermediates (XI) and (V) to reductive amination as shown in Scheme 7.

[0148]

Scheme 7: Preparation of compound (I)



15 [0149]

wherein each symbol is as defined above.

[0150]

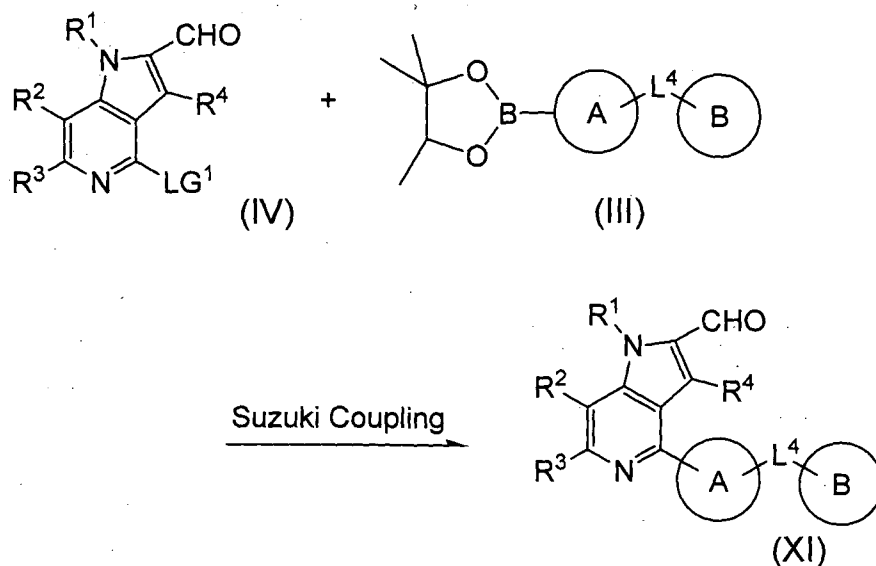
The reductive amination can be carried out in the same manner as in Scheme 2.

20 [0151]

Intermediate (XI) can be prepared by subjecting intermediates (IV) and (III) to Suzuki coupling as shown in Scheme 8.

[0152]

25 **Scheme 8:** Preparation of intermediate (XI)



[0153]

wherein each symbol is as defined above.

[0154]

5 The Suzuki coupling can be carried out in the same manner as in Scheme 1.

[0155]

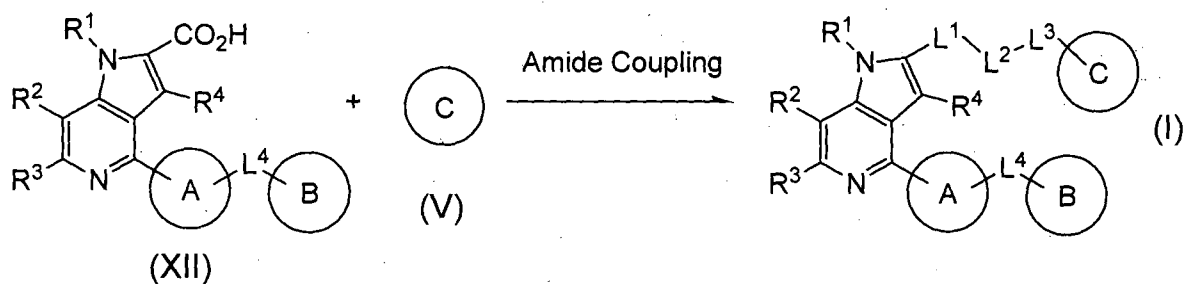
Intermediate (IV) may be commercially available, or can also be produced according to a method known per se or a
10 method analogous thereto.

[0156]

Compound (I) wherein $L^1-L^2-L^3$ is $-CO-$ can be prepared by subjecting intermediates (XII) and (V) to amide coupling reaction as shown in Scheme 9.

15 [0157]

Scheme 9: Preparation of compound (I)



[0158]

wherein each symbol is as defined above.

20 [0159]

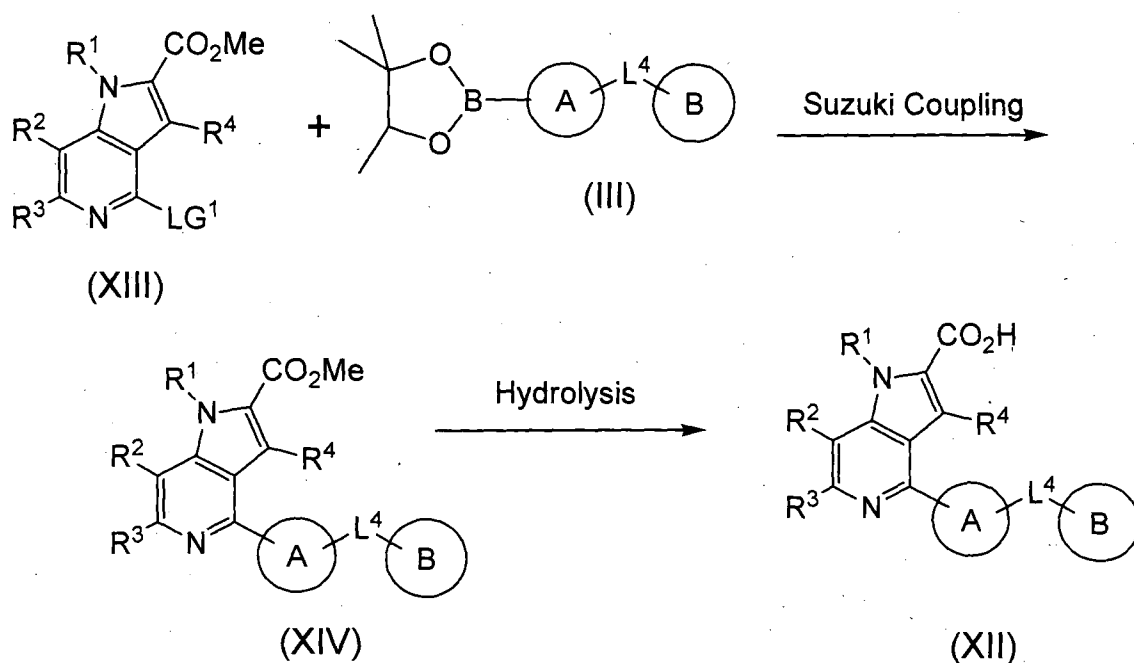
The amide coupling may be carried out using any suitable amide coupling reagents such as oxalyl chloride, thionyl chloride, BOP-Cl, DCC, HOBt, HOAt, HATU, EDCI, alkyl chloroformate and the like, in the presence of an organic non-nucleophilic base such as triethyl amine, di-isopropylethyl amine, pyridine, N-methyl pyrrolidine, N,N-dimethylaminopyridine, DBU, DABCO, other hindered amines and pyridines. The amide coupling reaction may be carried out in the presence of a solvent such as dichloromethane, dichloroethane, DMF, dimethylacetamide, THF, acetonitrile, and mixtures thereof, at a temperature ranging from -5 to 150°C. The reaction may be carried out optionally in presence of a catalytic amount of DMF. The amide coupling may also be carried out by heating the corresponding ester and amine either in the absence of a solvent or in presence of a high boiling solvent such as toluene, xylene and DMSO. The amide coupling may be carried out in presence of a trialkyl aluminium (Chem. Commun., 2008, 1100-1102).

[0160]

Intermediate (XII) can be prepared by subjecting intermediates (XIII) and (III) to Suzuki coupling to give intermediate (XIV) which on hydrolysis can give intermediate (XII) as shown in Scheme 10.

[0161]

Scheme 10: Preparation of intermediate (XII)



[0162]

wherein each symbol is as defined above.

[0163]

- 5 The Suzuki coupling can be carried out in the same manner as in Scheme 1.

[0164]

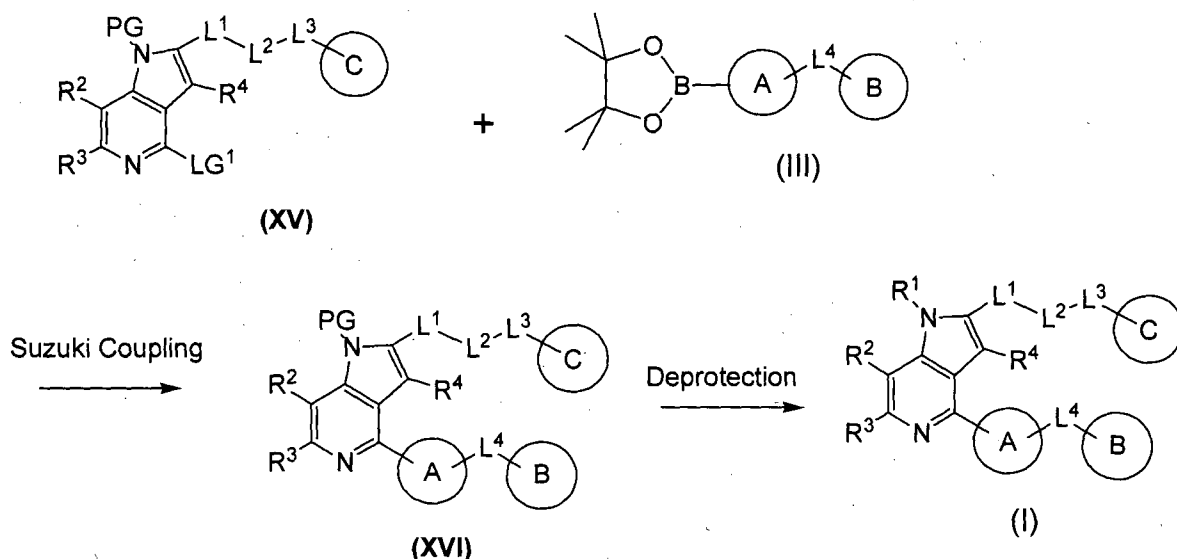
Intermediate (XIII) may be commercially available, or can also be produced according to a method known per se or a
 10 method analogous thereto.

[0165]

Compound (I) wherein R^1 is a hydrogen atom can alternatively be prepared by subjecting intermediate (XV) to Suzuki coupling with intermediate (III) to give intermediate
 15 (XVI) as shown in Scheme 11. Acid or base catalyzed deprotection of intermediate (XVI) can give compound (I).

[0166]

Scheme 11: Preparation of compound (I)



[0167]

wherein PG is a suitable protecting group such as benzenesulfonyl, tert-butoxycarbonyl or the like, and the
 5 other symbols are as defined above.

[0168]

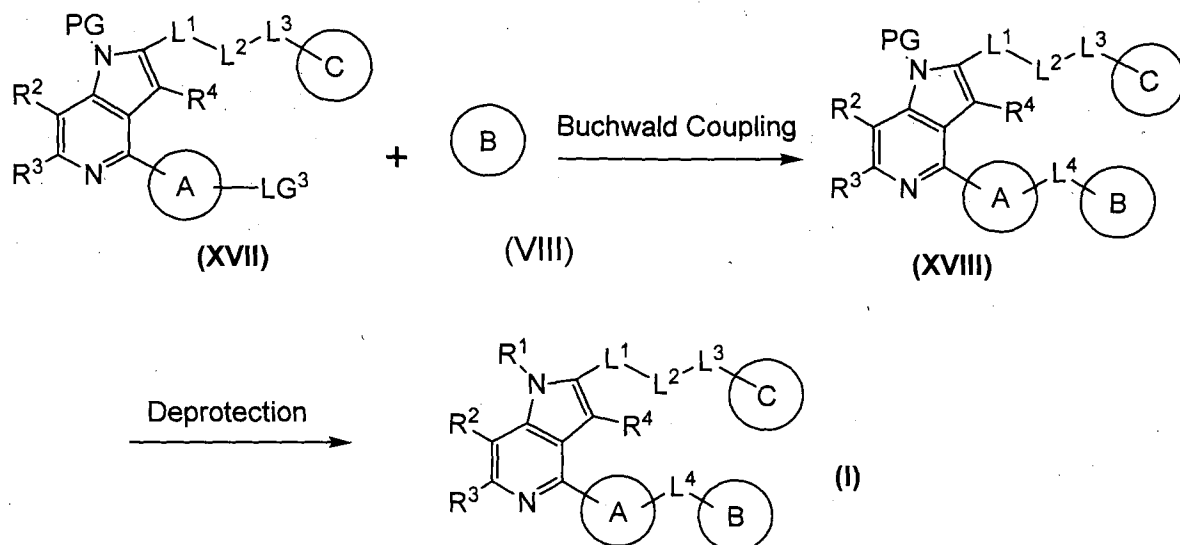
Intermediate (XV) can be produced according to a methods analogous to the synthesis of intermediate (II).

[0169]

10 Compound (I) wherein R^1 is a hydrogen atom can alternatively be prepared by subjecting intermediate (XVII) to Buchwald coupling with intermediate (VIII) to give intermediate (XVIII) as shown in Scheme 12. Acid or base catalyzed deprotection of intermediate (XVIII) can give
 15 compound (I).

[0170]

Scheme 12: Preparation of compound (I)



[0171]

wherein each symbol is as defined above.

[0172]

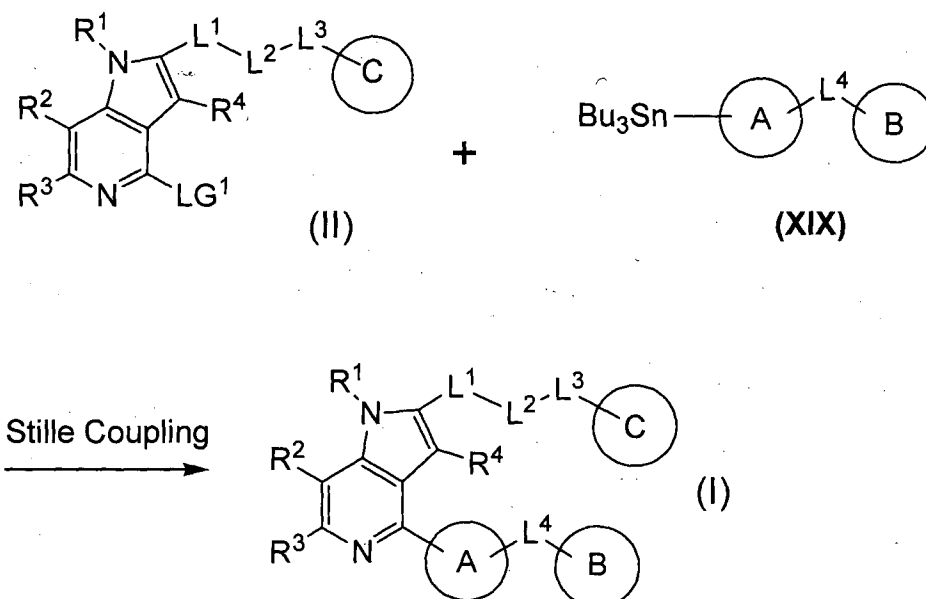
- 5 Intermediate (XVII) can be produced according to a method analogous to the synthesis of intermediate (VII).

[0173]

Compound (I) can alternatively be prepared by subjecting intermediate (II) to Stille coupling with intermediate (XIX) as shown in Scheme 13.

[0174]

Scheme 13: Preparation of compound (I)



[0175]

wherein each symbol is as defined above.

[0176]

Intermediate (XIX) can be produced according to the method known in literature or a method known per se or a method analogous thereto.

[0177]

The Stille coupling is a palladium catalyzed C-C bond forming reaction which involves coupling of an organotin compound (also known as organostannanes) with a halide or a pseudohalide [Angew. Chem. Int. Ed. Engl. 1986, 25, 508-524; J. Org. React. 1998, 50, 1-652]. Examples of the palladium catalysts to be used include tetrakis(triphenylphosphine)palladium, 1,1-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex and the like.

[0178]

Compound (I) obtained in each scheme can be isolated and purified by known separation and purification means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like. In addition, each material compound used in each scheme can be isolated and purified by those similar to the above-mentioned known separation and purification means. The material compound may be used directly in the next step as the reaction mixture without isolation.

When compound (I) has isomers such as an optical isomer, a stereoisomer, a regioisomer and a rotamer and the like, such isomers and a mixture thereof are also encompassed in compound (I). For example, when compound (I) has an optical isomer, the optical isomer resolved from racemate is also encompassed in compound (I). These isomers can be obtained as single products according to synthetic methods known per se, separation methods known per se (e.g., concentration, solvent extraction, column chromatography, recrystallization etc.), optical resolutions (e.g., fractional recrystallization method, chiral

column method, diastereomer method and the like).

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

The compound (I) may be a solvate (e.g., hydrate) or a non-solvate (e.g., non-hydrate etc.) and both are encompassed in compound (I).

The compounds labeled with isotopes (e.g., ^3H , ^{14}C , ^{35}S ,
10 ^{125}I etc.) and the like are also encompassed in compound (I).

A deuterium conversion form wherein ^1H is converted to $^2\text{H(D)}$ is also encompassed in compound (I).

Compound (I) labeled or substituted with an isotope can be used as, for example, a tracer (PET tracer) used for
15 Positron Emission Tomography (PET), and therefore, it is useful in the fields of medical diagnosis and the like.

[0179]

Since the compound of the present invention has a superior TLR7, TLR9, TLR7/8, TLR7/9 or TLR7/8/9 inhibitory
20 action, shows low toxicity (e.g., phototoxicity, acute toxicity, chronic toxicity, genetic toxicity, reproductive toxicity, cardiac toxicity, drug interactions, carcinogenicity and the like, particularly phototoxicity), and is superior in stability (particularly metabolic stability), pharmacokinetics
25 (absorption, distribution, metabolism, excretion etc.) and high solubility, it is useful as a medicament. The compound of the present invention has a TLR7, TLR9, TLR7/8, TLR7/9 or TLR7/8/9 inhibitory action to mammals (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine, horse, sheep, monkey, human
30 etc.), and can be used for the prophylaxis or treatment of the following diseases and symptoms:

(1) inflammatory disease (e.g., acute pancreatitis, chronic pancreatitis, asthma, adult respiratory distress syndrome, chronic obstructive pulmonary diseases (COPD), inflammatory
35 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, stomach mucosa injury,

5 meningitis, spondylitis, arthritis, dermatitis, chronic pneumonia, bronchitis, lung infarction, silicosis, pulmonary sarcoidosis, etc.),

(2) autoimmune disease (e.g., psoriasis, rheumatoid arthritis, inflammatory bowel disease (e.g., Crohn's disease, ulcerative

10 colitis), 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, lupus erythematosus profundus, chronic

15 thyroiditis, Graves' disease, autoimmune gastritis, Type I and Type II diabetes, autoimmune hemolytic anemia, autoimmune neutrophenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, graft-versus-host disease, Addison's disease, abnormal immune response, arthritis,

20 dermatitis, radiodermatitis, etc.),

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

(4) neoplastic disease (e.g., malignant tumor, neovascular glaucoma, infantile hemangioma, multiple myeloma, acute

25 myeloblastic leukemia, chronic sarcoma, multiple myeloma, chronic myeloid leukemia, metastasis melanoma, Kaposi's sarcoma, vascular proliferation, cachexia, metastasis of breast cancer and the like, cancer (e.g., colorectal cancer (e.g., familial colorectal cancer, hereditary nonpolyposis

30 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 ductal carcinoma, etc.), stomach cancer (e.g., papillary adenocarcinoma, mucinous

35 adenocarcinoma, adenosquamous carcinoma, etc.), breast cancer

(e.g., infiltrating ductal carcinoma, noninfiltrating ductal carcinoma, inflammatory breast cancer, etc.), ovarian cancer (e.g., epithelial ovarian cancer, extragonadal germ cell tumor, ovarian germ cell tumor, ovarian low malignant potential tumor, etc.), prostate cancer (e.g., hormone-dependent prostate cancer, hormone-independent 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 of renal pelvis 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 including multiple myeloma and the like, pituitary adenoma, glioma, acoustic schwannoma, retina sarcoma, pharyngeal cancer, laryngeal cancer, tongue cancer, thymoma, esophageal cancer, duodenal cancer, colon cancer, rectal cancer, hepatoma, pancreatic endocrine tumor, cholangiocarcinoma, gallbladder cancer, penile cancer, ureteral cancer, testicular tumor, vulvar cancer, cervical cancer, cancer of uterine body, uterus sarcoma, trophoblastic disease, vaginal cancer, skin cancer, mycosis fungoides, basal cell tumor, soft tissue sarcoma, malignant lymphoma, Hodgkin's disease, myelodysplastic syndrome, acute lymphocytic leukemia, chronic lymphocytic leukemia, adult T-cell leukemia, chronic myeloproliferative disorder, pancreatic endocrine tumor, fibrous histiocytoma, leiomyosarcoma, rhabdomyosarcoma, unknown primary cancer)).

The pharmaceutical agent of the present invention can be used as an agent for the prophylaxis or treatment of, preferably, autoimmune disease, inflammatory disease, osteoarticular degenerative disease or neoplastic disease, particularly preferably, psoriasis, rheumatoid arthritis, inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis), Sjogren's syndrome, Behcet's disease, multiple

sclerosis, systemic lupus erythematosus.

As used herein, the "prophylaxis" of the above-mentioned diseases means, for example, administration of a pharmaceutical containing the compound of the present invention to patients before onset of a disease but having a high risk of the onset due to some factor associated with the disease or patients who developed the disease but without subjective symptoms, or administration of a pharmaceutical containing the compound of the present invention to patients having a risk of recurrence of disease after treatment of the disease.

[0180]

In particular, the compound of the present invention is useful for the prophylaxis or treatment of TLR7, TLR9, TLR7/8, TLR7/9 or TLR7/8/9-related diseases such as autoimmune diseases, inflammatory diseases and the like, in particular, systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, psoriasis, inflammatory bowel disease and the like.

[0181]

Since the compound of the present invention is superior in metabolic stability, it can be expected to have an excellent therapeutic effect on the above-mentioned diseases even in a low dose.

Since the compound of the present invention has low toxicity, a pharmaceutical composition containing the compound of the present invention (hereinafter to be referred to as the "medicament of the present invention") is obtained as, for example, tablet (including sugar-coated tablet, film-coated tablet, sublingual tablet, orally disintegrating tablet, buccal tablet and the like), pill, powder, granule, capsule (including soft capsule, microcapsule), troche, syrup, liquid, emulsion, suspension, controlled-release preparation (e.g., immediate-release preparation, sustained-release preparation, sustained-release microcapsule), aerosol, films (e.g., orally disintegrable films, oral cavity mucosa patch film), injection

(e.g., subcutaneous injection, intravenous injection, intramuscular injection, intraperitoneal injection), drip infusion, transdermal absorption type preparation, ointment, lotion, adhesive preparation, suppository (e.g., rectal suppository, vaginal suppository), pellet, nasal preparations, pulmonary preparation (inhalant), eye drop and the like by using the compound of the present invention alone or along with a pharmacologically acceptable carrier according to a method known per se as a production method of pharmaceutical preparations (e.g., the method described in the Japanese Pharmacopoeia etc.). It can be safely administered orally or parenterally (e.g., intravenous, intramuscular, subcutaneous, intraorgan, intranasal, intradermal, instillation, intracerebral, rectal, vaginal, intraperitoneal, intratumor, tumor proximal administration, administration to a lesion and the like).

[0182]

Examples of the pharmacologically acceptable carrier include various organic or inorganic carrier substances conventionally used as preparation materials, which are added as excipient, lubricant, binder or disintegrant for solid preparations; as solvent, solubilizing agent, suspending agent, isotonicity agent, buffer or soothing agent for liquid preparation, and the like. Where necessary, preparation additives such as preservative, antioxidant, colorant, sweetener, absorbent, humectant and the like can also be appropriately used in suitable amounts.

[0183]

Examples of the excipient include lactose, sucrose, D-mannitol, D-sorbitol, starch, pregelatinized starch, cornstarch, dextrin, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, sodium carboxymethylcellulose, gum arabic, pullulan, light anhydrous silicic acid, synthetic aluminum silicate, magnesium aluminate metasilicate and the like.

Examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica and the like.

[0184]

Examples of the binder include pregelatinized starch, microcrystalline cellulose, sucrose, gum arabic, D-mannitol, trehalose, dextrin, pullulan, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, starch, saccharose, gelatin, methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose and the like.

10 [0185]

Examples of the disintegrant include lactose, sucrose, starch, carboxymethylcellulose, calcium carboxymethylcellulose, croscarmellose sodium, sodium carboxymethyl starch, light anhydrous silicic acid, low-substituted hydroxypropyl cellulose and the like.

[0186]

Examples of the solvent include water for injection, physiological saline, Ringer's solution, alcohol, propylene glycol, polyethylene glycol, macrogol, sesame oil, corn oil, olive oil, cottonseed oil and the like.

[0187]

Examples of the solubilizing agent include polyethylene glycol, propylene glycol, D-mannitol, trehalose, benzyl benzoate, ethanol, tris(hydroxymethyl)aminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, sodium salicylate, sodium acetate and the like.

[0188]

Examples of the suspending agent include surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glyceryl monostearate and the like; and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, sodium carboxymethylcellulose, methylcellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polysorbate,

polyoxyethylene hydrogenated castor oil and the like.

[0189]

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

5 Examples of the buffer include buffers such as phosphates, acetates, carbonates, citrates and the like, and the like.

Examples of the soothing agent include benzyl alcohol and the like.

10 Examples of the preservative include p-hydroxybenzoate, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like.

Examples of the antioxidant include sulfites, ascorbic acid, α -tocopherols and the like.

[0190]

15 Examples of the colorant include water-soluble edible tar pigments (e.g., Food Color Red Nos. 2 and 3, Food Color Yellow Nos. 4 and 5, Food Color Blue Nos. 1 and 2), water insoluble lake pigments (e.g., aluminum salts of the above-mentioned water-soluble edible tar pigment), natural pigments (e.g.,
20 beta-carotene, chlorophyll, red iron oxide) and the like.

Examples of the sweetening agent include saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia and the like.

[0191]

While the content of the compound of the present
25 invention in the medicament of the present invention 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%, preferably about 0.1-95 wt%.

[0192]

30 While the dose of the compound of the present invention varies depending on the subject of administration, administration route, target disease, symptom and the like, for example, for oral administration to a systemic lupus erythematosus patient (adult, about 60 kg weight), it is
35 generally about 0.1 - about 20 mg/kg body weight, preferably

about 0.2 - about 10 mg/kg body weight, more preferably about 0.5 - about 10 mg/kg body weight, which is desirably administered once to several times (e.g., once to 3 times) a day depending on the symptom.

5 [0193]

The compound of the present invention can be administered as a single active substance, or can be administered in combination with other medicaments such as other drugs used in the treatment of TLR7, TLR9, TLR7/8, TLR7/9 or TLR7/8/9-

10 related diseases such as autoimmune diseases, inflammatory diseases and the like, in particular, systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, psoriasis, inflammatory bowel disease and the like (hereinafter to be abbreviated as concomitant drug).

15 Examples of the concomitant drug include

(1) non-steroidal antiinflammatory drugs (NSAIDs)

(i) Classical NSAIDs

alcofenac, aceclofenac, sulindac, tolmetin, etodolac, fenoprofen, thiaprofenic acid, meclofenamic acid, meloxicam, 20 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, 25 floctafenine, piroxicam, epirizole, tiaramide hydrochloride, zaltoprofen, gabexate mesylate, camostat mesylate, ulinastatin, colchicine, probenecid, sulfinpyrazone, benzbromarone, allopurinol, sodium aurothiomalate, sodium hyaluronate, sodium salicylate, morphine hydrochloride, salicylic acid, atropine, 30 scopolamine, morphine, pethidine, levorphanol, oxymorphone or a salt thereof and the like.

(ii) cyclooxygenase inhibitor (COX-1 selective inhibitor, COX-2 selective inhibitor and the like)

salicylic acid derivatives (e.g., celecoxib, aspirin), 35 etoricoxib, valdecoxib, diclofenac, indomethacin, loxoprofen

- and the like.
- (iii) nitric oxide-releasing NSAIDs
 - (2) disease-modifying anti-rheumatic drugs (DMARDs)
 - (i) Gold preparation
 - 5 auranofin and the like.
 - (ii) penicillamine
 - D-penicillamine and the like.
 - (iii) aminosalicylic acid preparation
 - sulfasalazine, mesalazine, olsalazine, balsalazide and
 - 10 the like.
 - (iv) antimalarial drug
 - chloroquine and the like.
 - (v) pyrimidine synthesis inhibitor
 - leflunomide and the like.
 - 15 (vi) prograf
 - (3) anti-cytokine drug
 - (I) protein drug
 - (i) TNF inhibitor
 - etanercept, infliximab, adalimumab, certolizumab pegol,
 - 20 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.
 - 25 (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.
 - 30 (v) interleukin-12/23 inhibitor
 - ustekinumab, briakinumab (anti-interleukin-12/23 antibody) and the like.
 - (vi) B cell activation inhibitor
 - rituxan, benlysta and the like.
 - 35 (vii) co-stimulatory molecules-related protein preparation

- abatacept and the like.
- (II) non-protein drug
- (i) MAPK inhibitor
- BMS-582949 and the like.
- 5 (ii) gene modulator
- inhibitor of molecule involved in signal transduction, such as NF- κ , NF- κ B, IKK-1, IKK-2, AP-1 and the like, and the like.
- (iii) cytokine production inhibitor
- 10 igitatimod, tetomilast and the like.
- (iv) TNF- α converting enzyme inhibitor
- (v) interleukin-1 β converting enzyme inhibitor
- VX-765 and the like.
- (vi) interleukin-6 antagonist
- 15 HMPL-004 and the like.
- (vii) interleukin-8 inhibitor
- IL-8 antagonist, CXCR1 & CXCR2 antagonist, reparixin and the like.
- (viii) chemokine antagonist
- 20 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
- 25 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
- 30 receptor and the like.
- (xii) antisense compound
- ISIS-104838 and the like.
- (4) integrin inhibitor
- natalizumab, vedolizumab, AJM300, TRK-170, E-6007 and the
- 35 like.

(5) immunomodulator (immunosuppressant)

methotrexate, cyclophosphamide, MX-68, atiprimod
dihydrochloride, BMS-188667, CKD-461, rimexolone, cyclosporine,
tacrolimus, gusperimus, azathiopurine, antilymphocyte serum,
5 freeze-dried sulfonated normal immunoglobulin, erythropoietin,
colony stimulating factor, interleukin, interferon,
intravenous immunoglobulin, anti-thymocyte globulin, RSLV-132
and the like.

(6) proteasome inhibitor

10 bortezomib, MLN9708, MLN2238, delanzomib and the like.

(7) steroid

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

(8) angiotensin converting enzyme inhibitor

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

20 (9) angiotensin II receptor antagonist

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

(10) diuretic drug

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

(11) cardiotonic drug

digoxin, dobutamine and the like.

(12) β receptor antagonist

30 carvedilol, metoprolol, atenolol and the like.

(13) Ca sensitizer

MCC-135 and the like.

(14) Ca channel antagonist

nifedipine, diltiazem, verapamil and the like.

35 (15) anti-platelet drug, anticoagulator

- heparin, aspirin, warfarin and the like.
- (16) HMG-CoA reductase inhibitor
atorvastatin, simvastatin and the like.
- (17) contraceptive
- 5 (i) sex hormone or derivatives thereof
gestagen or a derivative thereof (e.g., progesterone,
17 α -hydroxy progesterone, medroxyprogesterone,
medroxyprogesterone acetate, norethisterone, norethisterone
enanathate, norethindrone, norethindrone acetate, norethynodrel,
10 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
15 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.
- 20 (ii) antiestrogen
ormeloxifene, mifepristone, Org-33628 and the like.
- (iii) spermatocide
ucarcide and the like.
- (18) others
- 25 (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
30 the like.
- (iv) thalidomide
- (v) cathepsin inhibitor
- (vi) matrix metalloprotease (MMPs) inhibitor
V-85546 and the like.
- 35 (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 A₂ inhibitor
- 5 (xi) iNOS inhibitor
VAS-203 and the like.
- (xii) microtubule stimulating drug
paclitaxel and the like.
- (xiii) microtubule inhibitor
10 reumacon and the like.
- (xiv) MHC class II antagonist
- (xv) prostacyclin agonist
iloprost and the like.
- (xvi) CD4 antagonist
15 zanolimumab and the like.
- (xvii) CD23 antagonist
- (xviii) LTB₄ receptor antagonist
DW-1305 and the like.
- (xix) 5-lipoxygenase inhibitor
20 zileuton and the like.
- (xx) cholinesterase inhibitor
galanthamine and the like.
- (xxi) tyrosine kinase inhibitor
Tyk2 inhibitor (the compounds described in WO
25 2010/142752) and the like.
- (xxii) cathepsin B inhibitor
- (xxiii) adenosine deaminase inhibitor
pentostatin and the like.
- (xxiv) osteogenesis stimulator
- 30 (xxv) dipeptidylpeptidase inhibitor
- (xxvi) collagen agonist
- (xxvii) capsaicin cream
- (xxviii) hyaluronic acid derivative
synvisc (hylan G-F 20), orthovisc and the like.
- 35 (xxix) glucosamine sulfate

(xxx) amiprilose

(xxxi) CD-20 inhibitor

rituximab, ibritumomab, tositumomab, ofatumumab and the like.

5 (xxxii) BAFF inhibitor

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

(xxxiii) CD52 inhibitor

alemtuzumab and the like.

(xxxiv) IL-17 inhibitor

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

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
15 agent, hypotensive diuretic drug, anticoagulant, tranquilizer, antipsychotic, antitumor drug, hypolipidemic drug, muscle relaxant, anticonvulsant, antidepressant, antiallergic drug, cardiac stimulants, therapeutic drug for arrhythmia, vasodilator, vasoconstrictor, hypotensive diuretic,
20 therapeutic drug for diabetes, antinarcotic, vitamin, vitamin derivative, antiasthmatic, therapeutic agent for pollakisuria/anischuria, antipruritic agent, therapeutic agent for atopic dermatitis, therapeutic agent for allergic rhinitis, hypertensor, endotoxin-antagonist or -antibody, signal
25 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.

30 (1) Antibacterial agent

(i) sulfa drug

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

35 (ii) quinolone antibacterial agent

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

5 (iii) antiphthisic

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

10 (iv) antiacidfast bacterium drug

diaphenylsulfone, rifampicin and the like.

(v) antiviral drug

idoxuridine, acyclovir, vidarabine, gancyclovir and the like.

15 (vi) anti-HIV agent zidovudine, didanosine, zalcitabine, indinavir sulfate ethanolate, ritonavir and the like.

(vii) antispirechetele

(viii) antibiotic

tetracycline hydrochloride, ampicillin, piperacillin,
20 gentamicin, dibekacin, kanendomycin, lividomycin, tobramycin, amikacin, fradiomycin, sisomicin, tetracycline, oxytetracycline, rolitetracycline, doxycycline, ticarcillin, cephalothin, cephapirin, cephaloridine, cefaclor, cephalixin, cefroxadine, cefadroxil, cefamandole, cefotoam, cefuroxime,
25 cefotiam, cefotiam hexetil, cefuroxime axetil, cefdinir, cefditoren pivoxil, ceftazidime, cefpiramide, cefsulodin, cefmenoxime, cefpodoxime proxetil, cefpirome, ceftazopran, cefepime, cefsulodin, cefmenoxime, cefmetazole, cefminox, cefoxitin, cefbuperazone, latamoxef, flomoxef, cefazolin,
30 cefotaxime, cefoperazone, ceftizoxime, moxalactam, thienamycin, sulfazecin, aztreonam or a salt thereof, griseofulvin, lankacidin-group [Journal of Antibiotics (J. Antibiotics), 38, 877-885(1985)], azole compounds [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)-
35 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.

(2) antifungal agent

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

(ii) griseofulvin, pyrrolnitrin and the like.

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

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

10 (v) triazole derivative (e.g. fluconazole and itraconazole)

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

(3) antiprotozoal agent

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

(4) antitussive and expectorant drug

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

(5) sedative

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

35 (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, etc.)

(ii) intravenous anesthetic (e.g., ketamine hydrochloride, droperidol, thiopental sodium, thiamylal sodium, pentobarbital, etc.) and the like.

(7) antiulcer drug

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

(8) antiarrhythmic agent

(i) Na 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) K channel blocker (e.g., amiodarone)

(iv) Ca channel blocker (e.g., verapamil, diltiazem) and the like.

(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, ozagrel sodium, ethyl icosapentate, beraprost sodium, alprostadil, ticlopidine hydrochloride, pentoxifylline, dipyridamole,
5 tisokinase, urokinase, streptokinase and the like.

(11) tranquilizer

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

10 (12) antipsychotic

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

(13) antitumor drug

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

(14) antihypolipidemic drug

clofibrate, ethyl 2-chloro-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionate [Chem. Pharm. Bull, 38, 2792-
35 2796 (1990)], pravastatin, simvastatin, probucol, bezafibrate,

clinfibrate, nicomol, cholestyramine, dextran sulfate sodium and the like.

(15) muscle relaxant

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

(16) anticonvulsant

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

(17) antidepressant

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

(18) antiallergic drug

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

(19) cardiac

trans- π -oxocamphor, terephylol, aminophylline,
etilefrine, dopamine, dobutamine, denopamine, bencirin,
amrinone, pimobendan, ubidecarenone, digitoxin, digoxin,
30 methyl digoxin, lanatoside C, G-strophanthin and the like.

(20) vasodilator

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

(21) vasoconstrictor

35 dopamine, dobutamine denopamine and the like.

(22) hypotensive diuretic

Hexamethonium bromide, pentolinium, mecamlamine, ecarazine, clonidine, diltiazem, nifedipine and the like.

(23) antidiabetic drug

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

(24) antinarcotic

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

(25) liposoluble vitamins

(i) vitamin A: vitamin A₁, vitamin A₂ and retinol palmitate

(ii) vitamin D: vitamin D₁, D₂, D₃, D₄ and D₅

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

(iv) vitamin K: vitamin K₁, K₂, K₃ and K₄

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

(26) vitamin derivative

20 various derivatives of vitamins, for example, vitamin D₃ derivatives such as 5,6-trans-cholecalciferol, 2,5-hydroxycholecalciferol, 1- α -hydroxycholecalciferol and the like, vitamin D₂ derivatives such as 5,6-trans-ergocalciferol and the like, and the like.

25 (27) antiasthmatic

isoprenaline hydrochloride, salbutamol sulfate, procaterol hydrochloride, terbutaline sulfate, trimetoquinol hydrochloride, tulobuterol hydrochloride, orciprenaline sulfate, fenoterol hydrobromide, ephedrine hydrochloride, 30 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, 35 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

5 sodium cromoglicate and the like.

[0194]

(30) therapeutic agent for allergic rhinitis

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

(31) hypertensive drug

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

(32) Others

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

[0195]

The dosage form of concomitant drugs is not particularly limited, and is acceptable as long as the compound of the
20 present invention is combined with concomitant drugs at the time of administration. Examples of such dosage forms are as follows:

(1) Administration of a single formula obtained simultaneous formulation of the compound of the present invention with a
25 concomitant drug,

(2) Simultaneous administration via the same administration route for two kinds of formulas obtained by independent formulations of the compound of the present invention and a concomitant drug,

30 (3) Administrations at different times via the same administration route for two kinds of formulas obtained by independent formulations of the compound of the present invention and a concomitant drug,

(4) Simultaneous administration via different administration
35 routes for two kinds of formulas obtained by independent

formulations of the compound of the present invention and a concomitant drug,

(5) Administrations at different times via different administration routes for two kinds of formulas obtained by independent formulations of the compound of the present invention and a concomitant drug (e.g., administration in the order of the compound of the present invention and then a concomitant drug, or administration in the reversed order).

These forms of administration are summarized below and abbreviated as a combination drug of the present invention.
[0196]

When administering the combination drug of the present invention, the concomitant drug and the compound of the present invention can be administered simultaneously.
Alternatively, the compound of the present invention can be administered after a concomitant drug is administered, or a concomitant drug can be administered after the compound of the present invention is administered. When administering at different times, the time difference depends upon the active ingredients to be administered, drug forms and methods of administration.

For example, when the concomitant drug or a pharmaceutical composition thereof is administered first, the compound of the present invention or a pharmaceutical composition thereof can be administered within 1 min. to 3 days, preferably within 10 min to 1 day and more preferably within 15 min to 1 hour after the concomitant drug or a pharmaceutical composition thereof is administered. When the compound of the present invention or a pharmaceutical composition thereof is administered first, the concomitant drug or a pharmaceutical composition thereof can be administered within 1 min to 1 day, preferably within 10 min to 6 hours and more preferably within 15 min to 1 hour after the compound of the present invention or a pharmaceutical composition thereof is administered.

[0197]

If there are no problems with side effects of the concomitant drugs, any dosages can be set. A dosage as a concomitant drug varies depending on dosages, administration subjects, administration routes, target diseases, symptoms, etc. For example, in the case of oral administration in patients with systemic lupus erythematosus (adults, body weight of approximately 60 kg), a dosage range is generally about 0.1 to 20 mg/kg body weight, preferably from about 0.2 to 10 mg/kg body weight and more preferably from about 0.5 to 10 mg/kg body weight. It is preferable that this dosage is administered once daily to several times daily (e.g., once to 3 times).

If the compound of the present invention is used in combination with a concomitant drug, the respective dosages can be reduced within a safe range with consideration of the opposite effects of the respective drugs.

[0198]

The combination drug of the present invention exhibits low toxicity. For example, the compound of the present invention or (and) the concomitant drug can be combined with a pharmaceutically acceptable carrier according to the known method to prepare a pharmaceutical composition such as tablets (including sugar-coated tablets and film-coated tablets), powder agents, granular agents, capsules (including soft capsules), liquids, injection solutions, suppositories, sustained-release agents, etc. These compositions can be administered safely orally or non-orally (e.g., including local, rectal, venous routes etc.).

[0199]

The pharmaceutically acceptable carriers that can be used for manufacturing the combination drug of the present invention can be the same as those used in the medicament of the present invention as mentioned above.

[0200]

A mixing ratio between the compound of the present invention and the concomitant drug in the combination drug of the present invention can be selected appropriately based on the administration subjects, administration routes, diseases
5 and the like.

The concomitant drug in the combination drug of the present invention can be combined at an appropriate proportion if two or more drugs are combined.

A dosage of the concomitant drug can be selected
10 appropriately based on the dosages used clinically. In addition, a mixing ratio between the compound of the present invention and the concomitant drug can be selected appropriately based on the administration subjects, administration routes, target diseases, symptoms, combinations,
15 etc. For example, if the administration subject is humans, a concomitant drug may be used in an amount ranging from about 0.01 to 100 parts by weight relative to 1 part by weight of the compound of the present invention.

[0201]

20 For example, the content of the compound of the present invention in the combination drug of the present invention varies with the form of formulations. Generally, it is present in a range from about 0.01 to 99.9 wt%, preferably from about 0.1 to about 50 wt% and more preferably from about 0.5 to
25 about 20 wt% relative to the entire formula.

[0202]

The content of the concomitant drug in the combination drug of the present invention varies with the form of formulations. Generally it is present in a range from about
30 0.01 to 99.9 wt%, preferably from about 0.1 to about 50 wt% and more preferably from about 0.5 to about 20 wt% relative to the entire formula.

[0203]

The content of an additive such as carriers in the
35 combination drug of the present invention varies with the form

of formulations. Generally it is present in a range from about 1 to 99.99 wt% and preferably from about 10 to about 90 wt% relative to the entire formula.

[0204]

5 When the compound of the present invention and a concomitant drug are formulated independently, the same contents can be applied.

[0205]

Since the dosages may fluctuate under various conditions
10 as mentioned above, a dosage less than the dosages may be sufficient or it may be necessary to administer at a dosage exceeding the range.

Example

[0206]

15 The present invention is explained in detail in the following by referring to Examples, Formulation Examples and Experimental Examples and which are merely exemplified and not to be construed as limitative, and the invention may be changed within the scope of the present invention. In the
20 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.

In silica gel column chromatography, NH means use of
25 aminopropylsilane-bonded 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.

¹H NMR (proton nuclear magnetic resonance spectrum) was
30 measured by Fourier-transform type NMR. Peaks with very mild protons such as a hydroxyl group, an amino group and the like are not described.

In the following Reference Examples and Examples, mass spectrum (MS), nuclear magnetic resonance spectrum (NMR) and
35 melting point were measured by the following apparatus.

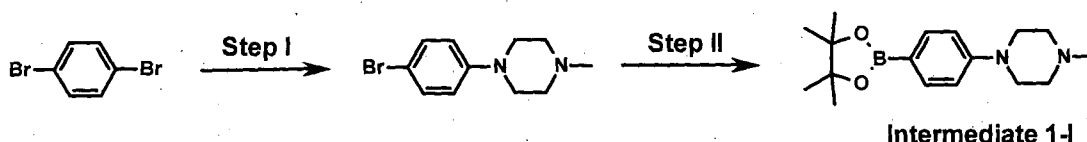
MS (mass spectrum) was measured by LC/MS (liquid chromatograph mass spectrometer). As the ionization method, API (Atmospheric Pressure Ionization, atmospheric pressure chemical ionization) method or ESI (Electron Spray Ionization) method was used. The data indicate measured value (found) found. Generally, a molecular ion peak is observed. In the case of a compound having an amino group ($-NH_2$), a peak after elimination of NH_3 may be observed as a fragment ion. In the case of a salt, a molecular ion peak or fragment ion peak of free form is generally observed.

[0207]

Synthesis of Intermediates:

Intermediate 1-I: 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine

15 [0208]



[0209]

Intermediate 1-I was prepared from 1,4-dibromobenzene in two steps according to the procedure described in WO 2008/088881.

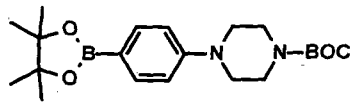
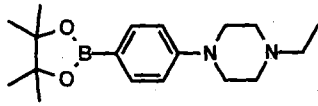
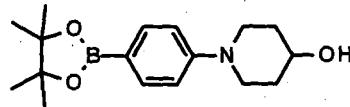
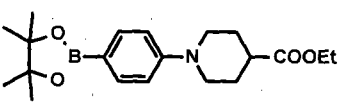
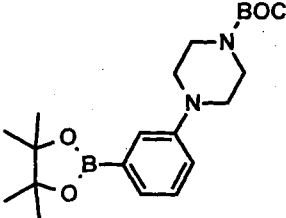
[0210]

Intermediates 1-II to 1-VII as shown in Table 2 were prepared in the same manner as **Intermediate 1-I**.

[0211]

25 Table 2

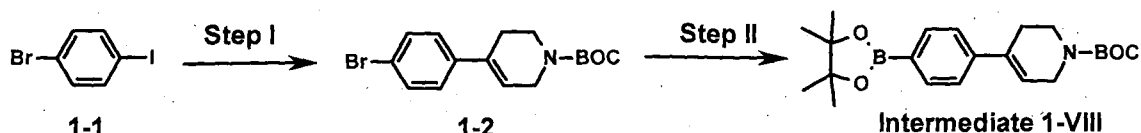
Int.No.	IUPAC name	Structure	LCMS
1-II	1-isopropyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine		LCMS: m/z 331.3 [$M^+ + 1$]

1-III	tert-butyl 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate		LCMS: m/z 389.2 $[M^++1]$
1-IV	1-ethyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine		LCMS: m/z 317.2 $[M^++1]$
1-V	1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidin-4-ol		LCMS: m/z 304.2 $[M^++1]$
1-VI	ethyl 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-4-carboxylate		LCMS: m/z 360.2 $[M^++1]$
1-VII	tert-butyl 4-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate		LCMS: m/z 389.2 $[M^++1]$

[0212]

Intermediate 1-VIII: tert-butyl 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate

5 [0213]



[0214]

Step I: tert-butyl 4-(4-bromophenyl)-3,6-dihydro-2H-pyridine-

1-carboxylate (**1-2**)

A mixture of 1-bromo-4-iodobenzene **1-1** (6 g, 212 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (4.62 g, 149.4 mmol) and K₂CO₃ (8.76 g, 635.4 mmol) in a 4:1 mixture of dioxane/water (40 mL) was degassed in a stream of argon for 15 minutes. To the mixture was added 1,1-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (0.345 g, 0.42 mmol), and the reaction mixture was again degassed for additional 15 minutes. After stirring at 100°C for 24 hours, the volatiles were removed by evaporation, and the obtained crude reaction mixture was diluted with water (100 mL), followed by extraction with ethyl acetate (75 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure, followed by purification on silica gel column chromatography (100-200 mesh) using 10% EtOAc in hexanes to give the desired product **1-2** as a yellow syrup (3.8 g, 53%); LCMS: m/z 284.0 [M⁺ - t-Bu + 2].

[0215]

1-Bromo-4-iodobenzene **1-1** may be commercially available, or can also be produced according to a method known per se or a method analogous thereto.

[0216]

Step II: tert-butyl 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate (**Intermediate 1-VIII**)

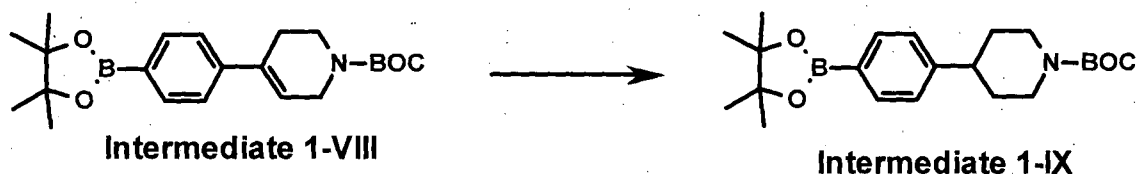
A mixture of **1-2** (3.8 g, 112 mmol), bis(pinacolato)diboron (3.41 g, 134 mmol) and KOAc (3.30 g, 336 mmol) in DMSO (50 mL) was degassed in a stream of argon for 15 minutes. To the mixture was added 1,1-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (0.182 g, 0.22 mmol), and the reaction mixture was again degassed for additional 15 minutes. After stirring at 100°C for 24 hours, the volatiles were removed by

evaporation, and the obtained crude reaction mixture was diluted with water (50 mL), followed by extraction with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure, followed by purification on silica gel column chromatography (100-200 mesh) using 10% EtOAc in hexanes to give the desired product **Intermediate 1-VIII** as a yellow solid (3.5 g, 81%); LCMS: *m/z* 330.1 [*M*⁺ -*t*-Bu +2].

10 [0217]

Intermediate 1-IX: tert-butyl 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine-1-carboxylate

[0218]



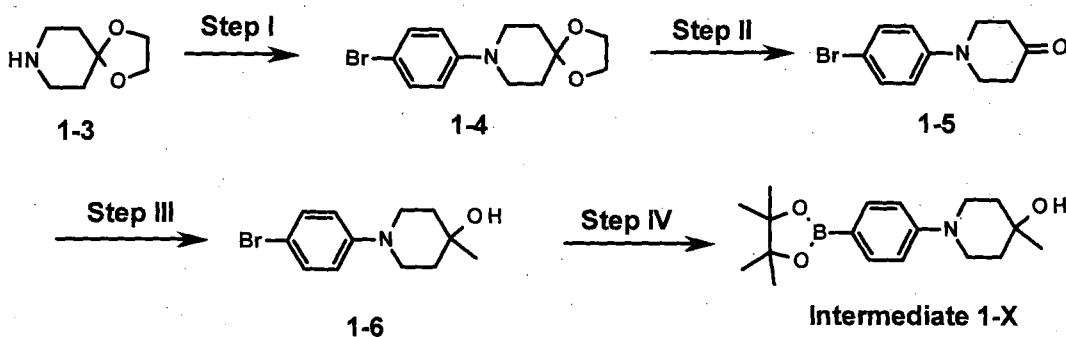
15 [0219]

A solution of **Intermediate 1-VIII** (4.1 g, 10.64 mmol) in EtOAc (60 mL) was treated with Pd/C (10% dry, 0.5 g), and the resulting reaction mixture was stirred under hydrogen atmosphere at room temperature for 18 hours. The catalyst was removed by filtration and washed with EtOAc (100 mL). The obtained filtrate was concentrated in vacuo to give the desired product **Intermediate 1-IX** as a white solid (3.4 g, 85%).

[0220]

25 **Intermediate 1-X**: 4-methyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidin-4-ol

[0221]



[0222]

Step I: 8-(4-bromophenyl)-1,4-dioxaspiro[4.5]decane (**1-4**)

5 A mixture of **1-3** (5.5 g, 38.4 mmol), 1,4-dibromobenzene (23 g, 96.1 mmol), BINAP (1.43 g, 7.6 mmol) and Cs₂CO₃ (18.70 g, 57.6 mmol) in 1,4-dioxane (150 mL) was degassed in a stream of argon for 30 minutes. To the mixture was added tris(dibenzylideneacetone)dipalladium(0) (0.703 g, 7.60 mmol),
 10 and the reaction mixture was again degassed for additional 15 minutes. After stirring at 100°C for 18 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (100 mL), followed by extraction with ethyl acetate (150 mL x 3). The combined organic layers were washed
 15 with brine (150 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (100-200 mesh) using 8% EtOAc in hexanes to give the desired product **1-4** as a yellow solid (3.1 g, 26%); LCMS: *m/z* 300.0[M⁺+1].

[0223]

Step II: 1-(4-bromophenyl)piperidin-4-one (**1-5**)

To a solution of **1-4** (3.0 g, 10.0 mmol) in methanol (15 mL) was added 1N aq.HCl (15 mL), and the mixture was stirred for 16 hours at 90°C. The volatiles were removed by
 25 evaporation, and the obtained residue was diluted with water (20 mL), and the mixture was basified using saturated aq.NaHCO₃ solution (50 mL) to pH 9, followed by extraction with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and

concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (100-200 mesh) using 10% EtOAc in hexanes to give the desired product **1-5** (1.5 g, 59%) as a yellow solid; LCMS: m/z 254.0 [$M^+ + 1$].

5 [0224]

Step III: 1-(4-bromophenyl)-4-methyl-piperidin-4-ol (**1-6**)

To a solution of **1-5** (1.4 g, 5.5 mmol) in anhydrous tetrahydrofuran (20 mL) was added methylmagnesium bromide (1.4 M in THF) at -78°C . After addition, the reaction mixture was
10 allowed to warm to 0°C and held at this temperature for another 1 hour. The reaction mixture was diluted with saturated aqueous NH_4Cl solution (10 mL) and ethyl acetate (25 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (25 mL x 2). The combined organic
15 layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (100-200 mesh) using 8% EtOAc in hexanes to give the desired product **1-6** as a yellow solid (1.1 g, 74%); LCMS: m/z 270.0
20 [$M^+ + 1$].

[0225]

Step IV: 4-methyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidin-4-ol (**Intermediate 1-X**)

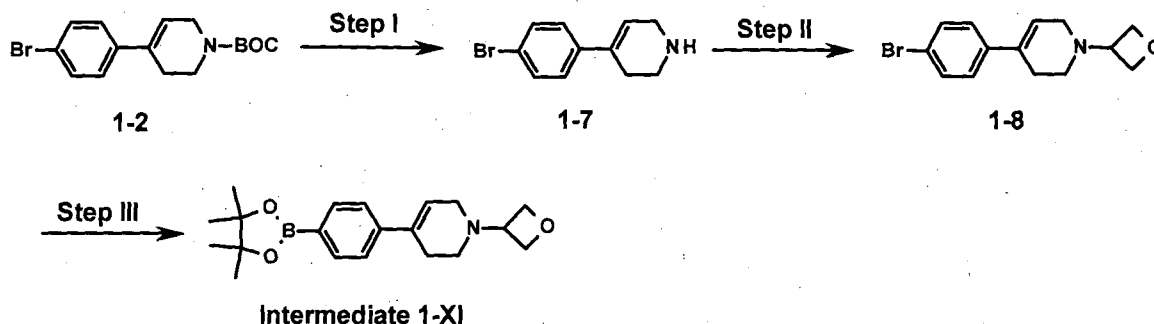
A mixture of **1-6** (0.9 g, 3.34 mmol),
25 bis(pinacolato)diboron (1.0 g, 4.01 mmol) and KOAc (0.984 g, 10.03 mmol) in 1,4-dioxane (20 mL) was degassed in a stream of argon for 15 minutes. To the mixture was added 1,1-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (0.055 g, 0.0669 mmol), and the
30 reaction mixture was again degassed for additional 15 minutes. After stirring at 80°C for 20 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (50 mL), followed by extraction with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine
35 (50 mL), dried over anhydrous Na_2SO_4 and concentrated under

reduced pressure. The obtained residue was purified by silica gel column chromatography (100-200 mesh) using 10% EtOAc in hexanes to give the desired product **Intermediate 1-X** (1.0 g, 94%) as a yellow solid; LCMS: m/z 318.2 [$M^+ + 1$].

5 [0226]

Intermediate 1-XI: 1-(oxetan-3-yl)-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3,6-dihydro-2H-pyridine

[0227]



10 [0228]

Step I: 4-(4-bromophenyl)-1,2,3,6-tetrahydropyridine (**1-7**)

A solution of **1-2** (6.4 g, 18.93 mmol) in methanol (50 mL) was treated with 2 M HCl ether solution (20 mL) at 0°C. After stirring for 3 hours at room temperature, the volatiles were removed by evaporation, and the obtained residue was basified with saturated aqueous NaHCO₃ solution (50 mL) to pH ~8, and the mixture was diluted with ethyl acetate (150 mL). The organic layer was separated, and the aqueous layer was again extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the desired product **1-7** as a white solid (3.8 g, 84%); LCMS: m/z 238.0 [$M^+ + 1$], 240.0 [$M^+ + 2$].

[0229]

25 Step II: 4-(4-bromophenyl)-1-(oxetan-3-yl)-3,6-dihydro-2H-pyridine (**1-8**)

To a solution of **1-7** (1.10 g, 4.61 mmol) in methanol (15 mL) were added oxetan-3-one (1.66 g, 23.01 mmol), 4Å molecular sieves (0.5 g) and zinc chloride (3.14 g, 23.01 mmol)

successively. After stirring for 2 hours, the reaction mixture was treated with sodium cyanoborohydride at 0°C, and stirring was continued for another 4 hours. The reaction mixture was diluted with water (20 mL), ethyl acetate (25 mL) and
5 saturated aqueous NaHCO₃ solution (10 mL). The organic layer was separated, and the aqueous layer was again extracted with ethyl acetate (25 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was
10 purified by silica gel column chromatography (100-200 mesh) using 50% EtOAc in hexanes to give the desired product **1-8** (1.1 g, 81%) as a colourless syrup; LCMS: *m/z* 294.0 [M⁺+1], 296.0 [M⁺+2].

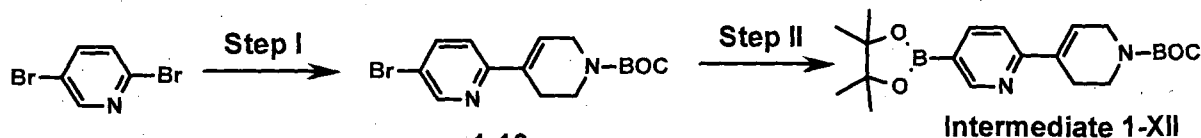
[0230]

15 Step III: 1-(oxetan-3-yl)-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3,6-dihydro-2H-pyridine
(**Intermediate 1-XI**)

A mixture of **1-8** (1.1 g, 3.74 mmol), bis(pinacolato)diboron (1.10 g, 4.48 mmol) and KOAc (1.09 g,
20 11.22 mmol) in 1,4-dioxane (10 mL) was degassed in a stream of argon for 15 minutes. To the mixture was added 1,1-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (0.091 g, 0.112 mmol), and the reaction mixture was again degassed for additional 15 minutes.
25 After stirring at 100°C for 20 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (50 mL), followed by extraction with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated
30 under reduced pressure. The obtained residue was purified by silica gel column chromatography (100-200 mesh) using 1% MeOH in dichloromethane to give the desired product **Intermediate 1-XI** (1.12 g, crude yield 88%) as a pale brown solid; LCMS: *m/z* 342.2 [M⁺+1].

35 [0231]

Intermediate 1-XII: tert-butyl 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]-3,6-dihydro-2H-pyridine-1-carboxylate
[0232]



[0233]

Step I: tert-butyl 4-(5-bromo-2-pyridyl)-3,6-dihydro-2H-pyridine-1-carboxylate (**1-10**)

1-10 was prepared from **1-9** according to the procedure described in WO 2011/008663.

[0234]

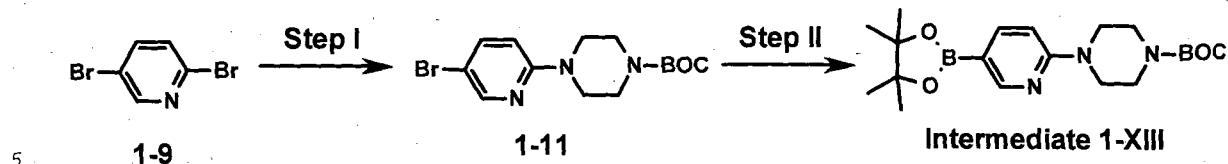
Step II: tert-butyl 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]-3,6-dihydro-2H-pyridine-1-carboxylate (**Intermediate 1-XII**)

A mixture of **1-10** (3.30 g, 9.73 mmol), bis(pinacolato)diboron (2.96 g, 11.68 mmol) and KOAc (2.27 g, 29.19 mmol) in 1,4-dioxane (30 mL) was degassed in a stream of argon for 15 minutes. To the mixture was added 1,1-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (0.237 g, 0.29 mmol), and the reaction mixture was again degassed for additional 15 minutes. After stirring at 100°C for 20 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (50 mL), followed by extraction with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (100-200 mesh) using 1% to 5% MeOH in dichloromethane to give the desired product **Intermediate 1-XII** as a mixture of minor boronate ester together with major boronic acid as a white solid (2.6 g, crude yield 70%); LCMS (for boronic acid): *m/z* 305.3 [*M*⁺+1].

[0235]

Intermediate 1-XIII: tert-butyl 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]piperazine-1-carboxylate

[0236]



[0237]

Step I: tert-butyl 4-(5-bromo-2-pyridyl)piperazine-1-carboxylate (**1-11**)

10 [0238]

1-11 was prepared from **1-9** according to the procedure described in WO 2008/146914.

[0239]

Step II: tert-butyl 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]piperazine-1-carboxylate (**Intermediate 1-XIII**)

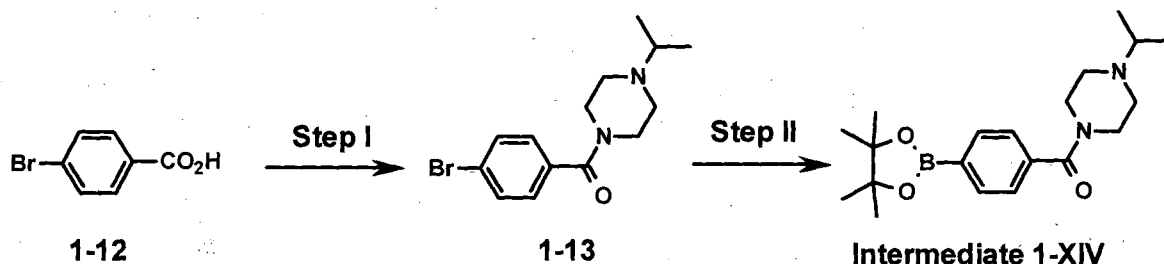
A mixture of **1-11** (4.30 g, 12.57 mmol), bis(pinacolato)diboron (3.82 g, 15.07 mmol) and KOAc (2.94 g, 37.69 mmol) in 1,4-dioxane (30 mL) was degassed in a stream of argon for 15 minutes. To the mixture was added 1,1-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (0.307 g, 0.376 mmol), and the reaction mixture was again degassed for additional 15 minutes. After stirring at 100°C for 20 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (50 mL), followed by extraction with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (100-200 mesh) using 50% EtOAc in hexanes to give the desired product **Intermediate 1-XIII** as a mixture of minor boronate ester together with major

boronic acid (4.8 g, crude yield 98%) as a yellow solid; LCMS (for boronate ester): m/z 390.2 [$M^+ + 1$]; LCMS (for boronic acid): m/z 308.1 [$M^+ + 1$].

[0240]

- 5 **Intermediate 1-XIV**: (4-isopropylpiperazin-1-yl)-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanone

[0241]



[0242]

- 10 Step I: (4-bromophenyl)-(4-isopropylpiperazin-1-yl)methanone (1-13)

To a stirred solution of 4-bromobenzoic acid **1-12** at 0°C (2 g, 9.94 mmol) in a mixture of MeCN:DMF (4:1, 20 mL) were added HATU (4.53 g, 11.93 mmol) and 1-isopropylpiperazine (1.91 g, 14.92 mmol). The reaction mixture was allowed to stir for 30 minutes, and then diisopropylethylamine (3.85 g, 5.2 mL, 29.84 mmol) was added thereto. The resulting reaction mixture was stirred for 16 hours at room temperature. After completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate (25 mL x 3). The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel (60-120 mesh size) column chromatography using 0-5 % methanol in dichloromethane as eluent to give the desired product **1-13** (3.0 g, 97%) as brown solid; LCMS: m/z 312.00 ($M^+ + 1$).

[0243]

Step II: (4-isopropylpiperazin-1-yl)-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanone (**Intermediate 1-XIV**)

- 30 A mixture of **1-13** (3.0 g, 9.64 mmol),

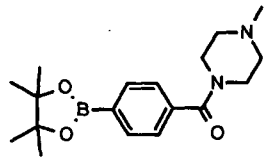
bis(pinacolato)diboron (3.65 g, 14.46 mmol) and potassium acetate (2.83 g, 28.92 mmol) in dioxane (35 mL) was degassed in a stream of argon for 30 minutes. To this reaction mixture was added dppf PdCl₂:CH₂Cl₂ complex (0.17 g, 0.21 mmol), and the reaction mixture was again degassed for additional 15 minutes. The reaction mixture was stirred at 90°C for 18 h. After completion of reaction, the reaction mixture was cooled to 25°C, the solid was removed by filtration through a celite pad, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel (60-120 mesh size) column chromatography using 0-5 % methanol in dichloromethane as eluent to give the desired product **Intermédiaire 1-XIV** (2.2 g, 63 %) as a brown oil; LCMS: *m/z* 359.10 (M⁺+1).

[0244]

Intermediate 1-XV as shown in Table 3 was prepared in the same manner as **Intermediate 1-XIV**

[0245]

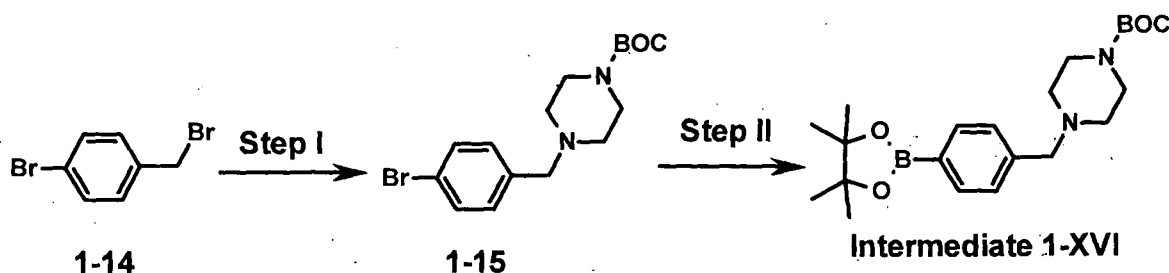
Table 3:

Int.No.	IUPAC name	Structure	LCMS
1-XV	(4-methylpiperazin-1-yl)-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanone		<i>m/z</i> 331.3 (M ⁺ +1)

[0246]

Intermediate 1-XVI: tert-butyl 4-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl]piperazine-1-carboxylate

[0247]



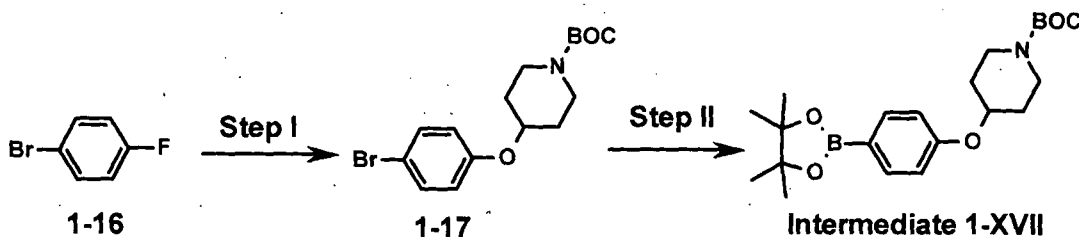
25 [0248]

Intermediate 1-XVI was prepared from **1-14** according to procedures described in WO 2013/157022.

[0249]

Intermediate 1-XVII: tert-butyl 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]piperidine-1-carboxylate

[0250]



[0251]

Step I: tert-butyl 4-(4-bromophenoxy)piperidine-1-carboxylate
(1-17)

To a stirred suspension of sodium hydride (5.96 g, 149.04 mmol) in 30 mL DMF was added tert-butyl 4-hydroxypiperidine-1-carboxylate (15 g, 74.52 mmol), and the mixture was stirred at 80°C for 2.5 hours. 1-Bromo-4-fluoro benzene **1-16** was added to the reaction mixture, and the mixture was again stirred at 120°C for 12 hours. The reaction mixture was cooled to 0°C and then poured into ice (200 g). The mixture was extracted with ethyl acetate (200 mL x 3). The organic layer was washed with brine (200 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (100-200 mesh) using 5% EtOAc in hexanes as eluent to give the desired product **1-17** (17.02 g, 64%); LCMS: *m/z* 301.9 [M⁺-t-Bu +2].

[0252]

Step II: tert-butyl 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]piperidine-1-carboxylate
(**Intermediate 1-XVII**)

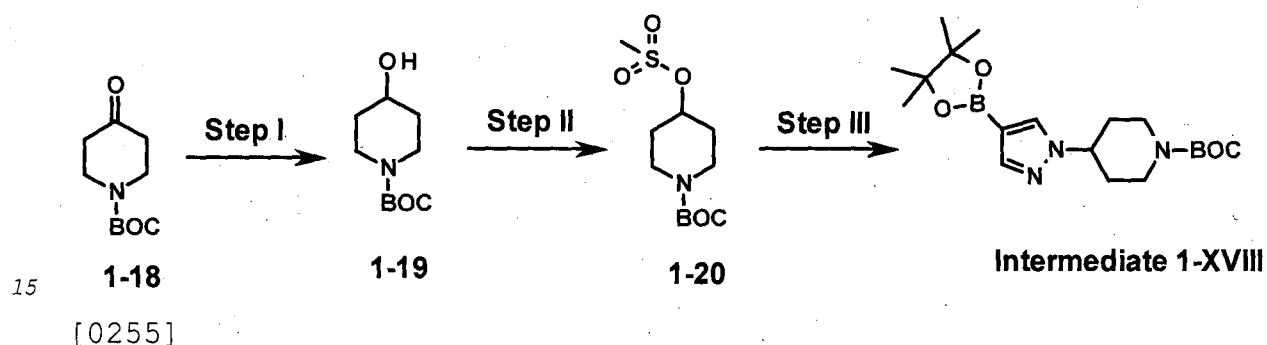
A mixture of **1-17** (5.0 g, 14.08 mmol), bis(pinacolato)diboron (5.36 g, 21.12 mmol) and potassium acetate (2.76 g, 28.92 mmol) in dioxane (70 mL) was degassed in a stream of argon for 30 minutes. To this reaction mixture

was added dppf PdCl₂:CH₂Cl₂ complex (1.15 g, 1.41 mmol), and the reaction mixture was again degassed for additional 15 minutes. The reaction mixture was stirred at 90°C for 18 h. After completion of reaction, the reaction mixture was cooled to 25°C, the solid was removed by filtration through a celite pad, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel (100-200 mesh size) column chromatography using 5% ethyl acetate in hexanes as eluent to give the desired product **Intermediate 1-XVII** (4.09 g, 72%); LCMS: *m/z* 348.1 [*M*⁺ -*t*-Bu +2].

[0253]

Intermediate 1-XVIII: tert-butyl 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]piperidine-1-carboxylate

[0254]



Step I: tert-butyl 4-hydroxypiperidine-1-carboxylate (**1-19**)

1-19 was prepared from **1-18** according to the procedure described in WO 2013/160810.

20 [0256]

Step II: tert-butyl 4-methylsulfonyloxypiperidine-1-carboxylate (**1-20**)

1-20 was prepared from **1-19** according to the procedure described in WO 2012/167733.

25 [0257]

Step III: tert-butyl 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]piperidine-1-carboxylate (**Intermediate 1-XVIII**)

Intermediate 1-XVIII was prepared from **1-20** according to the procedure described in WO 2012/167733; LCMS: *m/z* 378.1 [*M*⁺

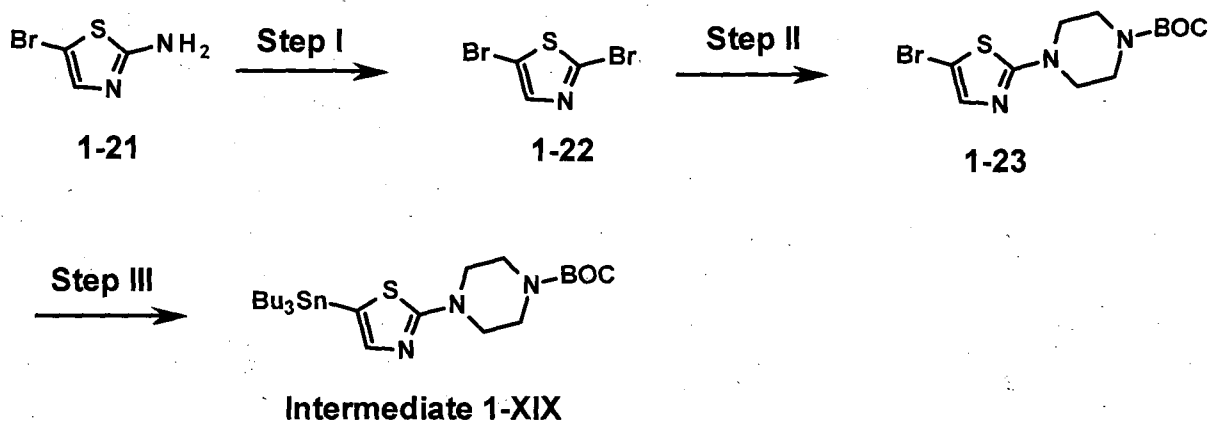
30

+1].

[0258]

Intermediate 1-XIX: [2-(4-tert-butoxycarbonylpiperazin-1-yl)thiazol-5-yl]-tert-butyl-tin

5 [0259]



[0260]

Step I: 2,5-dibromothiazole (**1-22**)

A solution of 2-amino-5-bromothiazole (**1-21**) (5.5 g, 30.72 mmol) in acetonitrile (50 mL) was treated with copper(II) bromide (3.43 g, 15.36 mmol) and isoamyl nitrite (4.9 mL, 36.87 mmol), and the resulting reaction mixture was heated at 60°C for 4 hours. The volatiles were removed by evaporation, and the obtained residue was diluted with water (50 mL), followed by extraction with ethyl acetate (25 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (60-120 mesh) using 10% EtOAc in hexanes to give the desired product **1-22** (5.05 g, 68%) as a yellow liquid; LCMS: *m/z* 243.6 [*M*⁺+2].

[0261]

Step II: tert-butyl 4-(5-bromothiazol-2-yl)piperazine-1-carboxylate (**1-23**)

A solution of **1-22** (5.0 g, 20.58 mmol) in DMF (50 mL) was treated with 1-Boc-piperazine (5.71 g, 30.87 mol) and K₂CO₃. After stirring at 70°C for 18 hours, the volatiles were removed

by evaporation, and the obtained residue was diluted with ice water (50 mL), followed by extraction with ethyl acetate (25 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (60-120 mesh) using 10% EtOAc in hexanes to give the desired product **1-23** (5.95 g, 83%) as a yellow syrup; LCMS: *m/z* 347.9 [M⁺+1].

[0262]

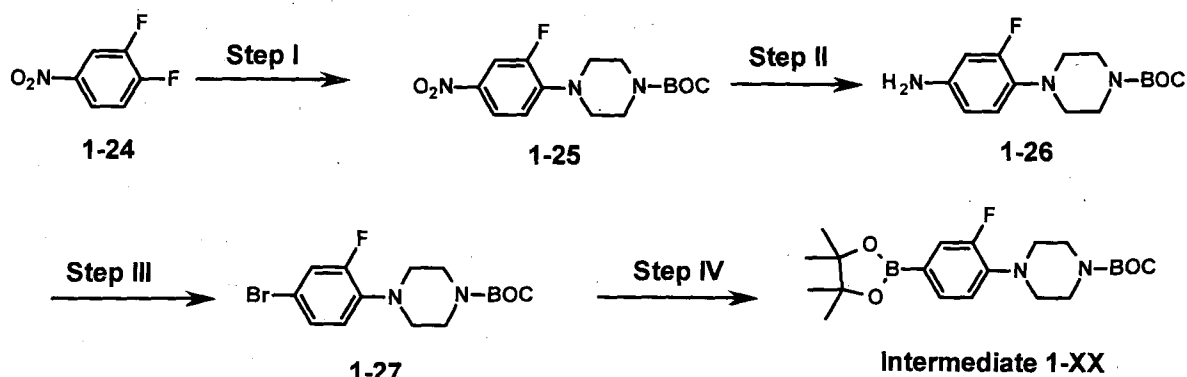
10 Step III: [2-(4-tert-butoxycarbonylpiperazin-1-yl)thiazol-5-yl]-tert-butyl-tin (**Intermediate 1-XIX**)

A solution of **1-23** (0.7 g, 0.2 mmol) in anhydrous THF (4 mL) was treated with *n*-BuLi (1.6 M in hexane, 1.50 mL, 2.41 mmol) at -78°C. The resulting reaction mixture was stirred for 15 2 hours, and then tri-*n*-butyltin chloride (0.708 mL, 2.61 mmol) was added dropwise thereto, and the mixture was stirred for another 1.5 hour at -78°C. The reaction mixture was diluted with saturated aqueous NH₄Cl solution (3 mL), water (20 mL) and EtOAc (25 mL). The organic layer was separated, and 20 the aqueous layer was back extracted with EtOAc (25 mL x 2). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (60-120 mesh) using 10% EtOAc in hexanes 25 to give the desired product **Intermediate 1-XIX** (0.51 g, crude yield 42%) together with the des-bromo compound as a pale yellow syrup. **Intermediate 1-XIX** was found to be highly unstable on silica gel column, and hence the crude product was used for the next step without purification.

30 [0263]

Intermediate 1-XX: tert-butyl 4-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate

[0264]



[0265]

Step I: tert-butyl 4-(2-fluoro-4-nitro-phenyl)piperazine-1-carboxylate (**1-25**)

5 **1-25** was prepared from **1-24** according to the procedure described in WO 2009/079597.

[0266]

Step II: tert-butyl 4-(4-amino-2-fluoro-phenyl)piperazine-1-carboxylate (**1-26**)

10 **1-26** was prepared from **1-25** according to the procedure described in WO 2009/079597.

[0267]

Step III: tert-butyl 4-(4-bromo-2-fluoro-phenyl)piperazine-1-carboxylate (**1-27**)

15 A solution of **1-26** (3 g, 10.16 mmol) in acetonitrile (30 mL) was treated with copper(II) bromide (1.13 g, 5.00 mmol) and heated at 60°C. To this reaction mixture was added dropwise isoamyl nitrite (2 mL, 15.25 mmol), and the mixture was stirred for another 4 hours. The volatiles were removed by

20 evaporation, and the obtained residue was diluted with water (50 mL), followed by extraction with ethyl acetate (25 mL x 2). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The obtained residue was purified by combiflash

25 using 30% EtOAc as mobile phase to give the desired product **1-27** (1.4 g, 39%) as a brown solid; LCMS: *m/z* 302.9 [*M*⁺-*t*-Bu +1], 305.0 [*M*⁺-*t*-Bu +2].

[0268]

Step IV: tert-butyl 4-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate

(**Intermediate 1-XX**)

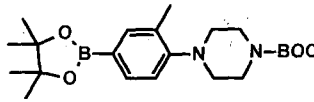
A mixture of **1-27** (1 g, 2.78 mmol),
 5 bis(pinacolato)diboron (0.849 g, 3.34 mmol) and KOAc (0.818 g, 8.34 mmol) in 1,4-dioxane (10 mL) was degassed in a stream of argon for 15 minutes. To the mixture was added 1,1-bis(diphenylphosphino)ferrocene-palladium(II) dichloride
 dichloromethane complex (0.068 g, 0.0834 mmol), and the
 10 reaction mixture was again degassed for additional 15 minutes. After stirring at 90°C for 16 hours, the reaction mixture was filtered through a celite pad and washed with EtOAc (50 mL), and the filtrate was concentrated under reduced pressure. The
 obtained residue was purified by combiflash using 20% EtOAc in
 15 hexanes to give the desired product **Intermediate 1-XX** (1.1 g, yield 98%) as an off white solid; LCMS: m/z 407 [M⁺ + 1].
¹HNMR (400 MHz, CDCl₃): δ 1.32 (s, 12H), 1.48 (s, 9H), 3.07 (t, J = 8.0 Hz, 4H), 3.59 (t, J = 8.0 Hz, 4H), 6.90 (app. t, J = 8.0 Hz, 1H), 7.44 (dd, J = 1.2 Hz, J = 13.2 Hz, 1H), 7.50 (dd,
 20 J = 0.8 Hz, J = 7.6 Hz, 1H)

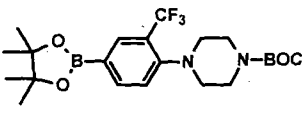
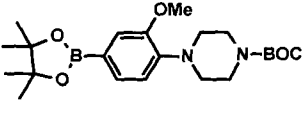
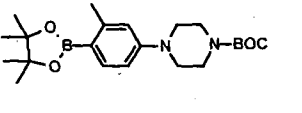
[0269]

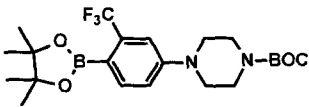
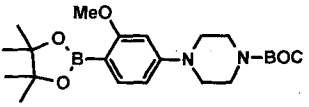
Intermediates 1-XXI to 1-XXVI as shown in Table 4 were prepared in the same manner as **Intermediate 1-XX**.

[0270]

25 Table 4:

Int.No.	IUPAC name	Structure	Analytical Data
1-XXI	tert-butyl 4-[2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate		LCMS: m/z 403 [M ⁺ +1] ¹ HNMR (400 MHz, CDCl ₃): δ 1.34 (s, 12H), 1.50 (s, 9H), 2.30 (s, 3H), 2.86-2.88 (m, 4H), 3.55-3.57

			(m, 4H), 6.96 (d, J = 8 Hz, 1H), 7.61-7.64 (m, 2H)
1-XXII	tert-butyl 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)phenyl]piperazine-1-carboxylate		LCMS: m/z 457 [M ⁺ +1] ¹ HNMR (400 MHz, CDCl ₃): δ 1.32 (s, 12H), 1.49 (s, 9H), 2.88-2.90 (m, 4H), 3.54-3.57 (m, 4H), 7.27 (s, 1H), 7.93 (d, J = 7.2 Hz, 1H), 8.06 (s, 1H)
1-XXIII	tert-butyl 4-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate		LCMS: m/z 419.3 [M ⁺ +1] ¹ HNMR (400 MHz, CDCl ₃): δ 1.33 (s, 12H), 1.48 (s, 9H), 3.03 (t, J = 4.8 Hz, 4H), 3.60 (t, J = 4.8 Hz, 4H), 3.91 (s, 3H), 6.90 (J = 7.6 Hz, 1H), 7.26-7.27 (m, 1H), 7.40 (d, J = 7.6 Hz, 1H)
1-XXIV	tert-butyl 4-[3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-		LCMS: m/z 403 [M ⁺ +1] ¹ HNMR (400 MHz, CDCl ₃):

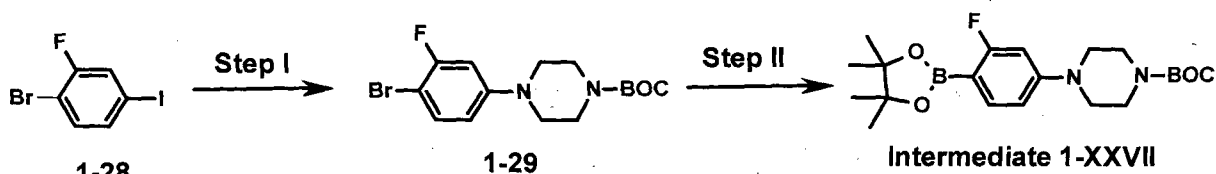
	yl)phenyl]piperazine-1-carboxylate		δ 1.12 (s, 12H), 1.48 (s, 9H), 2.50 (s, 3H), 3.18-3.20 (m, 4H), 3.54-3.57 (m, 4H), 6.69-6.70 (m, 2H), 7.67-7.69 (m, 1H)
1-XXV	tert-butyl 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)phenyl]piperazine-1-carboxylate		LCMS: m/z 457 $[M^++1]$ ^1H NMR (400 MHz, CDCl_3): δ 1.34 (s, 12H), 1.48 (s, 9H), 3.21-3.24 (m, 4H), 3.56-3.59 (m, 4H), 6.96 (dd, $J = 8$ Hz, 1H), 7.15 (s, 1H), 7.67 (d, $J = 8$ Hz, 1H)
1-XXVI	tert-butyl 4-[3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate		LCMS: m/z 419.3 $[M^++1]$ ^1H NMR (400 MHz, CDCl_3): δ 1.26 (s, 9H), 1.36 (s, 12H), 3.21 (t, $J = 10.0$ Hz, 4H), 3.57 (t, $J = 10.0$ Hz, 4H), 3.82 (s, 3H), 6.37-6.40 (m, 1H), 6.46 (dd, J

			= 2.0 Hz, J = 8.0 Hz, 1H), 7.60 (d, J= 8 Hz, 1H)
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[0271]

Intermediate 1-XXVII: tert-butyl 4-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate

5 [0272]



[0273]

Step I: tert-butyl 4-(4-bromo-3-fluorophenyl)piperazine-1-carboxylate (**1-29**)

10 A mixture of **1-28** (5.0 g, 16.6 mmol), 1-Boc-piperazine (1.2 g, 6.66 mmol), BINAP (0.610 g, 0.99 mmol) and Cs₂CO₃ (8.0 g, 24.9 mmol) in toluene (50 mL) was degassed in a stream of argon for 30 minutes. To the mixture was added tris(dibenzylideneacetone)dipalladium(0) (0.30 g, 0.33 mmol),
 15 and the reaction mixture was again degassed for additional 15 minutes. After stirring at 90°C for 18 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (50 mL), followed by extraction with ethyl acetate (50 mL x 3). The combined organic layers were washed
 20 with brine (150 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (60-120 mesh) using 10% EtOAc in hexanes to give the desired product **1-29** (1.5 g, 30%) as a yellow solid; LCMS: m/z 303 [M⁺ - ^tBu + 1],
 25 305.0 [M⁺ - ^tBu + 2].

[0274]

Step II: tert-butyl 4-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate

(Intermediate 1-XXVII)

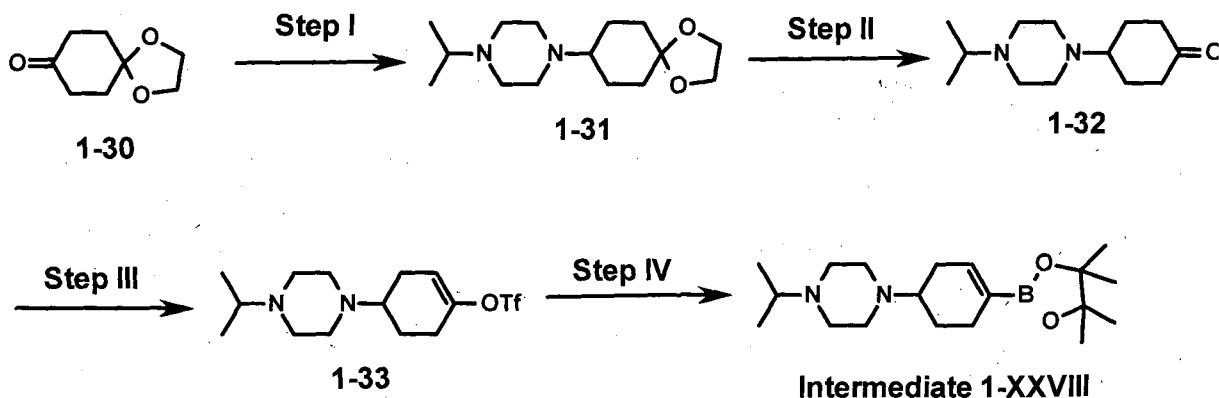
A mixture of **1-29** (0.8 g, 2.21 mmol), bis(pinacolato)diboron (0.723 g, 2.91 mmol) and KOAc (0.650 g, 6.62 mmol) in 1,4-dioxane (10 mL) was degassed in a stream of argon for 15 minutes. To the mixture was added 1,1-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (0.1 g, 0.0132 mmol), and the reaction mixture was again degassed for additional 15 minutes. After stirring at 90°C for 16 hours, the reaction mixture was filtered through a celite pad and washed with EtOAc (50 mL), and the filtrate was concentrated under reduced pressure. The obtained residue was purified by combiflash using 15% EtOAc in hexanes to give the desired product **Intermediate 1-XXVII** (0.25 g, 26%) as an off white solid; LCMS: m/z 407 [$M^+ + 1$].

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 1.27 (s, 12H), 1.41 (s, 9H), 3.23 (t, $J = 10.0$ Hz, 4H), 3.56 (t, $J = 10.0$ Hz, 4H), 6.49 (dd, $J = 2.0$ Hz, $J = 8.0$ Hz, 1H), 6.62 (dd, $J = 2.0$ Hz, $J = 8.0$ Hz, 1H), 7.61 (t, $J = 15.2$ Hz, 1H)

[0275]

Intermediate 1-XXVIII: 1-isopropyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl]piperazine

[0276]



[0277]

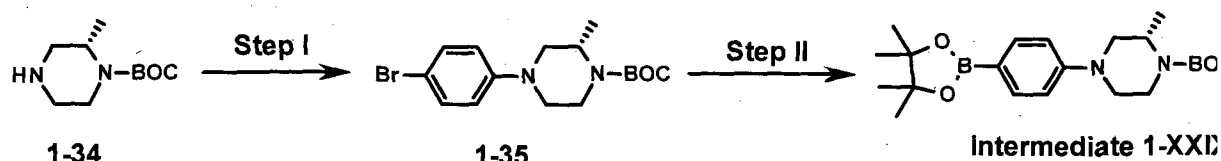
Intermediate 1-XXVIII was prepared from **1-30** according to the procedures described in WO 2008/095944.

[0278]

Intermediate 1-XXIX: tert-butyl (2S)-2-methyl-4-[4-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate

[0279]



5 [0280]

Step I: tert-butyl (2S)-4-(4-bromophenyl)-2-methyl-piperazine-1-carboxylate (**1-35**)

A mixture of **1-34** (10 g, 50 mmol), 1,4-dibromobenzene (29.4 g, 125 mmol), cesium carbonate (24.3 g, 75 mmol) and
 10 BINAP (1.5 g, 2.5 mmol) in 1,4-dioxane (250 mL) was degassed in a stream of argon for 15 minutes. To the mixture was added tris(dibenzylideneacetone)dipalladium(0) (0.900 g, 2.5 mmol), and the reaction mixture was again degassed for additional 15 minutes. After stirring at 90°C for 18 hours, the volatiles
 15 were removed by evaporation, and the obtained residue was diluted with water (250 mL), followed by extraction with ethyl acetate (250 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was
 20 purified by silica gel column chromatography (60-120 mesh) using 10% EtOAc in hexanes to give the desired product **1-35** as a white solid (5.5 g, 31%); LCMS: *m/z* 357.1 [M⁺+1], 359.1 [M⁺+2].

[0281]

25 Step II: tert-butyl (2S)-2-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine-1-carboxylate (**Intermediate 1-XXIX**)

A mixture of **1-35** (5.0 g, 14 mmol), bis(pinacolato)diboron (5.3 g, 21 mmol) and KOAc (2.7 g, 28
 30 mmol) in 1,4-dioxane (70 mL) was degassed in a stream of argon for 15 minutes. To the mixture was added 1,1-bis(diphenylphosphino)ferrocene-palladium(II) dichloride

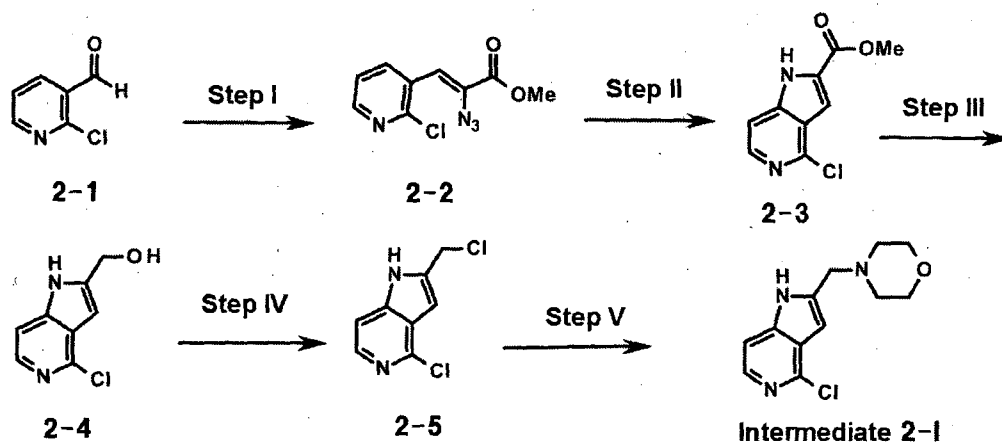
dichloromethane complex (1.1 g, 1.40 mmol), and the reaction mixture was again degassed for additional 15 minutes. After stirring at 90°C for 15 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (150 mL), followed by extraction with ethyl acetate (150 mL x 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (60-120 mesh) using 10% EtOAc in hexanes to give the desired product **Intermediate 1-XXIX** (5.0 g, 89%) as a white solid; LCMS: *m/z* 403.3 [M⁺+1].

¹HNMR (400 MHz, DMSO): δ 1.15-1.16 (m, methyl doublet proton merged in diborane impurity, 3H), 1.16 (s, 12H), 1.41 (s, 9H), 2.66-2.76 (m, 1H), 2.96 (dd, *J* = 12.4, 3.6 Hz, 1H), 3.13-3.20 (m, 1H), 3.57-3.67 (m, 2H), 3.76 (dt, *J* = 6.8, 3.6 Hz, 1H), 4.16-4.79 (m, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 9.2 Hz, 2H)

[0282]

Intermediate 2-I: 4-[(4-chloro-1H-pyrrolo[3,2-c]pyridin-2-yl)methyl]morpholine

[0283]



[0284]

Step I: methyl (Z)-2-azido-3-(2-chloro-3-pyridyl)prop-2-enoate (2-2)

To a stirred solution of 2-chloronicotinaldehyde **2-1** (5 g, 35.3 mmol) and methyl 2-azidoacetate (8.64 mL, 88.2 mmol) in

methanol (100 mL) was added a freshly prepared NaOMe methanol solution [prepared by dissolving sodium (2 g, 88.25 mmol) in methanol (100 mL)] at -20°C over 30 minutes. The resulting reaction mixture was stirred at 0-5°C for 16 hours. The
5 resulting pale yellow solid was removed by filtration from the reaction mixture. The filtrate was poured into ice-water (500 mL) containing saturated NH₄Cl (150 mL). The resulting solid was collected by filtration, and dried under vacuum to give the desired product **2-2** as a pale brown solid (3.9 g, 46%).

10 [0285]

2-Chloronicotinaldehyde **2-1** may be commercially available, or can also be produced according to a method known per se or a method analogous thereto.

[0286]

15 Step II: methyl 4-chloro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (**2-3**)

A solution of **2-2** (3.8 g, 12.1 mmol) in xylene (35 mL) was added dropwise to boiling xylene (250 mL) over a period of 30 minutes, and the mixture was stirred at the same
20 temperature for 6 hours. The reaction mixture was allowed to cool to room temperature, and then stirred at 0°C for additional 1 hour. The resulting solid was collected by filtration, and dried under vacuum to give the desired product **2-3** as a yellow solid (1.7 g, 56%); LCMS: *m/z* 211 (*M*⁺ + 1).

25 [0287]

Step III: (4-chloro-1H-pyrrolo[3,2-c]pyridin-2-yl)methanol (**2-4**)

To a stirred solution of **2-3** (1 g, 4.73 mmol) in anhydrous THF (25 mL) was added LiAlH₄ (0.36 g, 9.47 mmol) in
30 portions at 0°C. After stirring at the same temperature at for 2 hours, the reaction mixture was allowed to cool to room temperature, and stirred for additional 2 hours. Excess of LiAlH₄ was decomposed by adding saturated Na₂SO₄ solution and ethyl acetate (25 mL). The inorganic solid was removed by
35 filtration through a celite pad. The filtrate was concentrated

under reduced pressure, and the resulting solid was triturated with diethyl ether to give the desired product **2-4** as a yellow solid (0.86 g, 95%); LCMS: m/z 183 ($M^+ + 1$).

[0288]

5 Step IV: 4-chloro-2-(chloromethyl)-1H-pyrrolo[3,2-c]pyridine (**2-5**)

Thionyl chloride (0.77 mL, 10.3 mmol) was added to a stirred solution of **2-4** (0.95 g, 5.19 mmol) in 1:1 mixture of THF/ CH_2Cl_2 (30 mL) at 0°C. After stirring at room temperature
10 for additional 2 hours, the reaction mixture was cooled, and saturated aqueous $NaHCO_3$ solution (15 mL) was added thereto. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (15 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced
15 pressure to give the desired product **2-5** as a light brown solid (0.9 g, 87%); LCMS: m/z 201 ($M^+ + 1$).

[0289]

Step V: 4-[(4-chloro-1H-pyrrolo[3,2-c]pyridin-2-yl)methyl]morpholine (**Intermediate 2-I**)

20 To a mixture of **2-5** (0.85 g, 4.25 mmol) and morpholine (0.44 mL, 5.1 mmol) in DMF (10 mL) was added N,N -diisopropylethylamine (1.08 mL, 6.37 mmol) at room temperature. After stirring for 16 hours, the excess solvent was removed under reduced pressure, and the obtained residue was diluted
25 with ice water. The resulting solid was collected by filtration and triturated with diethyl ether to give the desired product **Intermediate 2-I** as a yellow solid (0.8 g, 75%); LCMS: m/z 252.1 ($M^+ + 1$).

1H NMR (400 MHz, $CDCl_3$): 2.50 (t, $J = 4$ Hz, 4H), 3.68 (s, 2H),
30 3.73 (t, $J = 4.8$ Hz, 4H), 6.51 (s, 1H), 7.21 (d, $J = 5.6$ Hz, 1H), 8.04 (d, $J = 6$ Hz, 1H), 9.04 (br s, 1H)

[0290]

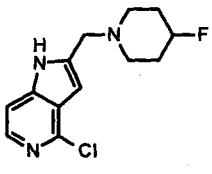
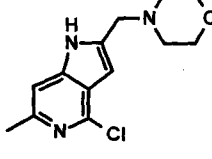
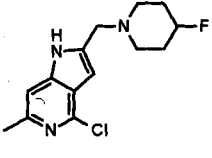
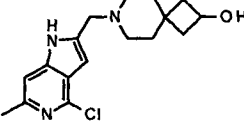
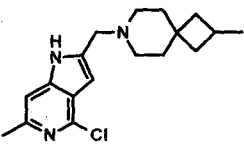
Intermediates 2-II to 2-XVI as shown in Table 5 were prepared from their corresponding starting materials [prepared
35 according to the procedures reported in literature] in the

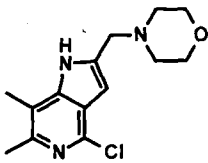
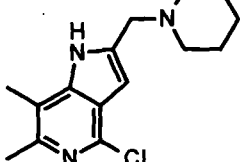
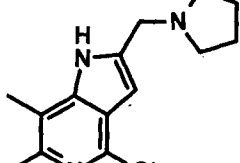
same manner as **Intermediate 2-I**.

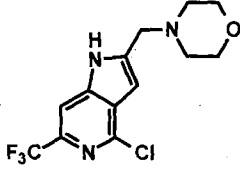
[0291]

Table 5:

Int.No.	IUPAC name	Structure	Analytical Data
2-II	1-[(4-chloro-1H-pyrrolo[3,2-c]pyridin-2-yl)methyl]piperidin-4-ol		LCMS: m/z 266.1 [$M^+ + 1$]
2-III	7-[(4-chloro-1H-pyrrolo[3,2-c]pyridin-2-yl)methyl]-7-azaspiro[3.5]nonan-2-ol		LCMS: m/z 306.1 [$M^+ + 1$]
2-IV	4-chloro-2-[(3-fluoroazetidin-1-yl)methyl]-1H-pyrrolo[3,2-c]pyridine		LCMS: m/z 240.1 [$M^+ + 1$]
2-V	4-chloro-2-(1-piperidylmethyl)-1H-pyrrolo[3,2-c]pyridine		LCMS: m/z 250.1 [$M^+ + 1$]
2-VI	4-chloro-2-[(3,3-difluoropyrrolidin-1-yl)methyl]-1H-pyrrolo[3,2-c]pyridine		LCMS: m/z 272.0 [$M^+ + 1$]
2-VII	4-chloro-2-(pyrrolidin-1-ylmethyl)-1H-pyrrolo[3,2-c]pyridine		LCMS: m/z 236.0 [$M^+ + 1$]

2-VIII	4-chloro-2-[(4-fluoro-1-piperidyl)methyl]-1H-pyrrolo[3,2-c]pyridine		-
2-IX	4-[(4-chloro-6-methyl-1H-pyrrolo[3,2-c]pyridin-2-yl)methyl]morpholine		LCMS: m/z 266.10 [M ⁺ +1]
2-X	4-chloro-2-[(4-fluoro-1-piperidyl)methyl]-6-methyl-1H-pyrrolo[3,2-c]pyridine		LCMS: m/z 282.1 [M ⁺ +1]
2-XI	7-[(4-chloro-6-methyl-1H-pyrrolo[3,2-c]pyridin-2-yl)methyl]-7-azaspiro[3.5]nonan-2-ol		LCMS: m/z 320.2 [M ⁺ +1]
2-XII	4-chloro-6-methyl-2-[(2-methyl-7-azaspiro[3.5]nonan-7-yl)methyl]-1H-pyrrolo[3,2-c]pyridine		-

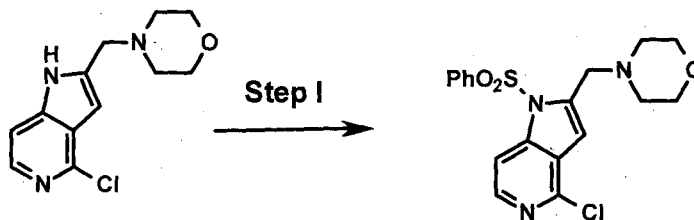
2-XIII	4-[(4-chloro-6,7-dimethyl-1H-pyrrolo[3,2-c]pyridin-2-yl)methyl]morpholine		LCMS: m/z 280.3 (M^++1) ^1H NMR (400 MHz, DMSO): δ 2.37 (s, 3H), 2.38-2.41 (m, 7H), 3.58 (t, J = 4.8 Hz, 4H), 3.61 (s, 2H), 6.32 (s, 1H), 11.4 (bs, 1H, -NH)
2-XIV	4-chloro-6,7-dimethyl-2-(1-piperidylmethyl)-1H-pyrrolo[3,2-c]pyridine		LCMS: m/z 278.2 (M^++1) ^1H NMR (400 MHz, DMSO): δ 1.33-1.40 (m, 2H), 1.47-1.52 (m, 4H), 2.36-2.40 (m, 7H), 2.50-2.51 (m, 2H), 3.56 (s, 3H), 6.29 (s, 1H), 11.4 (bs, 1H, -NH)
2-XV	4-chloro-6,7-dimethyl-2-(pyrrolidin-1-ylmethyl)-1H-pyrrolo[3,2-c]pyridine		LCMS: m/z 264.2 (M^++1) ^1H NMR (400 MHz, DMSO): δ 1.70-1.72 (m, 4H), 2.37 (s, 3H), 2.41 (s, 3H), 2.48-2.50 (m, 4H), 3.71 (s, 2H), 6.29 (s,

			1H), 11.4 (bs, 1H, -NH)
2-XVI	4-[[4-chloro-6-(trifluoromethyl)-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		LCMS: m/z 320.0 (M ⁺ +1) ¹ HNMR (400 MHz, DMSO): δ 2.41 (t, J = 4.4 Hz, 4H), 3.60 (t, J = 5.2 Hz, 4H), 3.72 (s, 2H), 6.62 (s, 1H), 7.79 (s, 1H), 12.42 (bs, 1H, -NH)

[0292]

Intermediate 2-XVII: 4-[[1-(benzenesulfonyl)-4-chloro-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine

[0293]

**Intermediate 2-I****Intermediate 2-XVII**

5

[0294]

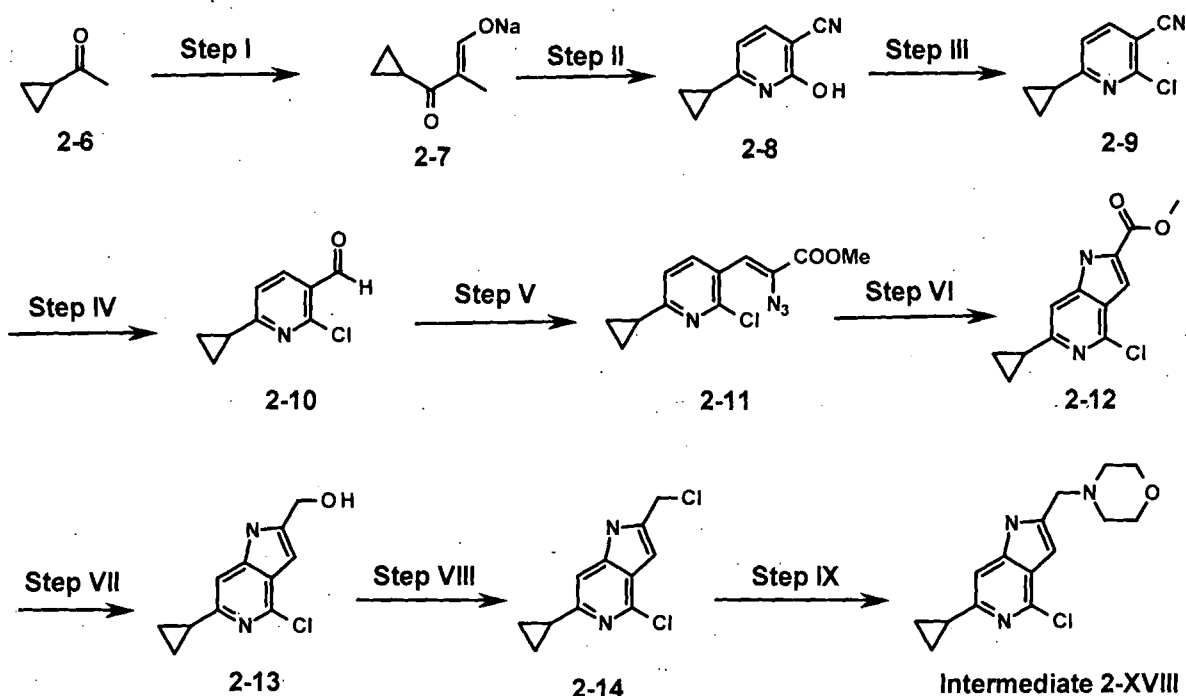
To a solution of **Intermediate 2-I** (1.40 g, 5.9 mmol) in dry THF (25 mL) at 0°C was added NaH (60% in mineral oil, 0.478 g, 11.9 mmol) portion wise. The resulting reaction mixture was gradually allowed to attain room temperature. After 1 hour, the reaction mixture was again cooled to 0°C, and benzenesulfonyl chloride (0.9 mL, 7.1 mmol) was added thereto over a period of 10 minutes. After stirring at room temperature for 16 hours, the reaction mixture was diluted

with saturated aqueous NH_4Cl solution (10 mL) and ice water (100 mL), followed by extraction using ethyl acetate (50 mL X 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using 2% MeOH in dichloromethane to give the desired product **Intermediate 2-XVII** (0.95 g, 44%) as a yellow solid; LCMS: m/z 392.0 [$\text{M}^+ + 1$].

[0295]

Intermediate 2-XVIII: 4-[(4-chloro-6-cyclopropyl-1H-pyrrolo[3,2-c]pyridin-2-yl)methyl]morpholine

[0296]



[0297]

Step I: (E)-1-cyclopropyl-2-methyl-but-2-en-1-one (**2-7**)

2-7 was prepared from **2-6** according to the procedure described in in US 5438033.

[0298]

Step II: 6-cyclopropyl-2-hydroxy-pyridine-3-carbonitrile (**2-8**)

2-8 was prepared from **2-7** according to the procedure described in in US 5438033.

[0299]

Step III: 2-chloro-6-cyclopropyl-pyridine-3-carbonitrile (**2-9**)

2-9 was prepared from **2-8** according to the procedure described in in US 5438033.

[0300]

5 Step IV: 2-chloro-6-cyclopropyl-pyridine-3-carbaldehyde (**2-10**)

To a stirred solution of **2-9** (7 g, 39.3 mmol) at -40°C in toluene (70 mL) was added DIBAL-H (1M in toluene, 5.59 g, 39.3 mmol, 39.3 mL) in drop wise manner over a period of 30 mins. The reaction mixture was stirred for additional 1 hour. After
10 completion of reaction (monitored by TLC), the reaction mixture was poured over cold 2 N HCl solution (300 mL). The resulting milky mass was stirred for 1 hour. EtOAc (300 mL) was added thereto, the layers were separated, and the aqueous layer was extracted with EtOAc (100 mL x 3). The combined
15 organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the desired product **2-10** (6 g, 84 %) as a yellow solid; LCMS: *m/z* 182.0 (M⁺ +1).

[0301]

20 Step V: methyl (Z)-2-azido-3-(2-chloro-6-cyclopropyl-3-pyridyl)prop-2-enoate (**2-11**)

2-11 was prepared from **2-10** in the same manner as in the preparation of **2-2** from **2-1**.

[0302]

25 Step VI: methyl 4-chloro-6-cyclopropyl-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (**2-12**)

2-12 was prepared from **2-11** in the same manner as in the preparation of **2-3** from **2-2**.

[0303]

30 Step VII: (4-chloro-6-cyclopropyl-1H-pyrrolo[3,2-c]pyridin-2-yl)methanol (**2-13**)

2-13 was prepared from **2-12** in the same manner as in the preparation of **2-4** from **2-3**.

[0304]

35 Step VIII: 4-chloro-2-(chloromethyl)-6-cyclopropyl-1H-

pyrrolo[3,2-c]pyridine (**2-14**)

2-14 was prepared from **2-13** in the same manner as in the preparation of **2-5** from **2-4**.

[0305]

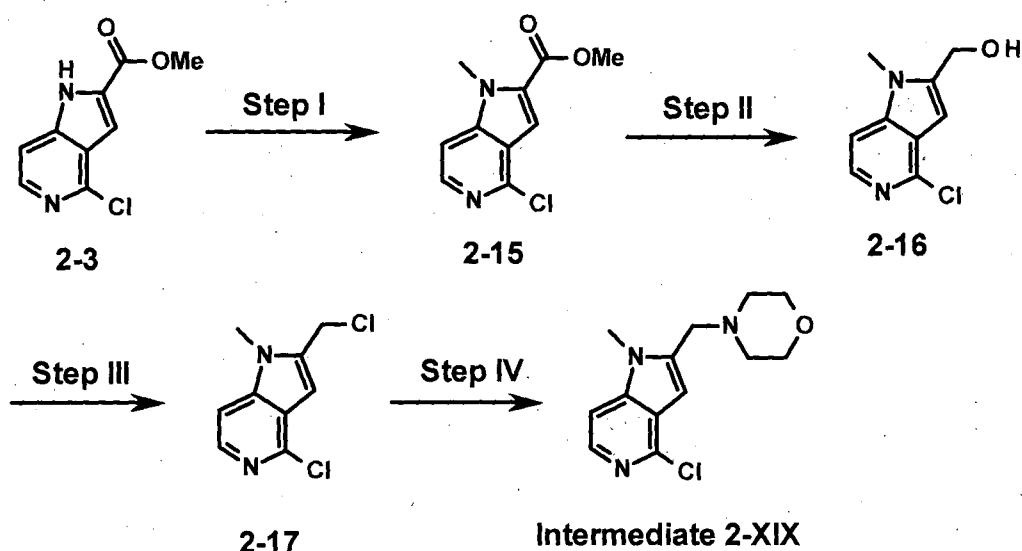
- 5 Step IX: 4-[(4-chloro-6-cyclopropyl-1H-pyrrolo[3,2-c]pyridin-2-yl)methyl]morpholine (**Intermediate 2-XVIII**)

Intermediate 2-XVIII was prepared from **2-14** in the same manner as in the preparation of **Intermediate 2-I** from **2-5**.

[0306]

- 10 **Intermediate 2-XIX**: 4-[(4-chloro-1-methyl-pyrrolo[3,2-c]pyridin-2-yl)methyl]morpholine

[0307]



[0308]

- 15 Step I: methyl 4-chloro-1-methyl-pyrrolo[3,2-c]pyridine-2-carboxylate (**2-15**)

To an ice cold solution of **2-3** (0.5 g, 2.36 mmol) in anhydrous DMF (3 mL) was added NaH (60% in mineral oil) (0.113 g, 2.84 mmol), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was recooled to 0°C and treated with MeI (0.402 g, 2.83 mmol), and stirring was continued for 1 hour. The reaction mixture was allowed to attain room temperature and stirred for 1 more hour. The reaction mixture was diluted with ice water, and the solid separated was collected by filtration and dried under vacuum

25

to give the desired product **2-15** (0.460 g, 86%) as a yellow solid; LCMS: m/z 225.0 ($M^+ + 1$).

[0309]

Step II: (4-chloro-1-methyl-pyrrolo[3,2-c]pyridin-2-yl)methanol (**2-16**)

To a stirred solution of **2-15** (0.46 g, 2.04 mmol) in anhydrous THF (5 mL) was added LiAlH_4 (0.116 g, 3.8 mmol) in portions at 0°C. After stirring at the same temperature for 2 hours, the reaction mixture was allowed to cool to room temperature and stirred for additional 2 hours. Excess of LiAlH_4 was decomposed by adding saturated Na_2SO_4 solution and ethyl acetate (25 mL). The inorganic solid was removed by filtration through a celite pad. The filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (60-120 mesh) by eluting with 1% MeOH in DCM to give the desired product **2-16** (0.32 g, 80%) as a pale brown solid; LCMS: m/z 197.1 ($M^+ + 1$).

[0310]

Step III: 4-chloro-2-(chloromethyl)-1-methyl-pyrrolo[3,2-c]pyridine (**2-17**)

Thionyl chloride (0.58 mL, 8.15 mmol) was added to a stirred solution of **2-16** (0.32 g, 1.63 mmol) in CH_2Cl_2 (15 mL) at 0°C. After stirring at room temperature for additional 2 hours, the reaction mixture was cooled, and saturated aqueous NaHCO_3 solution (15 mL) was added thereto. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (15 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the desired product **2-17** as a light brown solid (0.31 g, crude yield 88%); LCMS: m/z 215.0 ($M^+ + 1$).

[0311]

Step IV: 4-[(4-chloro-1-methyl-pyrrolo[3,2-c]pyridin-2-yl)methyl]morpholine (**Intermediate 2-XIX**)

To a mixture of **2-17** (0.3 g, 1.39 mmol) and morpholine (0.24 mL, 2.78 mmol) in DMF (2 mL) was added N,N-

diisopropylethylamine (0.7 mL, 4.17 mmol) at room temperature. After stirring for 16 hours, the excess solvent was removed under reduced pressure, and the obtained residue was diluted with ice water. The resulting solid was collected by

5 filtration and purified using preparative TLC in 50% EtOAc in hexanes to give the desired product **Intermediate 2-XIX** (0.250 g, 68%) as a pale yellow solid; LCMS: m/z 266.0 ($M^+ + 1$).

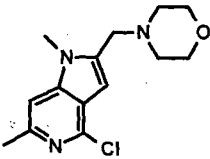
^1H NMR (400 MHz, CDCl_3): δ 2.43 (t, $J = 4.4$ Hz, 4H), 3.64 (s, 2H), 3.69 (t, $J = 4.8$ Hz, 4H), 3.82 (s, 3H), 6.50 (d, $J = 0.4$ Hz, 1H), 7.15 (dd, $J = 6, 0.8$ Hz, 1H), 8.06 (d, $J = 6$ Hz, 1H)
[0312]

Intermediate 2-XX as shown in Table 6 was prepared from its corresponding intermediate in the same manner as

Intermediate 2-XIX.

15 [0313]

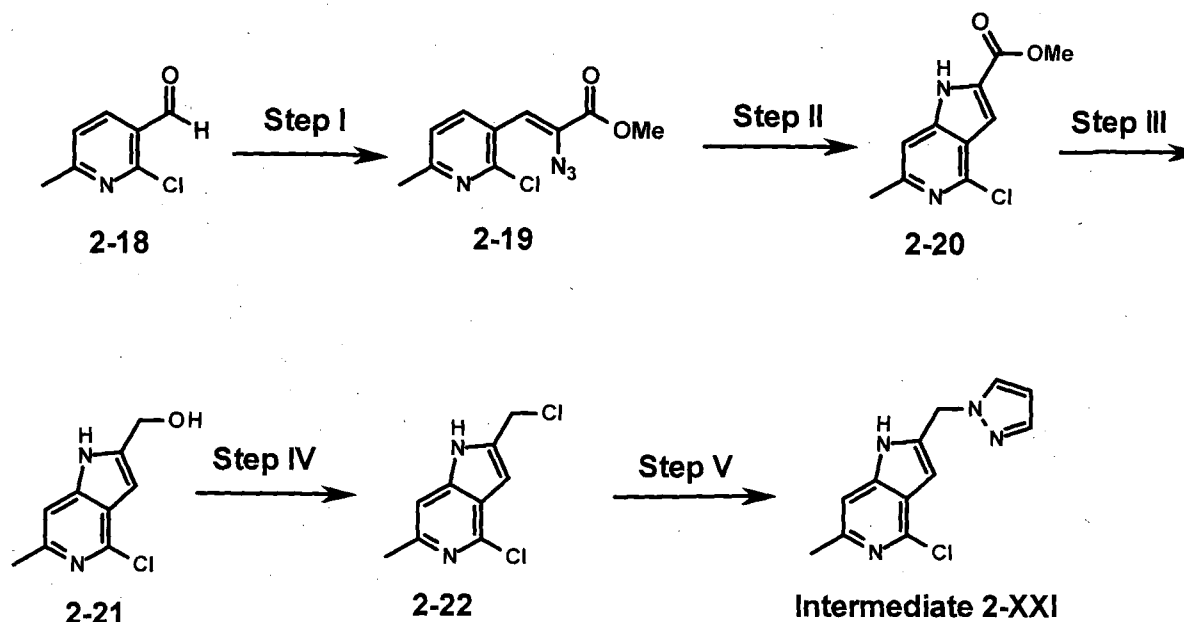
Table 6:

Int.No.	IUPAC name	Structure	Analytical Data
2-XX	4-[(4-chloro-1,6-dimethyl-pyrrolo[3,2-c]pyridin-2-yl)methyl]morpholine		LCMS: m/z 280.0 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3): δ 2.47 (t, $J = 4.4$ Hz, 4H), 2.61 (s, 3H), 3.61 (s, 2H), 3.67 (t, $J = 4.9$ Hz, 4H), 3.77 (s, 3H), 6.44 (s, 1H), 6.97 (s, 1H)

[0314]

Intermediate 2-XXI: 4-chloro-6-methyl-2-(pyrazol-1-ylmethyl)-1H-pyrrolo[3,2-c]pyridine

20 [0315]



[0316]

Step I: methyl (Z)-2-azido-3-(2-chloro-6-methyl-3-
 5 pyridyl)prop-2-enoate (**2-19**)

2-19 was prepared from **2-18** in the same manner as in the preparation of **2-2** from **2-1**.

[0317]

Step II: methyl 4-chloro-6-methyl-1H-pyrrolo[3,2-c]pyridine-2-
 10 carboxylate (**2-20**)

2-20 was prepared from **2-19** in the same manner as in the preparation of **2-3** from **2-2**.

[0318]

Step III: (4-chloro-6-methyl-1H-pyrrolo[3,2-c]pyridin-2-
 15 yl)methanol (**2-21**)

2-21 was prepared from **2-20** in the same manner as in the preparation of **2-4** from **2-3**.

[0319]

Step IV: 4-chloro-2-(chloromethyl)-6-methyl-1H-pyrrolo[3,2-
 20 c]pyridine (**2-22**)

2-22 was prepared from **2-21** in the same manner as in the preparation of **2-5** from **2-4**.

[0320]

Step V: 4-chloro-6-methyl-2-(pyrazol-1-ylmethyl)-1H-

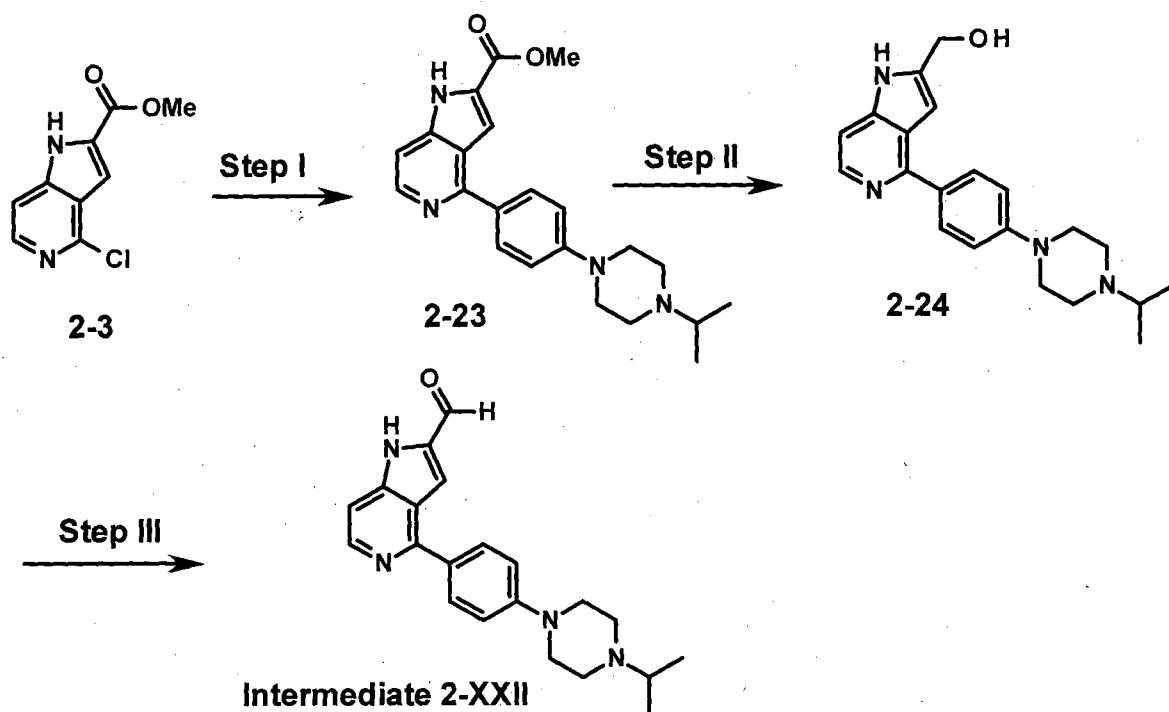
pyrrolo[3,2-c]pyridine (**Intermediate 2-XXI**)

A mixture of **2-22** (0.030 g, 0.441 mmol) and K_2CO_3 (0.183 g, 1.323 mmol) in DMF (3 mL) was heated at 45°C. After 3 hours, the excess solvent was removed under reduced pressure, and the
 5 obtained residue was diluted with ice water. The resulting solid was collected by filtration and taken into EtOAc (20 mL), and the mixture was washed with brine (15 mL). The organic layer was dried over anhydrous Na_2SO_4 , and solvent was evaporated to give the desired product **Intermediate 2-XXI**
 10 (0.055 g, 51%) as a brown syrup; LCMS: m/z 247.1 ($M^+ + 1$).

[0321]

Intermediate 2-XXII: 4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridine-2-carbaldehyde

[0322]



15

[0323]

Step I: methyl 4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (**2-23**)

A mixture of **2-3** (1.5 g, 7.10 mmol), **Intermediate 1-II**
 20 (2.64 g, 7.8 mmol) and K_2CO_3 (2.9 g, 21.3 mmol) in 4:1 mixture of dioxane/water (120 mL) was degassed in a stream of argon for 30 minutes. To the mixture was added tetrakis

(triphenylphosphine)palladium (0.411 g, 0.351 mmol), and the reaction mixture was again degassed for additional 30 minutes. After stirring at 90°C for 18 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with
5 water (50 mL), followed by extraction with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using 5% MeOH in dichloromethane to
10 give the desired product **2-23** (1.65 g, 62%) as a yellow solid; LCMS: *m/z* 379.1 [M⁺+1].

[0324]

Step II: [4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methanol (**2-24**)

15 To a stirred solution of **2-23** (1.50 g, 3.96 mmol) in anhydrous THF (25 mL) was added LiAlH₄ (0.377 g, 9.92 mmol) in portions at 0°C. After stirring at the same temperature for 2 hours, the reaction mixture was allowed to cool to room temperature and stirred for additional 2 hours. Excess of
20 LiAlH₄ was decomposed by adding saturated Na₂SO₄ solution (10 mL) and ethyl acetate (25 mL). The inorganic solid was removed by filtration through a celite pad. The filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (60-120 mesh)
25 by eluting with 10% MeOH in dichloromethane to give the desired product **2-24** (0.85 g, 61%) as a yellow solid; LCMS: *m/z* 351.1 (M⁺+1).

[0325]

Step III: 4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridine-2-carbaldehyde (**Intermediate 2-XXII**)
30

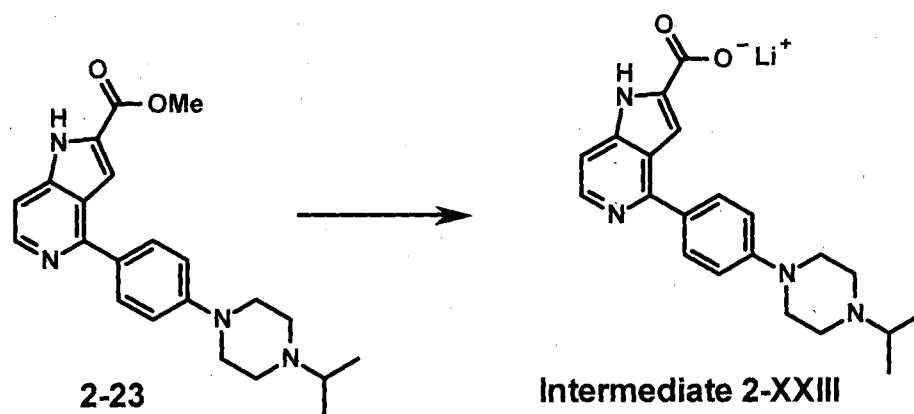
Dess Martin periodinate (1.18 g, 2.78 mmol) was added to a stirred solution of **2-24** (0.650 g, 1.857 mmol) in CH₂Cl₂ (20 mL) at 0°C, and the reaction mixture was stirred for 18 hours at room temperature. The reaction mixture was diluted with
35 dichloromethane (50 mL), and insoluble substance was removed

by filtration through a celite pad. The filtrate was washed with 10% aqueous sodium thiosulfate solution (20 mL), followed by saturated aqueous NaHCO₃ solution. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (50 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the desired product **Intermediate 2-XXII** (0.450 g, 70%) as a yellow solid; LCMS: *m/z* 349.2 (*M*⁺+1).

[0326]

10 **Intermediate 2-XXIII**: lithium 4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-*c*]pyridine-2-carboxylate

[0327]



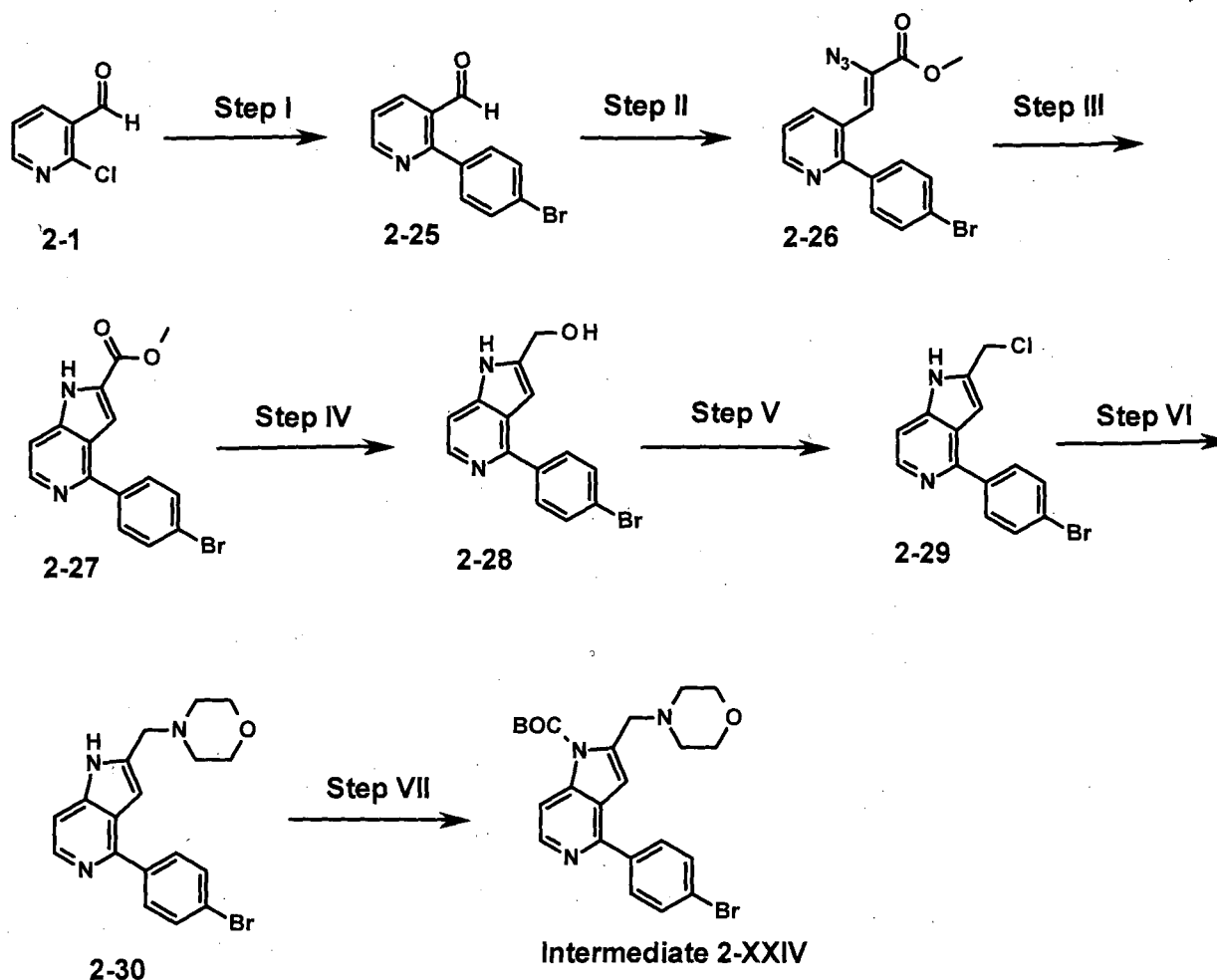
[0328]

15 LiOH H₂O (0.017 g, 0.396 mmol) was added to a stirred solution of **2-23** (0.150 g, 0.396 mmol) in a mixture of THF:MeOH:H₂O (3:2:1 ratio, 5 mL) at room temperature, and the reaction mixture was stirred for 18 hours at the same temperature. The volatiles were concentrated under reduced pressure to give the desired product **Intermediate 2-XXIII** (0.144 g, 83%) as a yellow solid; LCMS: *m/z* 365.1 [*M*⁺+1].

[0329]

Intermediate 2-XXIV: tert-butyl 4-(4-bromophenyl)-2-(morpholinomethyl)pyrrolo[3,2-*c*]pyridine-1-carboxylate

25 [0330]



[0331]

Step I: 2-(4-bromophenyl)pyridine-3-carbaldehyde (**2-25**)

A solution of **2-1** (10 g, 70.6 mmol), (4-bromophenyl)boronic acid (14 g, 70.6 mmol) and Na₂CO₃ (14.98 g, 141.2 mmol) in a mixture of toluene:EtOH:H₂O (4:2:2, 440 mL) was degassed for 30 minutes. To the mixture was added tetrakis(triphenyl phosphine)palladium (0.021 g, 0.018 mmol), and the reaction mixture was again degassed for additional 15 minutes.

After stirring at 90°C for 18 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (50 mL), followed by extraction with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using 8% EtOAc in hexanes as eluent to give the desired product **2-25** (8.5 g, 46%) as a white

solid; LCMS: m/z 263.10 [$M^+ + 1$], 264.0 [$M^+ + 2$].

[0332]

Step II: methyl (Z)-2-azido-3-[2-(4-bromophenyl)-3-pyridyl] prop-2-enoate (**2-26**)

5 To a stirred solution of **2-25** (8.5g, 32.43 mmol) and methyl 2-azidoacetate (9.33 g, 7.90 ml, 81.07 mmol) in methanol (210 mL) was added a freshly prepared NaOMe solution [prepared by dissolving sodium (1.86 g, 81.07 mmol) in methanol (60 mL)] at -10°C over 20 minutes. The resulting
10 reaction mixture was stirred at $0-5^\circ\text{C}$ for 12 hours. The reaction mixture was poured into cold saturated NH_4Cl solution (100 mL). The solid separated was collected by filtration and dried under vacuum to give the desired product **2-26** (2.5 g, 21%) as yellowish solid; LCMS: m/z 360.90 [$M^+ + 1$].

15 [0333]

Step III: methyl 4-(4-bromophenyl)-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (**2-27**)

A solution of **2-26** (2.5g, 6.96 mmol) in xylene (100 mL) was added dropwise to boiling xylene (200 mL) over a period of
20 20 minutes and held at this temperature for 2 hours. The reaction mixture was allowed to cool to room temperature and then stirred at 0°C for another 1 hour. The solid separated was collected by filtration and dried under vacuum to give the desired product **2-27** (1.4 g, 61%) as a white solid; LCMS: m/z
25 333.0 ($M^+ + 2$).

[0334]

Step IV: [4-(4-bromophenyl)-1H-pyrrolo[3,2-c]pyridin-2-yl]methanol (**2-28**)

To a stirred solution of **2-27** (1.4 g, 4.22 mmol) in
30 anhydrous THF (20 mL) was added LiAlH_4 (0.40 g, 10.56 mmol) in portions at 0°C . After completion of addition, the reaction mixture was allowed to warm at room temperature and stirred for 3 hours. Excess of LiAlH_4 was decomposed by adding saturated aqueous solution of Na_2SO_4 and ethyl acetate (50 mL).
35 The inorganic substance was removed by filtration through a

celite pad and washed with EtOAc (25 mL). The filtrate was concentrated under reduced pressure, and the resulting solid was triturated with diethyl ether to give the desired product **2-28** (1.0 g, 78 %) as a white solid; LCMS: m/z 304.00 [$M^+ + 1$],
5 305.00 [$M^+ + 2$].

[0335]

Step V: 4-(4-bromophenyl)-2-(chloromethyl)-1H-pyrrolo[3,2-c]pyridine (**2-29**)

Thionyl chloride (1.97 g, 1.2 mL, 16.4 mmol) and DMF
10 (catalytic, 1 drop) were added to a stirred solution of **2-28** (1 g, 3.29 mmol) in 1:1 mixture of THF/ CH_2Cl_2 (10 mL) at 0°C. After stirring at room temperature for additional 2 hours, the reaction mixture was cooled, and saturated aqueous $NaHCO_3$ solution (15 mL) was added thereto. The organic layer was
15 separated, and the aqueous layer was extracted with CH_2Cl_2 (15 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the desired product **2-29** (0.95 g, 90%) as a brown solid; LCMS: m/z 322.90 ($M^+ + 1$).

20 [0336]

Step VI: 4-[[4-(4-bromophenyl)-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine (**2-30**)

To a mixture of **2-29** (0.95 g, 2.95 mmol) and morpholine (0.28 mL, 3.25 mmol) in DMF (15 mL) was added *N,N*-
25 diisopropylethylamine (0.77 mL, 4.43 mmol) at room temperature. After stirring for 16 hours, the excess solvent was removed under reduced pressure, and the obtained residue was diluted with water (15 mL), and the mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with
30 brine (50 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using 5% MeOH in dichloromethane as eluent to give the desired product **2-30** (0.9 g, 82%) as a yellow solid; LCMS: m/z 374.0 ($M^+ + 2$).

35 [0337]

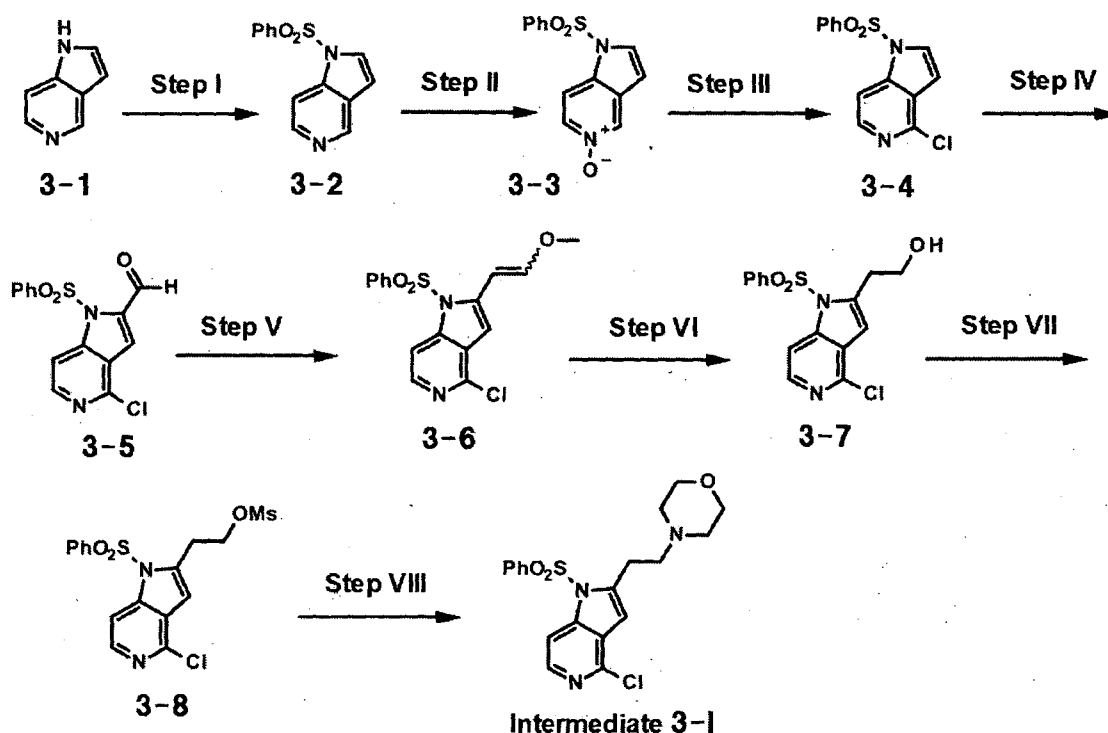
Step VII: tert-butyl 4-(4-bromophenyl)-2-(morpholinomethyl)pyrrolo[3,2-c]pyridine-1-carboxylate
(**Intermediate 2-XXIV**)

To a stirred solution of **2-30** (0.49 g, 0.40 mmol) in THF (5 mL) at room temperature were added Boc anhydride (0.105 g, 0.48 mmol), triethylamine (0.10 g, 0.14 mL, 1.0 mmol) and DMAP (0.005 g, 0.04 mmol). The resulting reaction mixture was stirred for 18 hours. The solvent was removed under reduced pressure. The obtained residue was taken into EtOAc (10 mL) and the mixture was washed with water (10 mL) followed by brine (10 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the desired product **Intermediate 2-XXIV** (0.34, 55%) as an off white solid; LCMS: m/z 474.0 (M⁺+2).

[0338]

Intermediate 3-I: 4-[2-[1-(benzenesulfonyl)-4-chloro-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine

[0339]



[0340]

Step I: 1-(benzenesulfonyl)pyrrolo[3,2-c]pyridine (**3-2**)

A solution of 5-azaindole **3-1** (5 g, 42.3 mmol) in THF (50

mL) was added to a suspension of NaH (60% in mineral oil, 2 g, 50.8 mmol) in THF (50 mL) at 0°C over 30 minutes. The resulting reaction mixture was allowed to warm to room temperature and stirred for 30 minutes. The reaction mixture was again cooled to 0°C, and benzenesulfonyl chloride (6.5 mL, 50.8 mmol) was added thereto over a period of 10 minutes, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with saturated NH₄Cl solution (25 mL) and ethyl acetate (50 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (25 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give the crude product **3-2** (10.5 g, 96%) which was used for next step without purification; LCMS: *m/z* 259.1 [M⁺ + 1].

[0341]

5-Azaindole **3-1** may be commercially available, or can also be produced according to a method known per se or a method analogous thereto.

[0342]

Step II: 1-(benzenesulfonyl)pyrrolo[3,2-*c*]pyridine-*N*-oxide (**3-3**)

m-Chloroperoxybenzoic acid (~70%, 63 g, 369.7 mmol) was added in portions to a stirred solution of **3-2** (9.5 g, 36.9 mmol) in CHCl₃ (250 mL) at room temperature, and the reaction mixture was stirred for 24 hours. The reaction mixture was cooled to 0°C, and 10% aqueous sodium sulfite solution (50 mL) was added thereto followed by saturated aqueous NaHCO₃ solution. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (50 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The obtained residue was triturated with diethyl ether to give the desired product **3-3** as a creamy solid (8.5 g, 84%); LCMS: *m/z* 275.1 [M⁺ + 1].

[0343]

Step III: 1-(benzenesulfonyl)-4-chloro-pyrrolo[3,2-c]pyridine
(3-4)

To a solution of POCl₃ (100 mL) at 0°C was added **3-3** (8.5 g, 31.11 mmol) in portions. The reaction mixture was heated at 90°C for 18 hours. The excess POCl₃ was removed under reduced pressure, and the residue was dissolved in ethyl acetate (200 mL). The solution was washed with saturated aqueous NaHCO₃ solution (100 mL). The organic layer was dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using 10% ethyl acetate in hexanes as eluent to give the desired product **3-4** as a white solid (5.5 g, 70%); LCMS: *m/z* 293.1[M⁺ + 1].

[0344]

Step IV: 1-(benzenesulfonyl)-4-chloro-pyrrolo[3,2-c]pyridine-2-carbaldehyde (3-5)

To a stirred mixture of **3-4** (5.5 g, 18.83 mmol) and tetramethylethylenediamine (2.95 mL, 18.83 mmol) in anhydrous THF was added dropwise lithium diisopropylamide heptane solution (1M in heptane, 38 mL, 37.67 mmol) at -20°C, and the mixture was stirred at this temperature for additional 45 minutes. DMF (2.75 g, 37.67 mmol) was added dropwise thereto over 15 min, and stirring was continued for additional 1 h. The reaction mixture was diluted with saturated aqueous NH₄Cl solution (20 mL) and ethyl acetate (100 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using 15% ethyl acetate in hexanes as eluent to give the desired product **3-5** as yellow solid (3.5 g, 58%); LCMS: *m/z* 321.1[M⁺ + 1].

[0345]

Step V: 1-(benzenesulfonyl)-4-chloro-2-[(*E,Z*)-2-methoxyvinyl]pyrrolo[3,2-c]pyridine (3-6)

To a suspension of methoxymethyltriphenylphosphonium chloride (4.88 g, 14.25 mmol) in anhydrous THF (20 mL) at 0°C was added t-BuOK (0.95 g, 8.55 mmol), and the resulting brown reaction mixture was stirred for 1.5 hour. The reaction
5 mixture was cooled to -78°C, and a solution of **3-5** (1.0 g, 9.25 mmol) in THF (5 mL) was added thereto, and the mixture was stirred at the same temperature for additional 1 hour. The reaction mixture was diluted with saturated NH₄Cl solution (15 mL) and ethyl acetate (25 mL). The organic layer was separated,
10 and the aqueous layer was extracted with ethyl acetate (25 mL x 2). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using 5% ethyl acetate in hexanes as
15 eluent to give the desired product **3-6** (0.62 g, 62%) as yellow oil together with inseparable impurity; LCMS: m/z 349.1 [M⁺+1]. [0346]

Step VI: 2-(1-(benzenesulfonyl)-4-chloro-pyrrolo[3,2-c]pyridin-2-yl)ethanol (**3-7**)

20 A solution of **3-6** (0.62 g, 1.78 mmol) in THF (30 mL) was treated with 6N aqueous HCl (15 mL) at room temperature and stirred at 60°C for 4 h. The volatiles were removed under reduced pressure. The obtained residue was dissolved in ethyl acetate (25 mL), and the solution was washed with saturated
25 aqueous NaHCO₃ solution (15 mL). The organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The obtained crude product 2-(1-(benzenesulfonyl)-4-chloro-pyrrolo[3,2-c]pyridin-2-yl)acetaldehyde (0.51 g) was used for next step without any
30 purification. To a solution of the crude aldehyde (0.51 g, 1.52 mmol) in THF (20 mL) and 10% aqueous methanol was added NaBH₄ (0.134 g, 3.56 mmol) in portions at 0°C, and the resulting reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with 10% aqueous NH₄Cl and
35 ethyl acetate (25 mL). The layers were separated, and the

organic layer was washed with brine (15 mL) and dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The obtained residue was purified by combiflash using 40% ethyl acetate in hexanes as eluent to give the desired product **3-7** (0.46 g, 77% over two steps) as thick yellow liquid; LCMS: *m/z* 337.0 [M⁺ + 1].

[0347]

Step VII: 2-(1-(benzenesulfonyl)-4-chloro-pyrrolo[3,2-c]pyridin-2-yl)ethyl methanesulfonate (**3-8**)

To a solution of **3-7** (0.46 g, 1.36 mmol) in CH₂Cl₂ (8 mL) were added methanesulfonyl chloride (0.16 mL, 2.05 mmol) and Et₃N at 0°C. After 1 h, the reaction mixture was diluted with water (15 mL) and CH₂Cl₂ (25 mL). The layers were separated, and the organic layer was washed with brine (15 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give the crude product **3-8** (0.47 g) as a pale yellow liquid which was used for next step as such without any purification.

[0348]

Step VIII: 4-[2-[1-(benzenesulfonyl)-4-chloro-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine (**Intermediate 3-I**)

To a mixture of crude **3-8** (0.470 g, 1.15 mmol) in anhydrous DMF (5 mL) were added morpholine (0.3g, 3.39 mmol) and *N,N*-diisopropylethylamine (0.44 g, 3.39 mmol) at room temperature. After stirring at 60°C for 16 hours, the excess solvent was removed in vacuo, and the obtained residue was diluted with ice water, followed by extraction with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using 50% ethyl acetate in hexanes as eluent to give the desired product **Intermediate 3-I** (0.17 g, 31% over two steps from mesylate intermediate) as a yellow solid; LCMS: *m/z* 406.0 [M⁺ + 1].

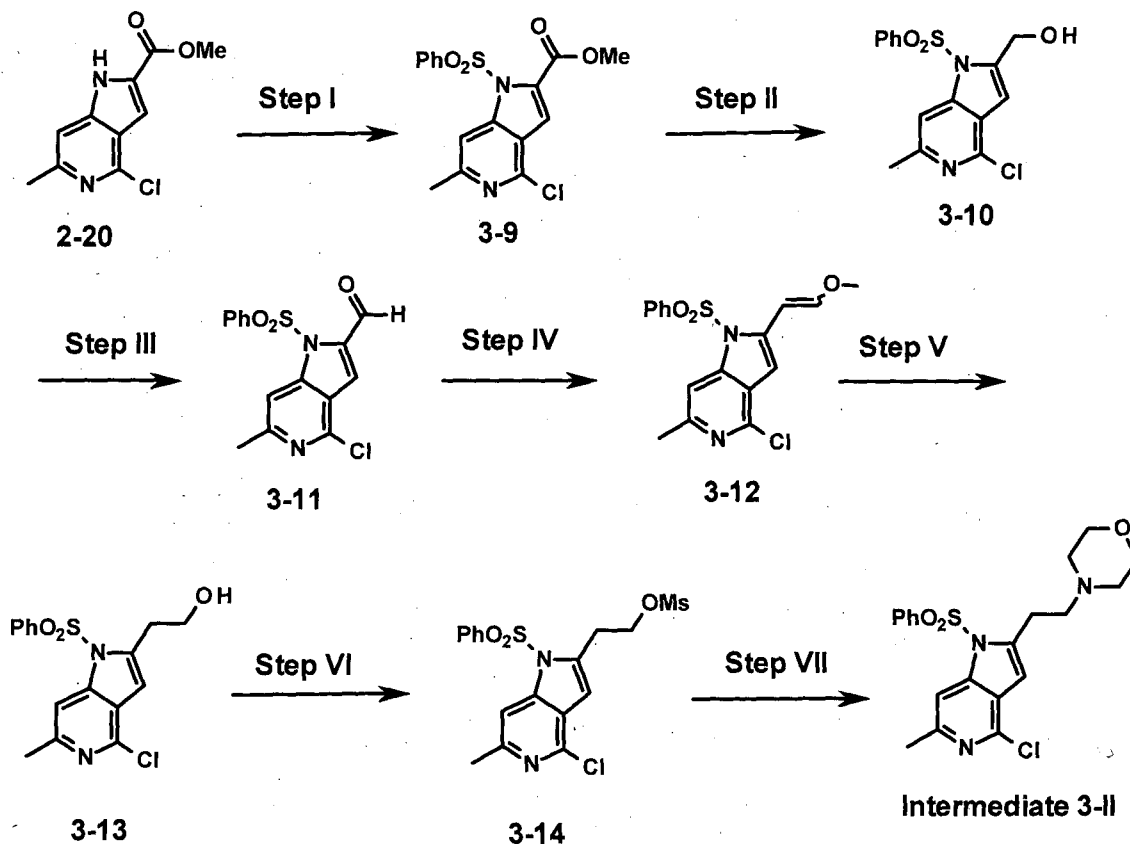
¹HNMR (400 MHz, CDCl₃): δ 2.52 - 2.58 (m, 2H), 2.78 (t, *J* = 7.6 Hz, 2H), 3.20 (t, *J* = 7.2 Hz, 2H), 3.40 (t, *J* = 4.8 Hz, 1H),

3.58 (t, $J = 4.8$ Hz, 1H), 3.67-3.75 (m, 4H), 6.57 (s, 1H),
 7.49 (app. t, $J = 7.6$ Hz, 2H), 7.62 (app. t, $J = 5.2$ Hz, 1H),
 7.78 (d, $J = 7.6$ Hz, 2H), 8.01 (d, $J = 6$ Hz, 1H), 8.21 (d, $J =$
 6 Hz, 1H)

5 [0349]

Intermediate 3-II: 4-[2-[1-(benzenesulfonyl)-4-chloro-6-methyl-
 pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine

[0350]



10 [0351]

Step I: methyl 1-(benzenesulfonyl)-4-chloro-6-methyl-
 pyrrolo[3,2-c]pyridine-2-carboxylate (**3-9**)

To a stirred solution of **2-20** (9 g, 40.17 mmol) in DMF
 (100 mL) at 0°C was added NaH (2.4 g, 60.26 mmol), and the
 15 mixture was stirred for 1.5 hours at room temperature. The
 reaction mixture was again cooled to 0°C, and benzenesulfonyl
 chloride (10.6 g, 7.77 mL, 60.26 mmol) was added thereto. The
 resulting reaction mixture was allowed to warm to room
 temperature, and stirred for 18 hours. The reaction mixture
 20 was poured into ice water, and the resulting precipitate was

filtered over a buchner funnel and dried under high vacuum to give the desired product **3-9** (13.8 g, 94%) as an off white solid which was used for next step without purification; LCMS: m/z 365.0 [$M^+ + 1$].

5 [0352]

Step II: [1-(benzenesulfonyl)-4-chloro-6-methyl-pyrrolo[3,2-c]pyridin-2-yl]methanol (**3-10**)

To a stirred solution of **3-9** (12.6 g, 34.53 mmol) in anhydrous THF (50 mL) was added $LiAlH_4$ (2.62 g, 69.0 mmol) in 10 portions at 0°C. After completion of addition, the reaction mixture was allowed to attain room temperature and stirred for 30 minutes. Excess of $LiAlH_4$ was decomposed by adding saturated solution of Na_2SO_4 . Ethyl acetate (100 mL) was added thereto, and the resulting inorganic solid was removed by 15 filtration through a celite pad. The filtrate was concentrated under reduced pressure, and the resulting solid was triturated with diethyl ether to give the desired product **3-10** (11 g, 95%) as a white solid; LCMS: m/z 337.1 ($M^+ + 1$).

[0353]

20 Step III: 1-(benzenesulfonyl)-4-chloro-6-methyl-pyrrolo[3,2-c]pyridine-2-carbaldehyde (**3-11**)

To a solution of **3-10** (11 g, 32.73 mmol) in CH_2Cl_2 (150 mL) at 0°C was added Dess-martin periodinate (20.8 g, 49.1 mmol) in portions, and the resulting reaction mixture was 25 stirred for 1 hour at 0°C. After completion of reaction (monitored by TLC), the reaction mixture was quenched with saturated sodium thiosulfate solution and washed with saturated sodium bicarbonate solution, water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated 30 under reduced pressure. The obtained residue was triturated with diethyl ether. The obtained solid was collected by filtration and dried under vacuum to give the desired product **3-11** (9 g, 82%) as a white solid ; LCMS: m/z 335.0 ($M^+ + 1$).

[0354]

35 Step IV: 1-(benzenesulfonyl)-4-chloro-2-[(E)-2-methoxyvinyl]-

6-methyl-pyrrolo[3,2-c]pyridine (**3-12**)

t-BuOK (12.09 g, 107.78 mmol) was added to a suspension of methoxymethyltriphenylphosphonium chloride (41.05 g, 119.7 mmol) in anhydrous THF (100 mL) at 0°C. The resulting brown
5 reaction mixture was stirred for 1.5 hours at room temperature. The reaction mixture was cooled to -78°C, **3-11** (8.0 g, 23.95 mmol) was added in one portion, and the resulting reaction mixture was allowed to attain room temperature and stirred for 12 hours. The reaction mixture was diluted with saturated
10 NH₄Cl solution (30 mL) and ethyl acetate (50 mL). The layers were separated. The aqueous layer was back extracted with ethyl acetate (30 mL x 3), and the combined organic layers were washed with brine (50 mL) and dried over anhydrous Na₂SO₄. The obtained residue after evaporation in vacuo was purified
15 by silica gel column chromatography using 15% EtOAc in hexanes to give the desired product **3-12** (3.1 g, 36%) as a yellow solid; LCMS: *m/z* 363.0 (M⁺+1).

[0355]

Step V: 2-[1-(benzenesulfonyl)-4-chloro-6-methyl-pyrrolo[3,2-
20 c]pyridin-2-yl]ethanol (**3-13**)

A stirred solution of **3-12** (3.1 g, 8.54 mmol) in THF (8 mL) was treated with 6N aqueous HCl (8 mL) at room temperature and heated to 60°C for 40 minutes. The reaction mixture was taken into ethyl acetate (20 mL), and the mixture was
25 neutralized with saturated aqueous NaHCO₃ solution (15 mL). The organic layer was separated and washed with brine (15 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was taken into THF:MeOH (3:1, 8 mL), and to this solution was added NaBH₄ (0.65 g, 17.08 mmol)
30 portion wise over a period of 15 minutes. The reaction mixture was stirred for 1 hour at room temperature. The reaction mixture was diluted with water (30 mL) and ethyl acetate (50 mL). The layers were separated. The aqueous layer was back extracted with ethyl acetate (30 mL x 3), and the combined
35 organic layers were washed with brine (50 mL) and dried over

anhydrous Na_2SO_4 . The organic layer was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography using 25% EtOAc in hexanes to give the desired product **3-13** (0.35 g, 12 %) as a yellow oil;

5 LCMS: m/z 350.9 ($M^+ + 1$).

[0356]

Step VI: 2-[1-(benzenesulfonyl)-4-chloro-6-methyl-pyrrolo[3,2-c]pyridin-2-yl]ethyl methanesulfonate (**3-14**)

To a solution of **3-13** (0.35 g, 1.0 mmol) in CH_2Cl_2 (8 mL) were added methanesulfonyl chloride (0.13 mL, 1.20 mmol) and Et_3N (0.30 g, 3.0 mmol) at 0°C . After 1 h, the reaction mixture was diluted with water (15 mL) and CH_2Cl_2 (25 mL). The layers were separated, and the organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure to give the crude product **3-14** (0.42 g) as a pale yellow liquid which was used for next step as such without any purification.

[0357]

Step VII: 4-[2-[1-(benzenesulfonyl)-4-chloro-6-methyl-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine (**Intermediate 3-II**)

To a mixture of crude **3-14** (0.42 g, 0.97 mmol) in anhydrous DMF (5 mL) were added morpholine (0.25 g, 2.93 mmol) and N,N -diisopropylethylamine (0.38 g, 2.93 mmol) at room temperature. After stirring at 60°C for 16 hours, the excess solvent was removed in vacuo, and the obtained residue was diluted with ice water, followed by extraction with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using 50% ethyl acetate in hexanes as eluent to give the desired product **Intermediate 3-II** (0.195 g, 68%, over two steps from mesylate) as a yellow solid; LCMS: m/z 420.0 [$M^+ + 1$].

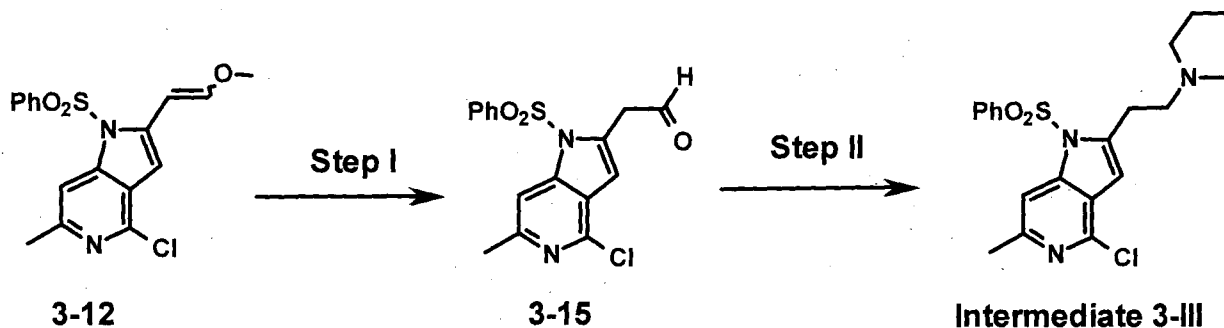
35 ^1H NMR (400 MHz, CDCl_3), δ 2.52 (t, $J = 4.4$ Hz, 4H), 2.64 (s,

3H), 2.75 (t, $J = 7.6$ Hz, 2H), 3.15 (t, $J = 7.6$ Hz, 2H), 3.73 (t, $J = 4.8$ Hz, 4H), 6.51 (s, 1H), 7.50 (d, $J = 8.0$ Hz, 2H), 7.61 (app.t, $J = 7.6$ Hz, 1H), 7.74 (d, $J = 7.6$ Hz, 2H), 7.85 (s, 1H)

5 [0358]

Intermediate 3-III: 4-chloro-6-methyl-1-methylsulfonyl-2-[2-(1-piperidyl)ethyl]pyrrolo[3,2-c]pyridine

[0359]



10 [0360]

Step I: 2-[1-(benzenesulfonyl)-4-chloro-6-methyl-pyrrolo[3,2-c]pyridin-2-yl]acetaldehyde (**3-15**)

A stirred solution of **3-12** (0.5 g, 1.37 mmol) in THF (8 mL) was treated with 6 N aqueous HCl (8 mL) at room

15 temperature and heated to 60°C for 1.5 hours. The reaction mixture was taken into ethyl acetate (20 mL), and the mixture was neutralized with saturated aqueous NaHCO₃ solution (15 mL). The organic layer was separated, washed with brine (15 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced

20 pressure. The crude **3-15** (0.42 g) obtained as a yellow oil was used for next step without any purification.

[0361]

Step II: 4-chloro-6-methyl-1-methylsulfonyl-2-[2-(1-piperidyl)ethyl]pyrrolo[3,2-c]pyridine (**Intermediate 3-III**)

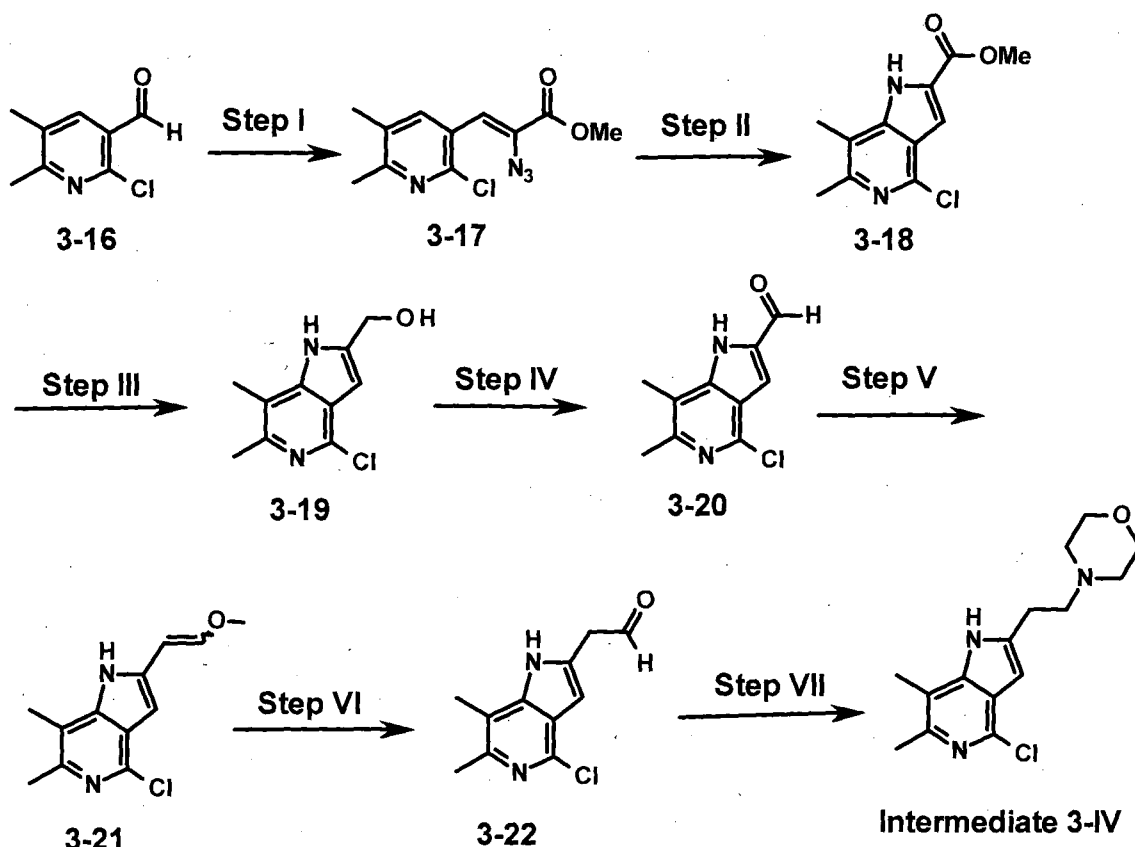
25 To a stirred solution of crude **3-15** (0.42 g, 1.20 mmol) and piperidine (0.15 g, 1.80 mmol) in a mixture of MeOH: dichloroethane (1:1, 8 mL) were added acetic acid (1 drop, catalytic amount) and powdered molecular sieves (1 g). The reaction mixture was stirred for 3 hours at room temperature.

Sodium cyanoborohydride (0.11 g, 1.80 mmol) was added thereto, and the reaction mixture was stirred for 16 hours. After completion of reaction, the reaction mixture was filtered through a celite pad, and the filtrate was concentrated under reduced pressure. The obtained residue was diluted with ethyl acetate (25 mL), and the mixture was washed with saturated aqueous NaHCO₃ solution (15 mL) followed by water and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by preparative TLC using 60% EtOAc in hexanes as solvent system to give the desired product **Intermediate 3-III** (0.22 g, 44%) as a brownish solid; LCMS: *m/z* 418.2 (*M*⁺+1). ¹H NMR (400 MHz, CDCl₃): δ 1.24-1.28 (m, 3H), 1.47-1.50 (m, 3H), 2.52-2.58 (m, 4H), 2.64 (s, 3H), 2.77 (t, *J* = 8.0 Hz, 2H), 3.19 (t, *J* = 8.0 Hz, 2H), 6.50 (s, 1H), 7.50 (d, *J* = 7.6 Hz, 2H), 7.61 (app. t, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 7.2 Hz, 2H), 7.85 (s, 1H)

[0362]

Intermediate 3-IV: 4-[2-(4-chloro-6,7-dimethyl-1H-pyrrolo[3,2-c]pyridin-2-yl)ethyl]morpholine

[0363]



[0364]

Step I: methyl (Z)-2-azido-3-(2-chloro-5,6-dimethyl-3-pyridyl)prop-2-enoate (**3-17**)

To a stirred solution of **3-16** (3.5g, 20.7 mmol) and methyl 2-azidoacetate (9.53 g, 8.07 mL, 82.8 mmol) in methanol (210 mL) was added a freshly prepared NaOMe solution [prepared by dissolving sodium (1.90 g, 82.8 mmol) in methanol (60 mL)] at 0-5°C over 20 minutes. The resulting reaction mixture was stirred at 0-5°C for 12 hours. The reaction mixture was poured into cold saturated NH₄Cl solution (50 mL). The solid separated was collected by filtration and dried under vacuum to give the desired product **3-17** as yellowish solid (3.5 g, 63 %).

[0365]

Step II: methyl 4-chloro-6,7-dimethyl-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (**3-18**)

A solution of **3-17** (3.5g, 14.58 mmol) in xylene (100 mL) was added dropwise to boiling xylene (200 mL) over a period of 20 minutes and held at this temperature for 2 hours. The

reaction mixture was allowed to cool to room temperature and then stirred at 0°C for another 1 hour. The solid separated was collected by filtration and dried under vacuum to give the desired product **3-18** as a white solid (1.1 g, 35 %); LCMS: m/z 239.0 ($M^+ + 1$).

[0366]

Step III: (4-chloro-6,7-dimethyl-1H-pyrrolo[3,2-c]pyridin-2-yl)methanol (**3-19**)

To a stirred solution of **3-18** (3.1 g, 13.02 mmol) in anhydrous THF (50 mL) was added LiAlH_4 (0.98 g, 26.05 mmol) in portions at 0°C. After completion of addition, the reaction mixture was allowed to attain room temperature and stirred for 3 hours. Excess of LiAlH_4 was decomposed by adding saturated solution of Na_2SO_4 and ethyl acetate (100 mL). The inorganic solid was removed by filtration through a celite pad. The filtrate was concentrated under reduced pressure, and the resulting solid was triturated with diethyl ether to give the desired product **3-19** as a white solid (2.51 g, 91%); LCMS: m/z 211.1 ($M^+ + 1$).

[0367]

Step IV: 4-chloro-6,7-dimethyl-1H-pyrrolo[3,2-c]pyridine-2-carbaldehyde (**3-20**)

To a solution of **3-19** (2.5 g, 11.9 mmol) in CH_2Cl_2 (30 mL) at 0°C was added Dess-martin periodinate (7.60 g, 17.8 mmol) in portions, and the resulting reaction mixture was stirred for 1 hour at 0°C. After completion of reaction (monitored by TLC), it was quenched with saturated sodium thiosulfate solution and washed with saturated sodium bicarbonate solution, water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained residue was triturated with diethyl ether, and the solid was collected by filtration and dried under vacuum to give the desired product **3-20** (1.87 g, 75%); LCMS: m/z 209.0 ($M^+ + 1$).

[0368]

Step V: 4-chloro-2-[(E,Z)-2-methoxyvinyl]-6,7-dimethyl-1H-

pyrrolo[3,2-c]pyridine (**3-21**)

t-BuOK (3.39 g, 30.28 mmol) was added to a suspension of methoxymethyltriphenylphosphonium chloride (10.38 g, 30.28 mmol) in anhydrous THF (30 mL) at 0°C, and t-butanol (2.87 mL, 30.28 mmol) was added thereto. The resulting brown reaction mixture was stirred for 3 hours at room temperature. The reaction mixture was cooled to -78°C, **3-20** (0.7 g, 3.36 mmol) was added thereto in one portion, and the resulting reaction mixture was allowed to attain room temperature and stirred for 12 hours. The reaction mixture was diluted with saturated NH₄Cl (30 mL) and ethyl acetate (50 mL). The organic layer was separated. The aqueous layer was back extracted with ethyl acetate (30 mL x 3), and the combined organic layers were washed with brine (50 mL) and dried over anhydrous Na₂SO₄. The obtained residue after evaporation in vacuo was purified by silica gel column chromatography using 15% EtOAc in hexanes to give the desired product **3-21** (0.789 g, 99%) as a yellow solid; LCMS: m/z 237.0 (M⁺+1).

[0369]

Step VI: 2-(4-chloro-6,7-dimethyl-1H-pyrrolo[3,2-c]pyridin-2-yl)acetaldehyde (**3-22**)

A stirred solution of **3-21** (0.65 g, 2.74 mmol) in THF (4 mL) was treated with 6N aqueous HCl (4 mL) at room temperature and heated to 60°C for 40 minutes. The reaction mixture was taken into ethyl acetate (20 mL), and the mixture was neutralized with saturated aqueous NaHCO₃ solution (15 mL). The organic layer was separated and washed with brine (15 mL) and dried over anhydrous Na₂SO₄. The crude compound **3-22** (0.60g, 98%) obtained after evaporation of organic layer was used for next step without any purification.

[0370]

Step VII: 4-[2-(4-chloro-6,7-dimethyl-1H-pyrrolo[3,2-c]pyridin-2-yl)ethyl]morpholine (**Intermediate 3-IV**)

To a stirred solution of **3-22** (0.60 g, 2.70 mmol) and morpholine (0.35 g, 4.05 mmol) in a mixture of

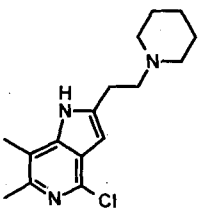
MeOH:dichloroethane (1:1, 10 mL) were added acetic acid (0.24 g, 4.05 mmol) and powdered molecular sieves (1 g), and the reaction mixture was stirred for 3 hours at room temperature. Sodium cyanoborohydride (0.25 g, 4.05 mmol) was added thereto, and the reaction mixture was stirred for 16 hours. After completion of reaction, the reaction mixture was filtered through a celite pad, and the filtrate was concentrated. The obtained residue was diluted with ethyl acetate (25 mL), and the mixture was washed with saturated aqueous NaHCO₃ solution (15 mL) followed by water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using 2% MeOH in dichloromethane to give the desired product **Intermediate 3-IV** (0.40 g, 50%) as a brownish solid; LCMS: m/z 294.1 ($M^+ + 1$).

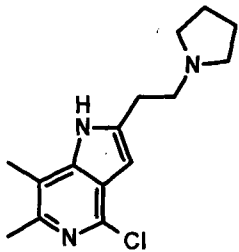
¹H NMR (400 MHz, CDCl₃): δ 2.35 (s, 3H), 2.54 (s, 3H), 2.60-2.64 (m, 4H), 2.77 (t, J = 6.0 Hz, 2H), 2.95 (t, J = 6.0 Hz, 2H), 3.84 (t, J = 4.4 Hz, 4H), 6.26 (s, 1H), 10.61 (bs, 1H, -NH)

[0371]

Intermediates 3-V and **3-VI** as shown in Table 7 were prepared from **3-9** in the same manner as **Intermediate 3-IV**

Table 7:

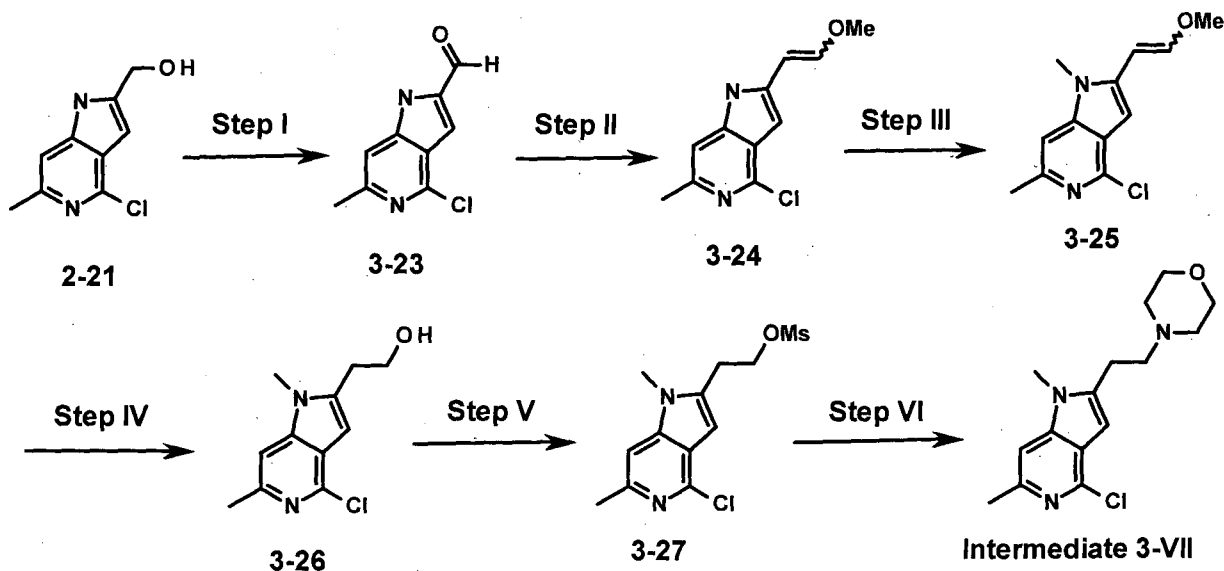
Int.No.	IUPAC name	Structure	Analytical Data
3-V	4-chloro-6,7-dimethyl-2-[2-(1-piperidyl)ethyl]-1H-pyrrolo[3,2-c]pyridine		LCMS: m/z 292.1 ($M^+ + 1$) ¹ H NMR (400 MHz, DMSO): δ 1.38-1.42 (m, 2H), 1.48-1.53 (m, 4H), 2.34 (s, 3H), 2.37-2.46 (m, 7H), 2.62 (t, J = 7.2 Hz, 2H), 2.89 (t, J = 7.2 Hz, 2H), 6.21 (s, 1H),

			11.42 (bs, 1H, -NH)
3-VI	4-chloro-6,7-dimethyl-2-(2-pyrrolidin-1-ylethyl)-1H-pyrrolo[3,2-c]pyridine		LCMS: m/z 278.2 ($M^+ + 1$) ^1H NMR (400 MHz, DMSO): δ 1.65-1.75 (m, 4H), 2.35 (s, 3H), 2.40 (s, 3H), 2.45-2.55 (m, 4H), 2.78-2.81 (m, 2H), 2.89-2.93 (m, 2H), 6.21 (s, 1H), 11.42 (bs, 1H, -NH)

[0372]

Intermediate 3-VII: 4-[2-(4-chloro-1,6-dimethyl-pyrrolo[3,2-c]pyridin-2-yl)ethyl]morpholine

[0373]



5

[0374]

Step I: 4-chloro-6-methyl-1H-pyrrolo[3,2-c]pyridine-2-carbaldehyde (**3-23**)

To a stirred solution of **2-21** (12 g, 61.22 mmol) in dichloromethane (200 mL) at 0°C was added Dess-martin reagent (31.1 g, 73.46 mmol) in portion wise manner over a period of 30 minutes. The resulting suspension was allowed to stir for additional 2 hours. After completion of reaction (monitored by

TLC), the reaction mixture was diluted with aqueous sodium thiosulfate saturated solution (100 mL) and aqueous saturated sodium bicarbonate solution (100 mL). The resulting suspension was then stirred for 1 hour. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (100 mL x 2). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the desired product **3-23** (10.1 g, 85%) as a yellow solid; LCMS: m/z 195.1 [$M^+ + 1$].

[0375]

Step II: 4-chloro-2-[(E,Z)-2-methoxyvinyl]-6-methyl-1H-pyrrolo[3,2-c]pyridine (**3-24**)

To a suspension of methoxymethyltriphenylphosphonium chloride (159 g, 463.86 mmol) and t-BuOH (15.2 g, 206.16 mmol) in anhydrous THF (300 mL) at 0°C was added t-BuOK (52.05 g, 463.86 mmol), and the resulting orange brown reaction mixture was stirred for 2 hours. The reaction mixture was cooled to -78°C, and a solution of **3-23** (10 g, 51.54 mmol) in THF (50 mL) was added thereto. The reaction mixture was allowed to warm to room temperature during 2 hours and stirred for next 18 hours. The reaction mixture was diluted with saturated NH₄Cl solution (150 mL) and ethyl acetate (500 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (500 mL x 3). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using 10% acetone in hexanes as eluent to give the desired product **3-24** (6.1 g, 54%) as a pale yellow solid; LCMS: m/z 222.9 [$M^+ + 1$].

[0376]

Step III: 4-chloro-2-[(E,Z)-2-methoxyvinyl]-1,6-dimethyl-pyrrolo[3,2-c]pyridine (**3-25**)

A solution of **3-24** (20 g, 90.04 mmol) in anhydrous DMF (150 mL) was treated with NaH (60% in mineral oil) (5.4 g,

135.17 mmol) at 0°C and stirred for 1 hour. To the mixture was added MeI (6.7 mL, 101.6 mmol), and stirring was continued for 1 h at 0°C and then for additional 1 hour at room temperature. The reaction mixture was diluted with ice water, and the solid
5 separated was collected by filtration and dried under vacuum to give the desired product **3-25** (21 g, crude yield 94%) as a yellow solid; LCMS: m/z 236.9 [$M^+ + 1$].

[0377]

Step IV: 2-(4-chloro-1,6-dimethyl-pyrrolo[3,2-c]pyridin-2-
10 yl)ethanol (**3-26**)

A solution of **3-25** (21 g, 88.98 mmol) in THF (250 mL) was treated with 6 N aqueous HCl (50 mL) at room temperature and stirred at 60°C for 4 hours. The volatiles were removed under reduced pressure. The obtained residue was dissolved in ethyl
15 acetate (250 mL), and the solution was washed with saturated aqueous NaHCO₃ solution (150 mL). The organic layer was washed with brine (150 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product 2-(4-chloro-1,6-dimethyl-pyrrolo[3,2-c]pyridin-2-yl)acetaldehyde
20 (18 g) obtained was used for next step without any purification.

To a solution of the crude aldehyde (18 g crude, 87.0 mmol) in THF (80 mL) and 10% aqueous methanol (20 mL) was added NaBH₄ (4.90 g, 133.47 mmol) in portions at 0°C, and the
25 resulting reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with 10% aqueous NH₄Cl and ethyl acetate (500 mL). The layers were separated, the organic layer was washed with brine (150 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The
30 obtained residue was purified by silica gel column chromatography using 2% methanol in DCM as eluent to give the desired product **3-26** (12.2 g, 61% over two steps) as thick yellow liquid; LCMS: m/z 224.9 [$M^+ + 1$].

[0378]

35 Step V: 2-(4-chloro-1,6-dimethyl-pyrrolo[3,2-c]pyridin-2-

yl)ethyl methanesulfonate (**3-27**)

To a solution of **3-26** (12.1 g, 5.38 mmol) in CH₂Cl₂ (200 mL) were added Et₃N (22.5 mL, 161.5 mmol) and methanesulfonyl chloride (6.50 g, 80.70 mmol) successively at 0°C. After 2 hours, the reaction mixture was diluted with water (150 mL) and CH₂Cl₂ (250 mL). The layers were separated, and the organic layer was washed with brine (150 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the crude product **3-27** (13.91 g, crude yield 85%) as a yellow liquid which was used for next step as such without any purification.

[0379]

Step VI: 4-[2-(4-chloro-1,6-dimethyl-pyrrolo[3,2-c]pyridin-2-yl)ethyl]morpholine (**Intermediate 3-VII**)

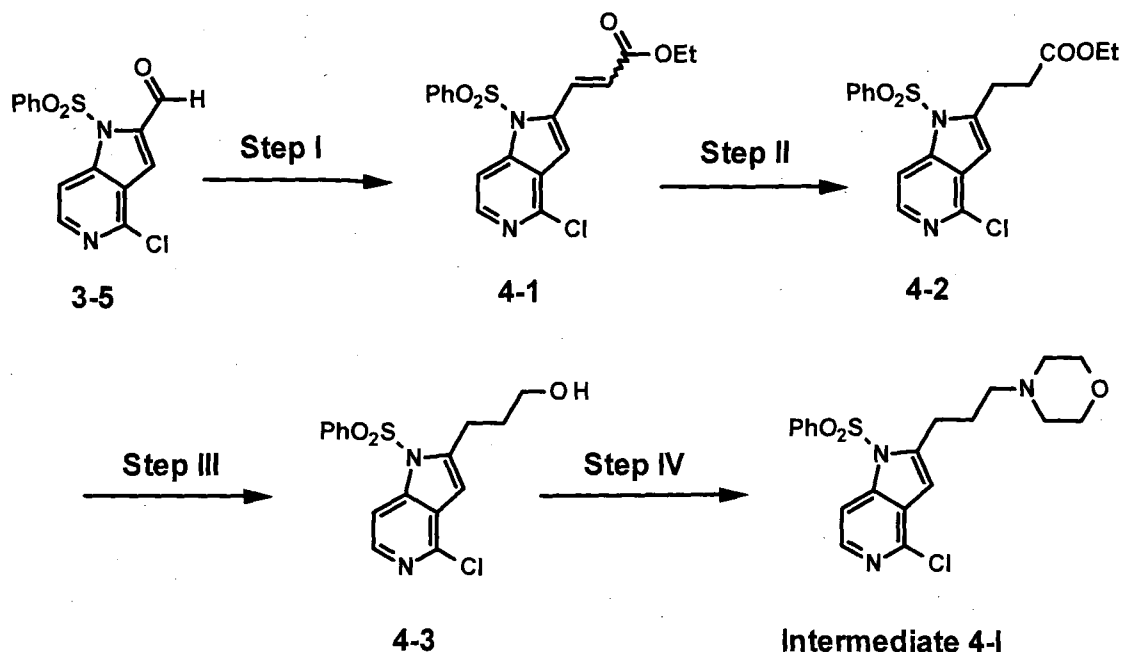
To a mixture of crude **3-27** (2.9 g, 9.57 mmol) in anhydrous DMF (20 mL) were added morpholine (2.50 g, 28.73 mmol) and N,N-diisopropylethylamine (3.70 g, 28.73 mmol) at room temperature. After stirring at 60°C for 16 hours, the excess solvent was removed in vacuo, and the obtained residue was diluted with ice water, followed by extraction with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by Combiflash using 1% MeOH in dichloromethane as eluent to give the desired product **Intermediate 3-VII** (1.88 g, 48% over two steps from mesylate intermediate) as a light yellow solid; LCMS: *m/z* 294.2 [*M*⁺+1].

¹HNMR (400 MHz, CDCl₃): δ 2.55 - 2.57 (t, *J* = 4.8 Hz, 4H), 2.60 (s, 3H), 2.73 - 2.77 (t, *J* = 8.8 Hz, 2H), 2.88 - 2.95 (t, *J* = 8.4 Hz, 2H), 3.66 (s, 3H), 3.74 - 3.77 (t, *J* = 4.8 Hz, 4H), 6.34 (s, 1H), 6.94 (s, 1H)

[0380]

Intermediate 4-I: 4-[3-[1-(benzenesulfonyl)-4-chloro-pyrrolo[3,2-c]pyridin-2-yl]propyl]morpholine

[0381]



[0382]

Step I: ethyl (*E,Z*)-3-[1-(benzenesulfonyl)-4-chloro-pyrrolo[3,2-c]pyridin-2-yl]prop-2-enoate (**4-1**)

5 A mixture of **3-5** (1.0 g, 3.11 mmol) and (carbethoxymethylene)triphenylphosphorane (2.11 g, 6.22 mmol) in toluene (30 mL) was refluxed for 16 hours. Excess of solvent was removed by evaporation under reduced pressure, and the obtained residue was purified by silica gel column chromatography to give the desired product **4-1** (1.05 g, 84%) as a white solid; LCMS: m/z 390.9 [$M^+ + 1$].

[0383]

Step II: ethyl 3-[1-(benzenesulfonyl)-4-chloro-pyrrolo[3,2-c]pyridin-2-yl]propanoate (**4-2**)

15 To a mixture of crude **4-1** (0.7 g, 1.79 mmol) in EtOAc (25 mL) was added PtO_2 (0.150 g) at room temperature. After stirring under hydrogen atmosphere (balloon pressure) at room temperature for 16 hours, the catalyst was removed by filtration through a celite pad and washed with EtOAc, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using 20% AcOEt in hexanes as eluent to give the desired product **4-2** (0.610 g, 86%) as a light yellow solid; 392.9 [$M^+ + 1$].

[0384]

Step III: 3-[1-(benzenesulfonyl)-4-chloro-pyrrolo[3,2-c]pyridin-2-yl]propan-1-ol (**4-3**)

A solution of **4-2** (0.75 g, 1.90 mmol) in dichloromethane (20 mL) was treated with DIBAL-H (1M in toluene; 5.40 mL, 3.81 mmol) at -78°C, and the reaction mixture was stirred at this temperature for another 30 minutes and allowed to warm to room temperature over 2 hours. Excess reagent was quenched with saturated aqueous NH₄Cl solution (30 mL), followed by extraction with ethyl acetate (25 mL x 3). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using 20% AcOEt in hexanes as eluent to give the desired product **4-3** (0.6 g, 89%) as a light yellow liquid; LCMS: *m/z* 351.0 [M⁺+1].

[0385]

Step IV: 4-[3-[1-(benzenesulfonyl)-4-chloro-pyrrolo[3,2-c]pyridin-2-yl]propyl]morpholine (**Intermediate 4-I**)

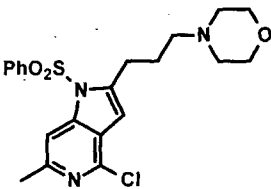
Intermediate 4-I was prepared from **4-3** in the same manner as in the preparation of **Intermediate 3-VII** from **3-26**; LCMS: *m/z* 420.0 [M⁺+1].

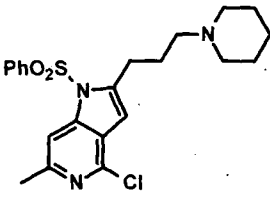
[0386]

Intermediates 4-II and **4-III** as shown in Table 8 were prepared from the corresponding starting material in the same manner as **Intermediate 4-I**

[0387]

Table 8:

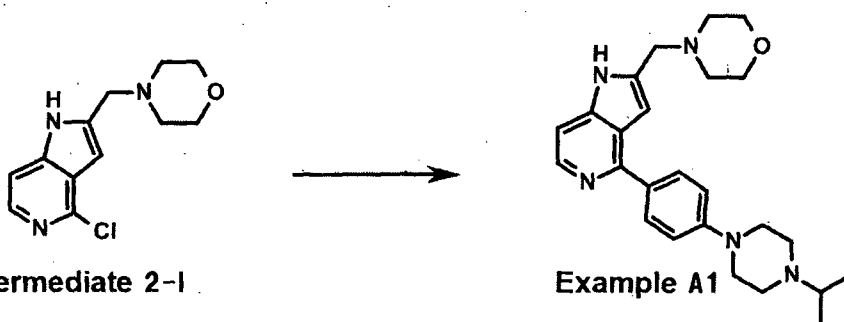
Int.No.	IUPAC name	Structure	Analytical Data
4-II	4-[3-1-(benzenesulfonyl)-(4-chloro-6-methyl-pyrrolo[3,2-c]pyridin-2-		LCMS: <i>m/z</i> 434.3 [M ⁺ +1] ¹ HNMR (400 MHz, CDCl ₃): δ 1.95 (quin., 2H), 2.42 - 2.50 (m, 6H),

	yl)propyl)morpholine		2.64 (s, 3H), 2.98 (t, J = 7.6 Hz, 2H), 3.70 - 3.72 (t, J = 4.4 Hz, 4H), 6.46 (s, 1H), 7.47 - 7.52 (m, 2H), 7.59 - 7.63 (m, 1H), 7.75 (dd, J = 8.4, 0.8 Hz, 2H), 7.86 (s, 1H)
4-III	1-(benzenesulfonyl)-4-chloro-6-methyl-2-[3-(1-piperidyl)propyl]pyrrolo[3,2-c]pyridine		LCMS: m/z 432.2 [M ⁺ +1]

[0388]

Example A1: 4-[[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine

[0389]



5

[0390]

A mixture of **Intermediate 2-I** (0.3 g, 1.19 mmol), 1-isopropyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine (**Intermediate 1-II**) (0.2 g, 1.43 mmol) and K₂CO₃ (0.49 g, 3.58 mmol) in 4:1 mixture of dioxane/water (6 mL) was degassed in a stream of argon for 15 minutes. To the

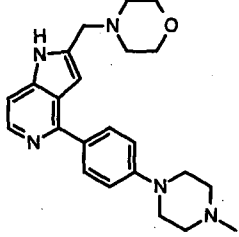
mixture was added tetrakis(triphenylphosphine)palladium (0.021g, 0.018 mmol), and the reaction mixture was again degassed for additional 15 minutes. After stirring at 90°C for 24 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (20 mL) followed by extraction with ethyl acetate (25 mL x 3). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure, followed by preparative TLC purification to give the desired product **Example A1** as a dark yellow solid (0.095 g, 19%); LCMS: *m/z* 420.2 [M⁺+1].

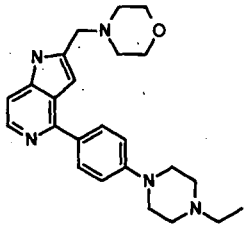
¹H NMR (400 MHz, CDCl₃): δ 1.44 (d, *J* = 6.4 Hz, 6H), 2.35 (s, 1H), 2.45-2.56 (m, 4H), 2.70-2.85 (m, 4H), 3.36 (t, *J* = 4.6 Hz, 4H), 3.68 (s, 2H), 3.71 (t, *J* = 4.4 Hz, 4H), 6.71 (s, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 7.13-7.25 (m, 1H), 7.92 (d, *J* = 8.4 Hz, 2H), 8.33 (d, *J* = 6 Hz, 1H), 9.11 (br s, 1H) [0391]

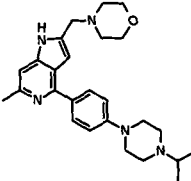
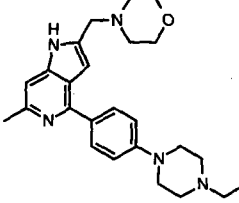
The following compounds **Examples A2-A40** as shown in Table 9 were prepared from the corresponding intermediates in the same manner as **Example A1**.

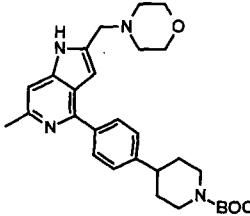
[0392]

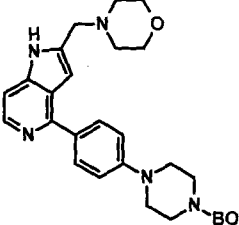
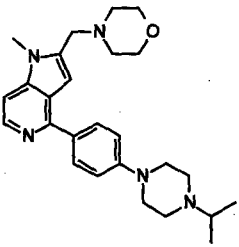
Table 9

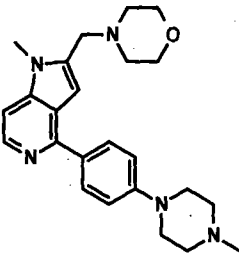
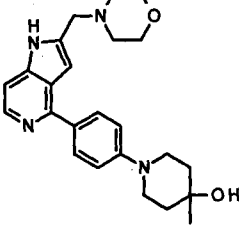
Ex.No.	IUPAC name	Structure	Int. from which prepared	Analytical Data
A2	4-[[4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		2-I and 1-I	LCMS: <i>m/z</i> 392.1 [M ⁺ +1] ¹ H NMR (400 MHz, CDCl ₃): δ 2.38 (s, 3H), 2.42-2.57 (m, 4H), 2.61 (t, <i>J</i> = 4.8 Hz, 4H), 3.32 (t, <i>J</i> = 4.8 Hz, 4H),

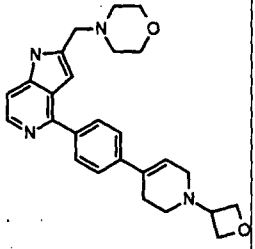
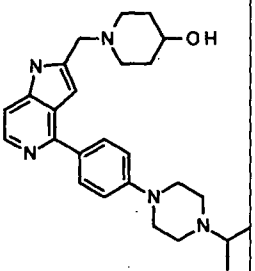
				3.68 (s, 2H), 3.72 (t, J = 4.4 Hz, 4H), 6.70 (s, 1H), 7.04 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 5.6 Hz, 1H), 7.91 (d, J = 8.8 Hz, 2H), 8.33 (d, J = 6 Hz, 1H), 8.99 (br s, 1H)
A3	4-[[4-[4-(4- ethylpiperazi n-1- yl)phenyl]- 1H- pyrrolo[3,2- c]pyridin-2- yl]methyl]mor pholine		2-I and 1-IV	LCMS: m/z 406.3 [M ⁺ +1] ¹ H NMR (400 MHz, CDCl ₃): δ 1.16 (t, J = 7.2 Hz, 3H), 2.48-2.54 (m, 6H), 2.66 (t, J = 4.8 Hz, 4H), 3.34 (t, J = 4.8 Hz, 4H), 3.68 (s, 2H), 3.72 (t, J = 4.4 Hz, 4H), 6.70 (s, 1H), 7.05 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 6 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 8.35 (d, J = 5.6 Hz, 1H),

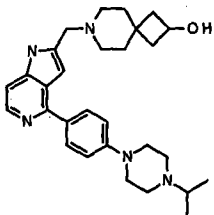
				8.92 (br s, 1H)
A4	4-[[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-6-methyl-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		2-IX and 1-II	LCMS: m/z 434.3 $[M^+ + 1]$ ^1H NMR (400 MHz, CDCl_3): δ 1.13 (d, J = 6.8 Hz, 6H), 2.45-2.50 (m, 4H), 2.68 (s, 3H), 2.73-2.77 (m, 5H), 3.33 (t, J = 4.4 Hz, 4H), 3.64 (s, 2H), 3.71 (t, J = 4.4 Hz, 4H), 6.61 (s, 1H), 7.02 (d, J = 8.8 Hz, 2H), 7.03 (s, 1H, merged in doublet), 7.89 (d, J = 8.8 Hz, 2H), 8.74 (s, 1H)
A5	4-[[4-[4-(4-ethylpiperazin-1-yl)phenyl]-6-methyl-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		2-IX and 1-IV	LCMS: m/z 420.3 $[M^+ + 1]$ ^1H NMR (400 MHz, DMSO-d_6): δ 1.05 (t, J = 7.2 Hz, 3H), 2.35-2.44 (m, 6H), 2.48-2.51 (m, 4H, merged

				in solvent residual peak), 2.52 (s, 3H), 3.20-3.28 (m, 4H), 3.55-3.60 (m, 4H), 3.61 (s, 2H), 6.56 (s, 1H), 7.02-7.09 (m, 3H), 7.86 (d, J = 8.8 Hz, 2H), 11.39 (bs, 1H)
A6	tert-butyl 4-[4-[6-methyl-2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]piperidine-1-carboxylate		2-IX and 1-IX	LCMS: m/z 491.2 $[M^+ + 1]$ ^1H NMR (400 MHz, CDCl_3): δ 1.49 (s, 9H), 1.82-1.89 (m, 2H), 2.45-2.52 (m, 4H), 2.68 (s, 3H), 2.70-2.89 (m, 4H), 3.65 (s, 2H), 3.72 (t, J = 4.4 Hz, 4H), 4.12-4.39 (m, 3H), 6.60 (s, 1H), 7.06 (s, 1H), 7.32 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.4 Hz, 2H), 8.68 (bs, 1H)

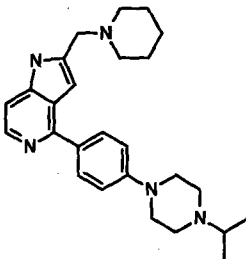
A7	tert-butyl 4-[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]piperazine-1-carboxylate		2-I and 1-III	LCMS: m/z 478.3 [$M^+ + 1$]
A8	4-[[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1-methylpyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		2-XIX and 1-II	LCMS: m/z 434.2 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3): 1.11 (d, J = 6.4 Hz, 6H), 2.46-2.49 (m, 4H), 2.72 (t, J = 4.8 Hz, 4H), 2.73-2.72 (m, 1H), 3.32 (t, J = 4.8 Hz, 4H), 3.65 (s, 2H), 3.68 (t, J = 4.4 Hz, 4H), 3.83 (s, 3H), 6.70 (s, 1H), 7.05 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 6 Hz, 1H), 7.92 (d, J = 8.8 Hz, 2H), 8.36 (d, J = 6 Hz, 1H)

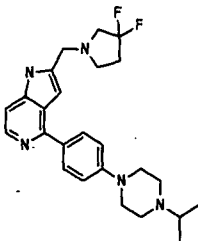
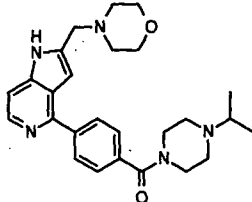
A9	4-[[1-methyl-4-[4-(4-methylpiperazin-1-yl)phenyl]pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		2-XIX and 1-I	LCMS: m/z 406.2 $[M^++1]$ 1H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.45-2.50 (m, 4H), 2.60 (t, J = 4.4 Hz, 4H), 3.16-3.30 (m, 4H), 3.64 (s, 2H), 3.65-3.70 (m, 4H), 3.83 (s, 3H), 6.69 (s, 1H), 7.05 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 6 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 8.38 (d, J = 5.6 Hz, 1H)
A10	4-methyl-1-[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]piperidin-4-ol		2-I and 1-X	LCMS: m/z 407.1 $[M^++1]$ 1H NMR (400 MHz, CD_3OD): δ 1.27 (s, 3H), 1.72-1.76 (m, 4H), 2.51 (t, J = 4.4 Hz, 4H), 3.29-3.34 (m, 2H), 3.46-3.50 (m, 2H), 3.70 (t, J = 5.8 Hz, 6H), 6.71 (s, 1H), 7.13 (d, J

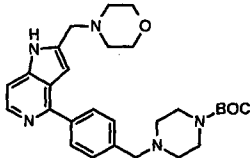
				= 8.8 Hz, 2H), 7.32 (d, J = 6 Hz, 1H), 7.77 (d, J = 8.8 Hz, 2H), 8.11 (d, J = 6 Hz, 1H)
A11	4-[[4-[4-[1-(oxetan-3-yl)-3,6-dihydro-2H-pyridin-4-yl]phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		2-I and 1-XI	LCMS: m/z 431.3 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3): δ 2.46-2.50 (m, 4H), 2.61-2.73 (m, 4H), 3.10 (d, J = 2.4 Hz, 2H), 3.67-3.75 (m, 7H), 4.74 (d, J = 6.8 Hz, 4H), 6.17 (m, 1H), 6.93 (s, 1H), 7.22 (d, J = 5.6 Hz, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.95 (d, J = 8.4 Hz, 2H), 8.39 (d, J = 6 Hz, 1H), 8.83 (br s, 1H)
A12	1-[[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-		2-II and 1-II	LCMS: m/z 434.3 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3): δ 1.11 (d, J = 6.8 Hz, 6H), 1.57-1.63 (m,

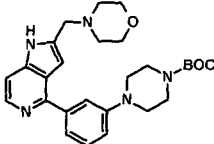
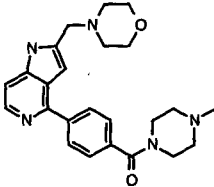
	yl)methyl]piperidin-4-ol			2H), 1.90-1.93 (m, 2H), 2.26 (t, J = 9.6 Hz, 2H), 2.71-2.80 (m, 7H), 3.32 (t, J = 5Hz, 4H), 3.69 (s, 2H), 3.77 (m, 1H), 6.67 (s, 1H), 7.04 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 6 Hz, 1H), 7.91 (d, J = 8.8 Hz, 2H), 8.34 (d, J = 6 Hz, 1H), 9.05 (br s, 1H)
A13	7-[[[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl)methyl]-7-azaspiro[3.5]nonan-2-ol		2-III and 1-II	LCMS: m/z 474.3 [M ⁺ +1] ¹ H NMR (400 MHz, (CD ₃ OD): δ 1.18 (d, J = 6.4 Hz, 6H), 1.62 (q, J = 7.7 Hz, 6H), 2.17-2.22 (m, 2H), 2.43 (s, 4H), 2.86 (t, J = 4.8 Hz, 5H), 3.40 (t, J = 5.0 Hz, 4H), 3.72 (s, 2H), 4.18 (quin, 1H), 6.77 (s, 1H), 7.16 (d, J

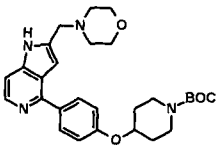
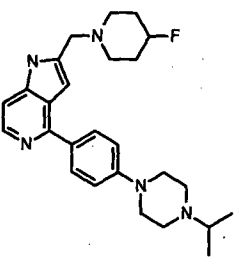
				= 8.8 Hz, 2H), 7.42 (d, J = 5.6 Hz, 1H), 7.81 (d, J = 8.8 Hz, 2H), 8.13 (d, J = 5.6 Hz, 1H)
A14	tert-butyl 4-[3-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]pyridin-2-yl]-3,6-dihydro-2H-pyridin-1-carboxylate		2-I and 1-XII	LCMS: m/z 476.2 [M ⁺ +1]
A15	tert-butyl 4-[3-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]pyridin-2-yl]piperazine-1-carboxylate		2-I and 1-XIII	LCMS: m/z 479.2 [M ⁺ +1]
A16	2-[(3-fluoroazetidin-1-yl)methyl]-4-[4-(4-isopropylpiperazin-1-		2-IV and 1-II	LCMS: m/z 408.3 [M ⁺ +1] ¹ H NMR (400 MHz, CDCl ₃): δ 1.16 (dd, J = 6.8 Hz, 6H), 2.79-2.84 (m,

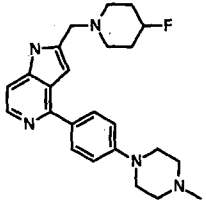
	yl)phenyl]- 1H- pyrrolo[3,2- c]pyridine			5H), 3.26-3.28 (m, 1H), 3.32- 3.34 (m, 1H), 3.35-3.95 (m, 4H), 3.63-3.69 (m, 2H), 3.85 (s, 2H), 5.05- 5.28 (m, 1H), 6.69 (s, 1H), 7.03 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 5.6 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 8.31 (d, J = 5.6 Hz, 1H), 9.20 (br.s, 1H)
A17	4-[4-(4- isopropylpipe razin-1- yl)phenyl]-2- (1- piperidylmeth yl)-1H- pyrrolo[3,2- c]pyridine		2-V and 1-II	LCMS: m/z 418.3 [M ⁺ +1] ¹ H NMR (400 MHz, CDCl ₃): δ 1.11 (d, J = 6.4 Hz, 6H), 1.49 (d, J = 4.4 Hz, 2H), 1.62 (quin, J = 5.6 Hz, 4H), 2.41-2.52 (m, 4H), 2.70-2.76 (m, 5H), 3.31 (t, J = 4.8 Hz, 4H), 3.67 (s, 2H), 6.67 (s, 1H), 7.04 (d, J

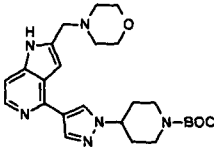
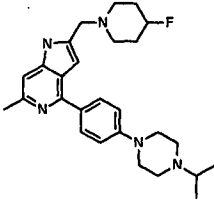
				= 8.8 Hz, 2H), 7.17 (d, J = 6 Hz, 1H), 7.92 (d, J = 8.8 Hz, 2H), 8.34 (d, J = 6 Hz, 1H), 9.20 (br s, 1H)
A18	2-[(3,3- difluoropyrro- lidin-1- yl)methyl]-4- [4-(4- isopropylpipe- razin-1- yl)phenyl]- 1H- pyrrolo[3,2- c]pyridine		2-VI and 1-II	LCMS: m/z 440.3 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3): δ 1.11 (d, J = 6.4 Hz, 6H), 2.31 (sep., 2H), 2.71-2.79 (m, 7H), 2.93 (t, J = 13 Hz, 2H), 3.31 (t, J = 5 Hz, 4H), 3.81 (s, 2H), 6.68 (s, 1H), 7.04 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 5.2 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 8.35 (d, J = 6 Hz, 1H), 8.77 (br.s, 1H)
A19	(4- isopropylpipe- razin-1-yl)- [4-[2- (morpholinome- thyl)-1H-		2-I and 1-XIV	LCMS: m/z 448.20 ($M^+ + 1$) ^1H NMR (400 MHz, CDCl_3): δ 1.08 (d, J = 6.4 Hz, 6H),

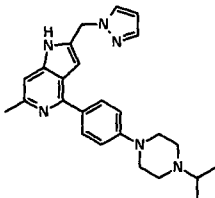
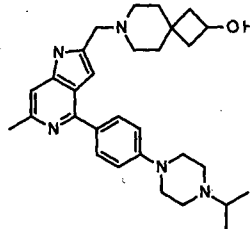
	pyrrolo[3,2-c]pyridin-4-yl]phenyl]methanone			2.45-2.55 (m, 6H), 2.60-2.70 (m, 2H), 2.75-2.82 (m, 1H), 3.48-3.56 (m, 2H), 3.71 (s, 2H), 3.74 (t, J = 4.4 Hz, 4H), 3.80-3.90 (m, 2H), 6.65 (s, 1H), 7.28 (s, 1H), 7.55 (d, J = 7.6 Hz, 2H), 8.00 (d, J = 7.6 Hz, 2H), 8.39 (d, J = 6.0 Hz, 1H), 9.01 (bs, 1H)
A20	tert-butyl 4-[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenylmethyl]piperazine-1-carboxylate		2-I and 1-XVI	LCMS: m/z 492.20 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3) : δ 1.46 (s, 9H), 2.41-2.45 (m, 4H), 2.49 (t, J = 4.4 Hz, 4H), 3.44 (t, J = 4.8 Hz, 4H), 3.59 (s, 2H), 3.69 (s, 2H), 3.73 (t, J = 4.4 Hz, 4H), 6.68 (s, 1H), 7.21 (d, J = 5.6 Hz, 1H),

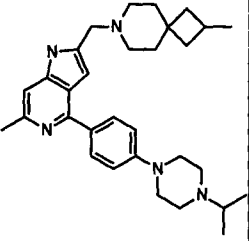
				7.45 (d, J = 7.6 Hz, 2H), 7.93 (d, J = 7.6 Hz, 2H), 8.39 (d, J = 5.2 Hz, 1H), 8.93 (bs, 1H).
A21	tert-butyl 4-[3-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]piperazine-1-carboxylate		2-I and 1-VII	LCMS: m/z 478.3 [M ⁺ +1]
A22	(4-methylpiperazin-1-yl)-[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]methanone		2-I and 1-XV	LCMS: m/z 420.10 [M ⁺ +1] ¹ HNMR (400 MHz, CDCl ₃): δ 2.33 (s, 3H), 2.35-2.46 (m, 2H), 2.51 (t, J = 4.0 Hz, 6H), 3.47-3.52 (m, 2H), 3.70 (s, 2H), 3.73 (t, J = 4.8 Hz, 4H), 3.80-3.90 (m, 2H), 6.65 (s, 1H), 7.27 (d, J = 6.0 Hz, 1H), 7.54 (d, J = 8.4 Hz, 2H), 8.00 (d, J =

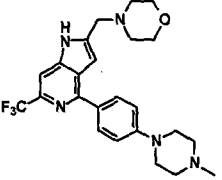
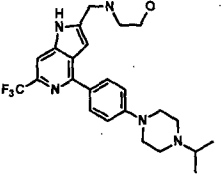
				8.4 Hz, 2H), 8.39 (d, J = 5.6 Hz, 1H), 9.01 (bs, 1H)
A23	tert-butyl 4-[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenoxy]piperidine-1-carboxylate		2-I and 1-XVII	LCMS: m/z 493.10 [M ⁺ +1] ¹ HNMR (400 MHz, CDCl ₃): δ 1.48 (s, 9H), 1.80 - 1.85 (m, 2H), 1.90 - 2.00 (m, 2H), 2.50 (t, J = 4.0 Hz, 4H), 3.30 - 3.40 (m, 2H), 3.65 - 3.69 (m, 4H), 3.73 (t, J = 4.4 Hz, 4H), 4.50 - 4.51 (m, 1H), 6.67 (s, 1H), 7.04 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 5.9 Hz, 1H), 7.92 (d, J = 8.8 Hz, 2H), 8.36 (d, J = 5.8 Hz, 1H), 8.95 (s, 1H)
A24	2-[(4-fluoropiperidyl)methyl]-4-[4-(4-isopropylpiperidyl)]		2-VIII and 1-II	LCMS: m/z 436.3 [M ⁺ +1] ¹ H NMR (400 MHz, CDCl ₃): δ 1.12 (d, J =

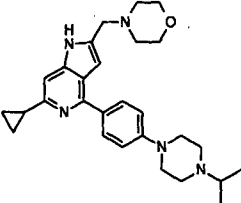
	razin-1- yl)phenyl]- 1H- pyrrolo[3,2- c]pyridine			6 Hz, 6H), 1.87-1.92 (m, 4H), 2.40-2.52 (m, 2H), 2.55- 2.69 (s, 2H), 2.71-2.85 (m, 5H), 3.28-3.42 (m, 4H), 3.70 (s, 2H), 4.62- 4.82 (m, 1H), 6.68 (s, 1H), 7.04 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 6 Hz, 1H), 7.92 (d, J = 7.6 Hz, 2H), 8.34 (d, J = 5.6 Hz, 1H), 9.01 (br s, 1H)
A25	2-[(4-fluoro- 1- piperidyl)met hyl]-4-[4-(4- methylpiperaz in-1- yl)phenyl]- 1H- pyrrolo[3,2- c]pyridine		2-VIII and 1-I	LCMS: m/z 408.3 [M ⁺ +1] ¹ H NMR (400 MHz, CDCl ₃): δ 1.85-1.94 (m, 4H), 2.37 (s, 3H), 2.44 (t, J = 5.8 Hz, 2H), 2.61 (t, J = 4.8 Hz, 6H), 3.32 (t, J = 4.8 Hz, 4H), 3.68 (s, 2H), 4.62-4.82 (m, 1H), 6.67 (s, 1H), 7.04 (d, J

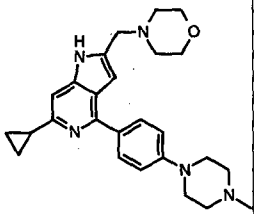
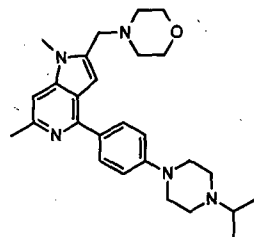
				= 8.8 Hz, 2H), 7.17 (d, J = 6 Hz, 1H), 7.92 (d, J = 8.8 Hz, 2H), 8.34 (d, J = 6 Hz, 1H), 9.00 (br s, 1H)
A26	tert-butyl 4- [4-[2- (morpholinome- thyl)-1H- pyrrolo[3,2- c]pyridin-4- yl]pyrazol-1- yl]piperidine -1- carboxylate		2-I and 1-XVIII	LCMS: m/z 467.3 [$M^+ + 1$]
A27	2-[(4-fluoro- 1- piperidyl)met hyl]-4-[4-(4- isopropylpipe razin-1- yl)phenyl]-6- methyl-1H- pyrrolo[3,2- c]pyridine		2-X and 1-II	LCMS: m/z 450.3 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3): δ 1.14 (d, J = 5.2 Hz, 6H), 1.82-2.08 (m, 5H), 2.42-2.58 (m, 3H), 2.64- 2.76 (m, 9H), 3.25-3.45 (m, 3H), 3.69 (s, 2H), 4.66-4.78 (m, 1H), 6.61 (s, 1H), 7.01- 7.04 (m, 3H), 7.89 (d, J = 7.6 Hz, 2H),

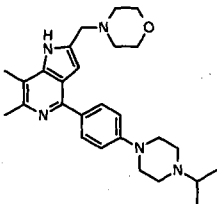
				9.01 (br.s, 1H)
A28	4-[4-(4-isopropylpiperazin-1-yl)phenyl]-6-methyl-2-(pyrazol-1-ylmethyl)-1H-pyrrolo[3,2-c]pyridine		2-XXI and 1-II	LCMS: m/z 415.3 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3): δ 1.16 (d, J = 6 Hz, 6H), 2.66 (s, 3H), 2.71-2.90 (m, 5H), 3.32-3.45 (m, 4H), 5.44 (s, 2H), 6.28 (s, 1H), 6.72 (s, 1H), 6.99-7.02 (m, 3H), 7.50 (s, 1H), 7.59 (s, 1H), 7.86 (d, J = 8.8 Hz, 2H), 9.10 (br.s, 1H)
A29	7-[[[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-6-methyl-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]-7-azaspiro[3.5]nonan-2-ol		2-XI and 1-II	LCMS: m/z 488.3 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3): δ 1.12 (d, J = 6.4 Hz, 6H), 1.60-1.69 (m, 6H), 2.25 (t, J = 10 Hz, 2H), 2.32-2.55 (m, 4H), 2.66 (s, 3H), 2.71-2.78 (m, 5H), 3.30 (t, J = 5 Hz, 4H), 3.67 (s,

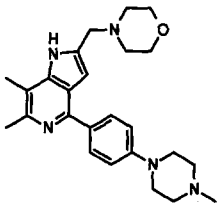
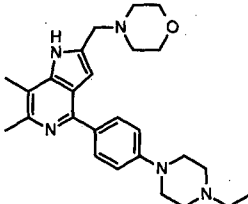
				2H), 4.29 (quin. 1H), 6.59 (s, 1H), 7.03 (d, J = 6.4 Hz, 3H), 7.88 (d, J = 8.8 Hz, 2H), 9.01 (br. s, 1H)
A30	4-[4-(4-isopropylpiperazin-1-yl)phenyl]-6-methyl-2-[(2-methyl-7-azaspiro[3.5]nonan-7-yl)methyl]-1H-pyrrolo[3,2-c]pyridine		2-XII and 1-II	LCMS: m/z 486.4 $[M^+ + 1]$ 1H NMR (400 MHz, $CDCl_3$): δ 1.03 (d, J = 6.8 Hz, 3H), 1.11 (d, J = 6.4 Hz, 6H), 1.32 (t, J = 10 Hz, 2H), 1.54-1.62 (m, 2H), 1.64-1.67 (m, 2H), 1.94 (t, J = 10.2 Hz, 2H), 2.28-2.30 (m, 5H), 2.66 (s, 3H), 2.70-2.75 (m, 5H), 3.29 (t, J = 5 Hz, 4H), 3.66 (s, 2H), 6.58 (s, 1H), 7.01-7.03 (m, 3H), 7.88 (d, J = 8.4 Hz, 2H), 9.05 (br. s, 1H)

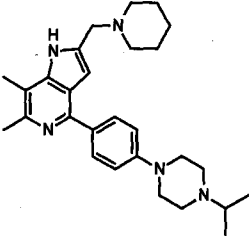
A31	4-[[4-[4-(4-methylpiperazin-1-yl)phenyl]-6-(trifluoromethyl)-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		2-XVI and 1-I	LCMS: m/z 460.2 (M^++1) ^1H NMR (400 MHz, CDCl_3): δ 2.37 (s, 3H), 2.49 (t, J = 4.4 Hz, 4H), 2.61 (t, J = 4.8 Hz, 4H), 3.32 (t, J = 4.8 Hz, 4H), 3.71 (s, 2H), 3.73 (t, J = 4.8 Hz, 4H), 6.76 (s, 1H), 7.04 (d, J = 8.8 Hz, 2H), 7.57 (s, 1H), 7.97 (d, J = 8.8 Hz, 2H), 9.25 (bs, 1H, -NH)
A32	4-[[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-6-(trifluoromethyl)-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		2-XVI and 1-II	LCMS: m/z 488.3 (M^++1) ^1H NMR (400 MHz, CDCl_3): δ 1.11 (d, J = 6.0 Hz, 6H), 2.49 (t, J = 4.4 Hz, 4H), 2.72 (t, J = 4.8 Hz, 4H), 2.72-2.77 (m, 1H), 3.32 (t, J = 5.2 Hz, 4H),

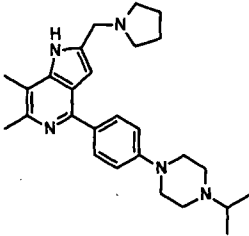
				3.70 (s, 2H), 3.72 (t, J = 4.8 Hz, 4H), 6.76 (s, 1H), 7.04 (d, J = 8.8 Hz, 2H), 7.56 (s, 1H), 7.96 (d, J = 8.8 Hz, 2H), 9.18 (bs, 1H, - NH)
A33	4-[[6- cyclopropyl- 4-[4-(4- isopropylpipe razin-1- yl)phenyl]- 1H- pyrrolo[3,2- c]pyridin-2- yl]methyl]mor pholine		2-XVIII and 1-II	LCMS: m/z 460.4 [M ⁺ +1] ¹ HNMR (400 MHz, CDCl ₃): δ 0.91-0.95 (m, 2H), 1.05- 1.09 (m, 2H), 1.11 (d, J = 6.8 Hz, 6H), 2.11-2.15 (m, 1H), 2.45-2.49 (m, 4H), 2.68- 2.75 (m, 5H), 3.29 (t, J = 5.2 Hz, 4H), 3.63 (s, 2H), 3.70 (t, J = 4.4 Hz, 4H), 6.61 (s, 1H), 6.95 (s, 1H), 7.02 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 8.8 Hz, 2H),

				8.57 (bs ,1H)
A34	4-[[6-cyclopropyl-4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		2-XVIII and 1-I	LCMS: m/z 432.3 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3): δ 0.92-0.95 (m, 2H), 1.04-1.08 (m, 2H), 2.18-2.26 (m, 1H), 2.40 (s, 3H), 2.45-2.52 (m, 4H), 2.62-2.70 (m, 4H), 3.60-3.67 (m, 4H), 3.65 (s, 2H), 3.70-3.78 (m, 4H), 6.61 (s, 1H), 6.96 (s, 1H), 7.02 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 8.8 Hz, 2H), 8.78 (bs ,1H)
A35	4-[[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1,6-dimethylpyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		2-XX and 1-II	LCMS: m/z 448.3 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3): δ 1.13 (d, J = 6.8 Hz, 6H), 2.40-2.50 (m, 4H), 2.70-2.75 (m, 8H), 3.30-3.40 (m, 4H), 3.62 (s, 2H), 3.67 (t, J = 4.4

				Hz, 4H), 3.79 (s, 3H), 6.62 (s, 1H), 6.98 (s, 1H), 7.04 (d, J = 9.3 Hz, 2H), 7.89 (d, J = 8.3 Hz, 2H)
A36	4-[[4-[4-(4- isopropylpipe razin-1- yl)phenyl]- 6,7-dimethyl- 1H- pyrrolo[3,2- c]pyridin-2- yl]methyl]mor pholine		2-XIII and 1-II	LCMS: m/z 448.3[M ⁺ +1] ¹ H NMR (400 MHz, CDCl ₃): δ 1.12 (d, J = 6.4 Hz, 6H), 2.43 (s, 3H), 2.48 (t, J = 4.4 Hz, 4H), 2.66 (s, 3H), 2.72 (t, J = 4.8 Hz, 4H), 2.71-2.79 (m, 1H), 3.30 (t, J = 4.8 Hz, 4H), 3.65 (s, 2H), 3.72 (t, J = 4.4 Hz, 4H), 6.62 (s, 1H), 7.03 (d, J = 8.8 Hz, 2H), 7.88 (d, J = 8.8 Hz, 2H), 8.58 (bs, 1H, - NH)

A37	4-[[6,7-dimethyl-4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		2-XIII and 1-I	LCMS: m/z 420.3 [$M^+ + 1$] 1H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.42 (s, 3H), 2.48 (t, J = 4.0 Hz, 4H), 2.60 (t, J = 4.8 Hz, 4H), 2.65 (s, 3H), 3.29 (t, J = 4.8 Hz, 4H), 3.65 (s, 2H), 3.72 (t, J = 4.4 Hz, 4H), 6.61 (s, 1H), 7.03 (d, J = 8.8 Hz, 2H), 7.88 (d, J = 8.8 Hz, 2H), 8.61 (bs, 1H, -NH)
A38	4-[[4-[4-(4-ethylpiperazin-1-yl)phenyl]-6,7-dimethyl-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		2-XIII and 1-IV	LCMS: m/z 434.3 [$M^+ + 1$] 1H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, J = 7.2 Hz, 3H), 2.42 (s, 3H), 2.47-2.53 (m, 6H), 2.63-2.65 (m, 4H), 2.66 (s, 3H), 3.31 (t, J = 4.8 Hz,

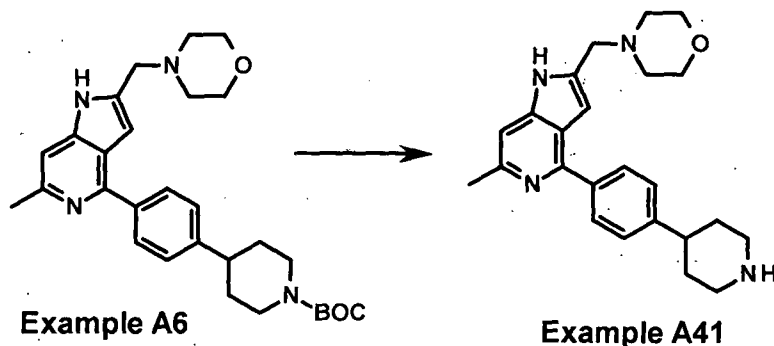
				4H), 3.66 (s, 2H), 3.72 (t, J = 5.2 Hz, 4H), 6.62 (s, 1H), 7.03 (d, J = 8.8 Hz, 2H), 7.88 (d, J = 8.8 Hz, 2H), 8.78 (bs, 1H, -NH)
A39	4-[4-(4-isopropylpiperazin-1-yl)phenyl]-6,7-dimethyl-2-(1-piperidylmethyl)-1H-pyrrolo[3,2-c]pyridine		2-XIV and 1-II	LCMS: m/z 446.3 [M ⁺ +1] ¹ H NMR (400 MHz, CDCl ₃): δ 1.10 (d, J = 6.4 Hz, 6H), 1.45-1.48 (m, 2H), 1.56-1.60 (m, 4H), 2.37-2.42 (m, 4H), 2.42 (s, 3H), 2.64 (s, 3H), 2.71 (t, J = 4.8 Hz, 4H), 2.72-2.76 (m, 1H), 3.28 (t, J = 4.8 Hz, 4H), 3.60 (s, 2H), 6.57 (s, 1H), 7.02 (d, J = 8.8 Hz, 2H), 7.87 (d, J = 8.8 Hz, 2H), 8.72 (bs, 1H, -NH)

A40	4-[4-(4-isopropylpiperazin-1-yl)phenyl]-6,7-dimethyl-2-(pyrrolidin-1-ylmethyl)-1H-pyrrolo[3,2-c]pyridine		2-XV and 1-II	LCMS: m/z 432.3 ($M^+ + 1$) 1H NMR (400 MHz, $CDCl_3$): δ 1.10 (d, $J = 6.4$ Hz, 6H), 1.81-1.89 (m, 4H), 2.41 (s, 3H), 2.53-2.59 (m, 4H), 2.64 (s, 3H), 2.71 (t, $J = 4.8$ Hz, 4H), 2.72-2.76 (m, 1H), 3.28 (t, $J = 4.8$ Hz, 4H), 3.77 (s, 2H), 6.57 (s, 1H), 7.02 (d, $J = 8.8$ Hz, 2H), 7.87 (d, $J = 8.8$ Hz, 2H), 8.69 (bs, 1H, -NH)
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[0393]

Example A41: 4-[[6-methyl-4-[4-(4-piperidyl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine

[0394]



5

[0395]

To a solution of **Example A6** (0.23 g, 0.46 mmol) in CH₂Cl₂ (3 mL) was added 2M HCl in diethyl ether (3 mL) at room temperature, and the reaction mixture was stirred overnight. After completion of reaction (monitored by TLC), the solvent was removed in vacuum, and the residue was neutralized with aqueous saturated sodium bicarbonate solution, and the mixture was dried under vacuum. The resulting solid was washed with 5% methanol-CH₂Cl₂ mixture, and dried in vacuum to give the desired product **Example A41** (0.17g, 92 %) as an off white solid; LCMS: *m/z* 391.1 [M⁺+1].

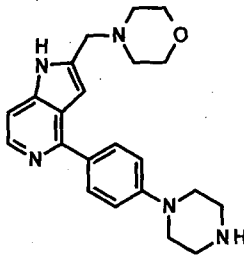
¹H NMR (400 MHz, CDCl₃): δ 1.62-1.73 (m, 2H), 1.78-1.85 (m, 2H), 2.44-2.50 (m, 4H), 2.67 (s, 3H), 2.70-2.74 (m, 1H), 2.77-2.84 (m, 2H), 3.24-3.30 (m, 2H), 3.64 (s, 2H), 3.71 (t, *J* = 4.40 Hz, 4H), 6.60 (s, 1H), 7.05 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 2H), 8.70 (bs, 1H)

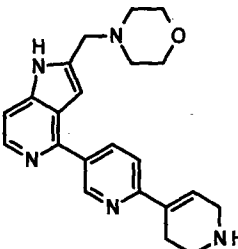
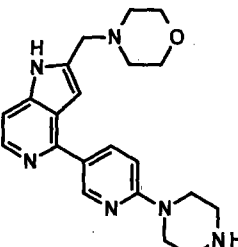
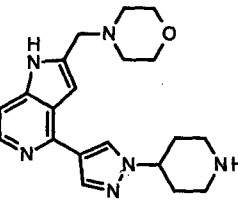
[0396]

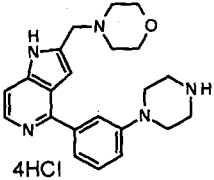
The following compounds **Examples A42 to A46** as shown in Table 10 were prepared in the same manner as **Example A41**. However, for preparation of compounds **Examples A42, A43 and A44**, 3M HCl in methanol was used for deprotection instead of 2M HCl in diethyl ether (as used for **Examples A41**). **Example A46** was prepared as a tetrahydrochloride salt.

[0397]

Table 10:

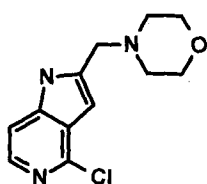
Ex.No.	IUPAC name	Structure	Ex. from which prepared	Analytical data
A42	4-[[4-(4-(piperazin-1-yl)phenyl)-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		A7	LCMS: <i>m/z</i> 378.3 [M ⁺ +1] ¹ H NMR (400 MHz, CD ₃ OD): δ 2.51 (t, <i>J</i> = 4.4 Hz, 4H), 3.01 (t, <i>J</i> = 5.2 Hz, 4H), 3.25 (t, <i>J</i> = 4.8

				Hz, 4H), 3.69-3.71 (m, 6H), 6.66 (s, 1H), 7.11 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 5.6 Hz, 1H), 7.78 (d, J = 8.8 Hz, 2H), 8.12 (d, J = 6 Hz, 1H)
A43	4-[[4-[6-(1,2,3,6-tetrahydropyridin-4-yl)-3-pyridyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		A14	LCMS: m/z 376.1 [M ⁺ +1]
A44	4-[[4-(6-(piperazin-1-yl)-3-pyridyl)-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		A15	LCMS: m/z 379.1 [M ⁺ +1]
A45	4-[[4-[1-(4-piperidyl)pyrazol-4-yl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		A26	LCMS: m/z 367.3 [M ⁺ +1] ¹ H NMR (400 MHz, DMSO-D ₆): 2.17-2.32 (m, 4H), 2.40-2.43 (m, 4H), 3.09 (ddd, J = 15.6, 12.4, 3.6 Hz, 2H), 3.69-3.45 (m, 2H),

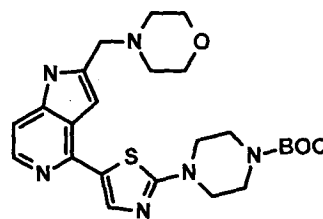
				3.60 (t, J = 4.4 Hz, 4H), 3.67 (s, 2H), 4.60 (sep. 1H), 6.81 (s, 1H), 7.21 (d, 1H), 8.10 (d, J = 5.2 Hz, 1H), 8.19 (s, 1H), 8.31 (s, 1H), 8.47 (br. s, 1H), 8.74 (br. s, 1H)
A46	4-[[4-(3-(piperazin-1-yl)phenyl)-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine	 4HCl	A21	LCMS: m/z 378.3 [M⁺+1] ¹H NMR (400 MHz, DMSO-d₆): δ 3.20-3.28 (m, 6H), 3.32-3.38 (m, 2H), 3.62 (t, J = 5.4 Hz, 4H), 3.82-3.88 (m, 4H), 4.67 (s, 2H), 7.36 (dd, J = 1.9, 8.8 Hz, 1H), 7.47 (d, J = 7.4 Hz, 2H), 7.59 (apt, J = 7.4 Hz, 2H), 8.02 (d, J = 6.4 Hz, 1H), 8.43 (d, J = 6.9 Hz, 1H), 9.41 (s, 2H), 12.15 (bs, 1H), 13.60 (s, 1H), 15.4 (bs, 1H)

[0398]

Example A47: tert-butyl 4-[5-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]thiazol-2-yl]piperazine-1-carboxylate
[0399]



Intermediate 2-I



Example A47

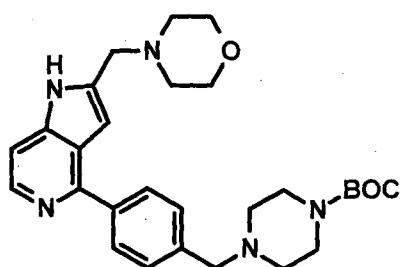
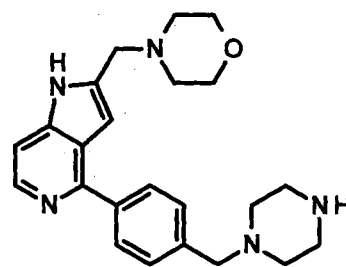
[0400]

A mixture of **Intermediate 2-I** (0.10 g, 0.398 mmol) and crude **Intermediate 1-XIX** (0.5 g, excess) in DMF (1.5 mL) was degassed in a stream of argon for 15 minutes. To this mixture
10 was added 1,1-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (0.028 g, 0.0398 mmol), and the reaction mixture was again degassed for additional 15 minutes. After stirring at 80°C for 18 hours, the volatiles were removed by evaporation, and the obtained residue was
15 diluted with water (20 mL), followed by extraction with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using 1% MeOH in
20 dichloromethane as eluent to give the desired product **Example A47** (0.042 g, 20%) as a brown solid; LCMS: *m/z* 485.1 [M⁺+1].

[0401]

Example A48: 4-[[4-[4-(piperazin-1-ylmethyl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine

25 [0402]

**Example A20****Example A48**

[0403]

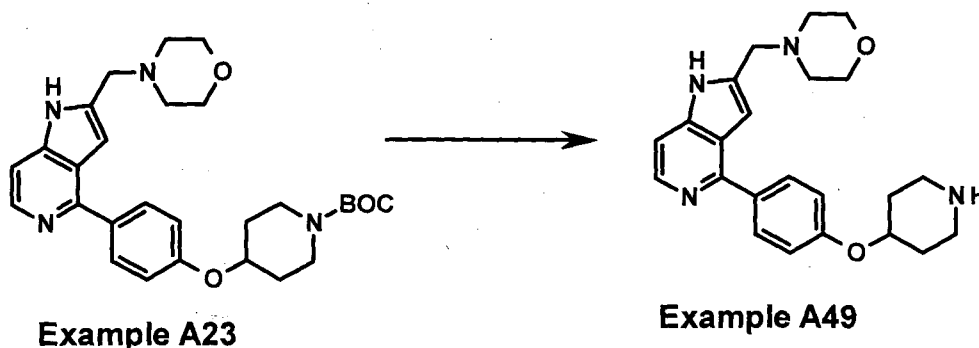
To a stirred solution of **Example A20** (0.64 g, 1.30 mmol) in dichloromethane (2 mL) was added 2 M HCl in diethyl ether (2 mL). The reaction mixture was stirred for 2 hours at room temperature. After completion of reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure to obtain a residue, which was neutralized with saturated aqueous sodium bicarbonate solution (25 mL). The resulting reaction mixture was concentrated under reduced pressure to obtain a white solid, which was dissolved in 5% MeOH in dichloromethane, and the solution was filtered through a celite pad. The obtained filtrate was concentrated under reduced pressure to give the desired product **Example A48** (0.42 g, 82 %) as a brown solid; LCMS: m/z 392.10 $[M^+ + 1]$.

^1H NMR (400 MHz, CDCl_3): δ 2.43 (m, 8H), 2.90 (t, $J = 5.2$ Hz, 4H), 3.57 (s, 2H), 3.68 (s, 2H), 3.72 (t, $J = 4.4$ Hz, 4H), 6.67 (s, 1H), 7.21 (d, $J = 5.6$ Hz, 1H), 7.45 (d, $J = 8.4$ Hz, 2H), 7.92 (d, $J = 8.0$ Hz, 2H), 8.38 (d, $J = 5.6$ Hz, 1H), 8.93 (bs, 1H)

[0404]

Example A49: 4-[[4-[4-(4-piperidyloxy)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine

[0405]

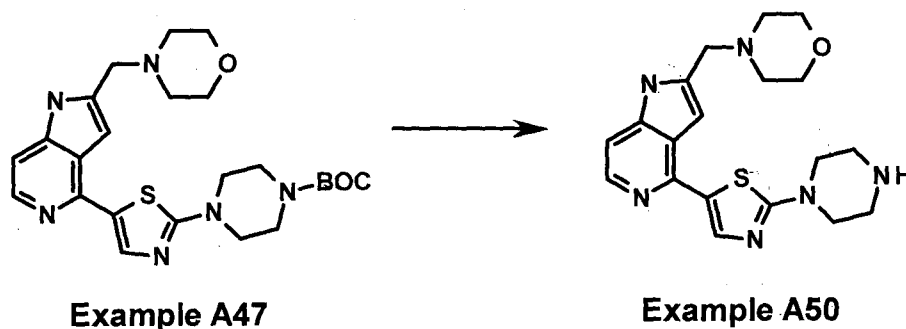


[0406]

To a stirred solution of **Example A23** (0.23 g, 0.46 mmol) in dichloromethane (3 mL) was added 2 M HCl in diethyl ether (3 mL). The reaction mixture was stirred for 18 hours at room temperature. After completion of reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure to give a tetrahydrochloride salt of the desired product **Example A49** (0.17 g, 92%) as a yellow solid; LCMS: m/z 393.3 [M⁺+1].

¹H NMR (400 MHz, DMSO-d₆): 1.85-1.98 (m, 2H), 2.12-2.23 (m, 2H), 3.05-3.30 (m, 8H), 3.80-3.95 (m, 4H), 4.63 (s, 2H), 4.85-4.95 (m, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.96 (d, J = 6.4 Hz, 1H), 8.00 (d, J = 8.8 Hz, 2H), 8.39 (d, J = 6.3 Hz, 2H), 9.04 (aromatics, 2H), 12.0 (bs, 1H), 13.4 (bs, 1H), 15.0 (bs, 1H) [0407]

Example A50: 4-[[4-(2-(piperazin-1-yl)thiazol-5-yl)-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine [0408]



20

[0409]

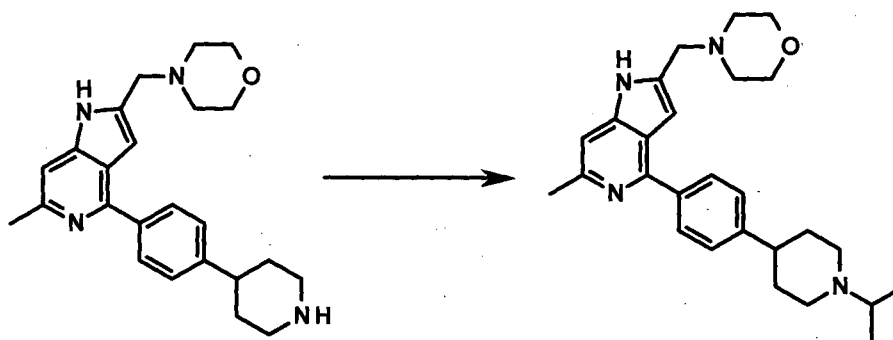
To a solution of **Example A47** (0.060 g, 0.123 mmol) in methanol (1 mL) at 0°C was added 4M HCl in 1,4-dioxane (1 mL).

After stirring at room temperature for 6 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (2 mL), and pH was adjusted to ~8 using saturated aqueous NaHCO₃ solution (3 mL). The resulting solution was evaporated to dryness, and the obtained residue was diluted with 5% MeOH in dichloromethane (20 mL), and the inorganic substance was removed by filtration. The filtrate was concentrated to give the desired product **Example A50** (0.048 g, 99%) as a white solid. The obtained crude product was used for next step without purification; LCMS: m/z 385.1 [M⁺+1].

[0410]

Example A51: 4-[[4-[4-(1-isopropyl-4-piperidyl)phenyl]-6-methyl-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine

15 [0411]

**Example A41****Example A51**

[0412]

To a solution of **Example A41** (0.17 g, 0.43 mmol) and acetone (0.28 g, 0.35 mL, 4.7 mmol) in a mixture of dichloroethane and methanol (2:1, 5 mL) were added a drop of acetic acid and powdered molecular sieves. The reaction mixture was stirred for 3 hours. Sodium cyanoborohydride (0.35 g, 5.6 mmol) was added thereto, and the mixture was stirred overnight. After completion of reaction (monitored by TLC), the resulting solid was removed by filtration, and the filtrate was diluted with water and ethyl acetate. The layers were separated, and the organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, dried

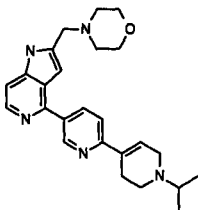
over anhydrous Na₂SO₄, and concentrated in vacuum. The obtained residue was purified by preparative TLC to give the desired product **Example A51** (0.06 g, 32%) as an off white solid; LCMS: *m/z* 433.4 [M⁺+1].

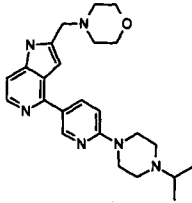
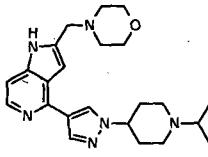
5 ¹H NMR (400 MHz, DMSO-d₆): δ 1.02 (d, *J* = 6.0 Hz, 6H), 1.62-1.73 (m, 2H), 1.78-1.85 (m, 2H), 2.22-2.34 (m, 2H), 2.38-2.42 (m, 4H), 2.49-2.50 (m, 1H, merged in solvent residual peak), 2.53 (s, 3H), 2.72-2.80 (m, 1H), 2.90-2.99 (m, 2H), 3.56-3.59 (m, 4H), 3.61 (s, 2H), 6.55 (s, 1H), 7.09 (s, 1H), 7.36 (d, *J* =
10 8.4 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 2H), 11.42 (s, 1H)
[0413]

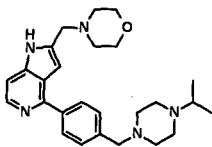
The following compounds **Examples A52 to A58** as shown in Table 11 were prepared in the same manner as **Example A51**.

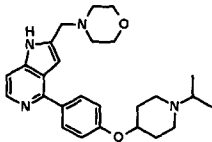
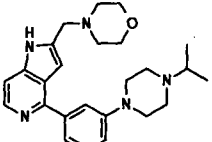
[0414]

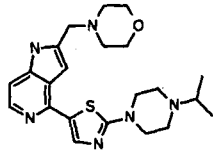
15 Table 11:

Ex.No.	IUPAC name	Structure	Ex. from which prepared	Analytical data
A52	4-[[4-[6-(1-isopropyl-3,6-dihydro-2H-pyridin-4-yl)-3-pyridyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		A43	LCMS: <i>m/z</i> 418.3 [M ⁺ +1] ¹ H NMR (400 MHz, CD ₃ OD): δ 1.41 (d, <i>J</i> = 6.8 Hz, 6H), 2.49-2.5.3 (m, 4H), 3.05-3.11 (m, 2H), 3.46-3.52 (m, 3H), 3.71 (t, <i>J</i> = 4.4 Hz, 4H), 3.74 (s, 2H), 3.91-3.93 (m, 2H), 6.68 (s, 1H), 6.80 (br. s, 1H), 7.41 (d, <i>J</i> = 5.6 Hz, 1H), 7.81

				(d, J = 8.4 Hz, 1H), 8.26 (d, J = 5.6 Hz, 1H), 8.31 (dd, J = 8, 2 Hz, 1H), 9.06 (d, J = 2 Hz, 1H)
A53	4-[[4-[6-(4-isopropylpiperazin-1-yl)-3-pyridyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		A44	LCMS: m/z 421.4 [M ⁺ +1] ¹ H NMR (400 MHz, CDCl ₃): δ 1.13 (d, J = 6.4 Hz, 6H), 2.49 (t, J = 4.4 Hz, 4H), 2.71 (t, J = 4.4 Hz, 4H), 2.73-2.76 (m, 1H), 3.68 (s, 2H), 3.71-3.73 (m, 8H), 6.71 (s, 1H), 6.80 (d, J = 8.8 Hz, 1H), 7.21 (dd, J = 6, 1.2 Hz, 1H), 8.18 (dd, J = 8, 2.4 Hz, 1H), 8.35 (d, J = 5.6 Hz, 1H), 8.32 (d, J = 2.4 Hz, 1H), 8.85 (br s, 1H)
A54	4-[[4-[1-(1-isopropyl-4-piperidyl)pyrazol-4-yl]-1H-pyrrolo[3,2-		A45	LCMS: m/z 409.4 [M ⁺ +1] ¹ H NMR (400 MHz, CDCl ₃): δ 1.13 (d, J = 6.8 Hz, 6H), 2.12-2.20 (m,

	c]pyridin-2-yl)methyl]morpholine			2H), 2.30-2.36 (m, 2H), 2.45-2.49 (m, 1H), 2.51 (t, J = 4.4 Hz, 4H), 3.10-3.13 (m, 2H), 3.49 (s, 2H), 3.71-3.74 (m, 6H), 4.24-4.28 (m, 1H), 6.67 (s, 1H), 7.17 (d, J = 6 Hz, 1H), 8.14 (s, 1H), 8.19 (s, 1H), 8.24 (d, J = 6 Hz, 1H), 9.10 (br. s, 1H)
A55	4-[[4-[4-isopropylpiperazin-1-yl)methyl]phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl)methyl]morpholine		A48	LCMS: m/z 434.30 [M ⁺ +1] ¹ HNMR (400 MHz, CDCl ₃): δ 1.11 (d, J = 6.9 Hz, 6H), 2.49 (t, J = 4.4 Hz, 4H), 2.58-2.70 (m, 8H), 2.75-2.80 (m, 1H), 3.61 (s, 2H), 3.68 (s, 2H), 3.72 (t, J = 4.4 Hz, 4H), 6.67 (s, 1H), 7.23 (d, J = 5.4 Hz, 1H), 7.45 (d, J = 7.9 Hz, 2H), 7.92 (d, J = 8.3 Hz, 2H), 8.38

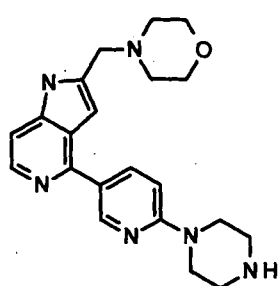
				(d, J = 5.9 Hz, 1H), 8.93 (bs, 1H).
A56	4-[[4-[4- [(1- isopropyl-4- piperidyl)ox yl]phenyl]- 1H- pyrrolo[3,2- c]pyridin-2- yl]methyl]mo rpholine		A49	LCMS: m/z 435.4 [M ⁺ +1] ¹ H NMR (400 MHz, CDCl ₃): δ 1.05-1.20 (m, 6H), 1.85-1.95 (m, 2H), 2.10-2.20 (m, 2H), 2.45-2.55 (m, 6H), 2.80-2.92 (m, 3H), 3.68 (s, 2H), 3.73 (t, J = 4.4 Hz, 4H), 4.40-4.50 (m, 1H), 6.66 (s, 1H), 7.04 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 5.7 Hz, 1H), 7.92 (d, J = 8.8 Hz, 2H), 8.36 (d, J = 5.3 Hz, 1H), 8.83 (bs, 1H)
A57	4-[[4-[3-(4- isopropylpip erazin-1- yl)phenyl]- 1H- pyrrolo[3,2- c]pyridin-2- yl]methyl]mo rpholine		A46	LCMS: m/z 420.3 [M ⁺ +1] ¹ H NMR (400 MHz, CDCl ₃): δ 1.12 (d, J = 6.3 Hz, 6H), 2.49 (t, J = 3.9 Hz, 4H), 2.74 (t, J = 4.4 Hz, 4H),

				2.76-2.78 (m, 1H), 3.34 (t, J = 4.8 Hz, 4H), 3.68 (s, 2H), 3.72 (t, J = 4.4 Hz, 4H), 6.67 (s, 1H), 7.01 (dd, J = 1 Hz, 7.9 Hz, 1H), 7.23 (d, J = 5.8 Hz, 1H), 7.35-7.44 (aromatics, 2H), 7.52 (s, 1H), 8.37 (d, J = 5.8 Hz, 1H), 8.85 (bs, 1H)
A58	4-[[4-[2-(4-isopropylpiperazin-1-yl)thiazol-5-yl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		A50	LCMS: m/z 427.3 [M ⁺ +1] ¹ H NMR (400 MHz, CDCl ₃): δ 1.10 (d, J = 6 Hz, 6H), 2.50-2.53 (m, 4H), 2.68-2.70 (m, 4H), 2.80-2.81 (m, 1H), 3.63-3.65 (m, 4H), 3.72-3.75 (m, 6H), 6.66 (s, 1H), 7.10 (d, J = 5.6 Hz, 1H), 7.86 (s, 1H), 8.21 (d, J = 5.6 Hz, 1H), 8.84 (br. s, 1H)

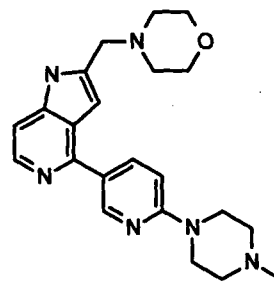
[0415]

Example A59: 4-[[4-[6-(4-methylpiperazin-1-yl)-3-pyridyl]-1H-

pyrrolo[3,2-c]pyridin-2-yl)methyl]morpholine
[0416]



Example A44



Example A59

5 [0417]

To a solution of **Example A44** (0.16 g, 0.42 mmol) in MeOH (3 mL) were added 37% aqueous HCHO (0.19 g, 6.34 mmol) and two drops of acetic acid, and the mixture was stirred at 70°C for 2 hours. The reaction mixture was cooled to 0°C and sodium
10 cyanoborohydride (0.398 g, 6.34 mmol) was added thereto, and the mixture was stirred overnight. The reaction mixture was diluted with water (10 mL) and extracted with AcOEt (20 mL x 3). The layers were separated, and the organic layer was washed with saturated aqueous sodium bicarbonate solution and
15 brine, dried over anhydrous Na₂SO₄ and concentrated in vacuum. The obtained residue was purified by preparative TLC to give the desired product **Example A59** (0.061 g, 37%) as a yellow solid; LCMS: *m/z* 393.3 [M⁺+1].

¹H NMR (400 MHz, CDCl₃): δ 2.38 (s, 3H), 2.49 (t, *J* = 4.4 Hz, 4H), 2.58 (t, *J* = 5.2 Hz, 4H), 3.68 (s, 2H), 3.69–3.75 (m, 8H),
20 6.71 (s, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 7.20 (dd, *J* = 5.6, 0.8 Hz, 1H), 8.20 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.35 (d, *J* = 5.6 Hz, 1H), 8.37 (d, *J* = 2 Hz, 1H), 8.89 (br. s, 1H)

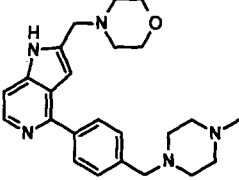
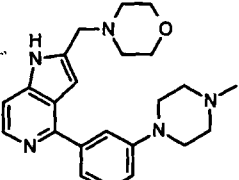
[0418]

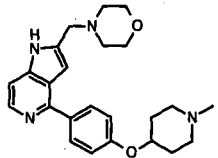
25 The following compounds **Examples A60 to A63** as shown in Table 12 were prepared in the same manner as **Example A59**.

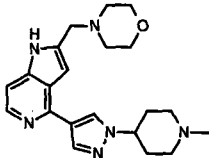
[0419]

Table 12:

Ex.No.	IUPAC name	Structure	Ex. from	Analytical data
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			which prepared	
A60	4-[[4-[4- [(4- methylpipera zin-1- yl)methyl]ph enyl]-1H- pyrrolo[3,2- c]pyridin-2- yl)methyl]mo rpholine		A48	LCMS: m/z 406.30 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3): δ 2.35 (s, 3H), 2.49 (t, $J = 4.4$ Hz, 4H), 2.52- 2.70 (m, 8H), 3.60 (s, 2H), 3.69 (s, 2H), 3.73 (t, $J = 4.9$ Hz, 4H), 6.68 (s, 1H), 7.23 (d, $J = 1.2$ Hz, 1H), 7.46 (d, J $= 8.4$ Hz, 2H), 7.91 (d, $J = 8.4$ Hz, 2H), 8.36 (d, $J = 5.3$ Hz, 1H), 9.00 (bs, 1H)
A61	4-[[4-[3-(4- methylpipera zin-1- yl)phenyl]- 1H- pyrrolo[3,2- c]pyridin-2- yl)methyl]mo rpholine		A46	LCMS: m/z 392.30 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3): δ 2.37 (s, 3H), 2.49 (t, $J = 4.4$ Hz, 4H), 2.62 (t, $J = 4.8$ Hz, 4H), 3.33 (t, $J = 5.3$ Hz, 4H), 3.68 (s, 2H), 3.72 (t, J

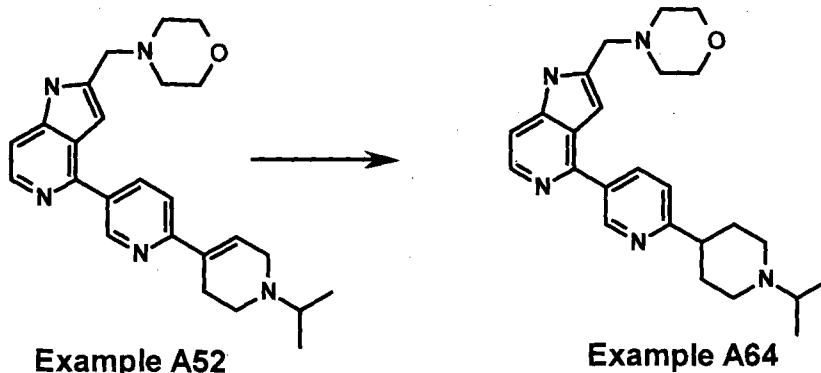
				= 4.9 Hz, 4H), 6.66 (s, 1H), 7.01 (dd, J = 1.5, 2.4 Hz, 1H), 7.23 (d, J = 5.9 Hz, 1H), 7.35-7.44 (aromatics, 2H), 7.52 (s, 1H), 8.38 (d, J = 5.9 Hz, 1H), 8.92 (bs, 1H)
A62	4-[[4-[4- [(1-methyl- 4- piperidyl)ox ylphenyl]- 1H- pyrrolo[3,2- c]pyridin-2- yl]methyl]mo rpholine		A49	LCMS: m/z 407.3 [M ⁺ +1] ¹ H NMR (400 MHz, CDCl ₃): δ 1.85-1.98 (m, 2H), 2.05-2.15 (m, 2H), 2.36 (s, 3H), 2.38- 2.42 (m, 2H), 2.49 (t, J = 3.9 Hz, 4H), 2.70-2.80 (m, 2H), 3.68 (s, 2H), 3.73 (t, J = 4.4 Hz, 4H), 4.40-4.50 (m, 1H), 6.67 (s, 1H), 7.04 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 5.9 Hz, 1H), 7.92 (d, J = 8.8 Hz, 2H), 8.36 (d, J

				= 5.9 Hz, 1H), 8.87 (bs, 1H)
A63	4-[[4-[1-(1-methyl-4-piperidyl)pyrazol-4-yl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		A45	LCMS: m/z 381.3 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3): δ 2.11-2.22 (m, 4H), 2.23-2.26 (m, 2H), 2.35 (s, 3H), 2.50 (t, J = 4.4 Hz, 4H), 3.00-3.03 (m, 2H), 3.70 (s, 2H), 3.73 (t, J = 4.4 Hz, 4H), 4.21 (sep. 1H), 6.66 (s, 1H), 7.15 (d, J = 6 Hz, 1H), 8.14 (s, 1H), 8.17 (s, 1H), 8.26 (d, J = 5.6 Hz, 1H), 8.40 (br. s, 1H)

[0420]

Example A64: 4-[[4-[6-(1-isopropyl-4-piperidyl)-3-pyridyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine

[0421]



[0422]

To a solution of **Example A52** (0.130 g, 0.311 mmol) in EtOAc:MeOH (9:1 ratio, 10 mL) was added 10% dry Pd/C (15 mg), and the mixture was stirred under hydrogen atmosphere at room temperature (balloon pressure). After 16 hours, the catalyst was removed by filtration, and the filtrate was evaporated to dryness. The obtained residue was purified by preparative TLC (10% MeOH in dichloromethane) to give the desired product

10 **Example A64** (0.065 g, 50%) as a yellow solid; LCMS: m/z 420.4 $[M^+ + 1]$.

^1H NMR (400 MHz, CDCl_3): δ 1.14 (d, $J = 5.6$ Hz, 6H), 1.96–2.10 (m, 4H), 2.40–2.45 (m, 2H), 2.49 (t, $J = 4.4$ Hz, 4H), 2.84–2.88 (m, 2H), 3.03–3.15 (m, 2H), 3.69 (m, s, 2H), 3.72 (t, $J =$

15 4.8 Hz, 4H), 6.67 (s, 1H), 7.25–7.26 (m, merged in residual solvent peak, 1H), 7.36 (d, $J = 8$ Hz, 1H), 8.24 (dd, $J = 8$, 2.4 Hz, 1H), 8.40 (d, $J = 5.6$ Hz, 1H), 8.84 (br. s, 1H), 9.11 (d, $J = 2$ Hz, 1H)

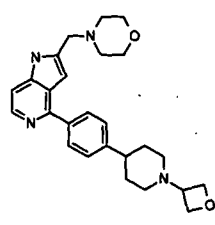
[0423]

20 The following compound **Example A65** as shown in Table 13 was prepared in the same manner as **Example A64**.

[0424]

Table 13:

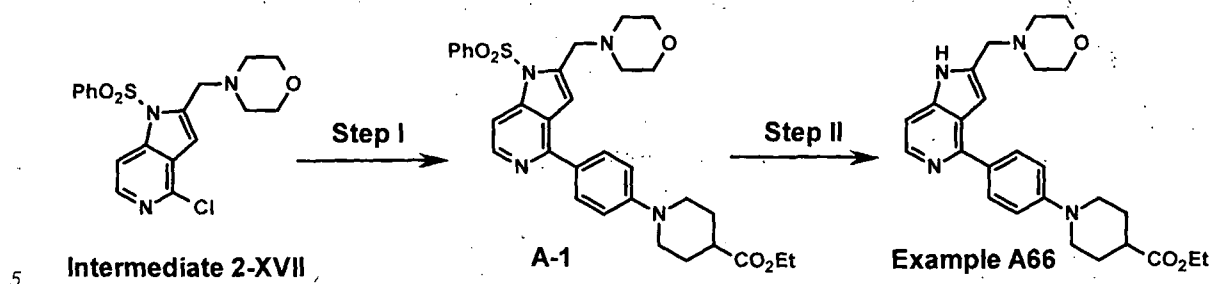
Ex.No.	IUPAC name	Structure	Ex. from which prepared	Analytical data
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A65	4-[[4-[4-[1-(oxetan-3-yl)-4-piperidyl]phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine		A11 LCMS: m/z 433.3 [M^++1] ^1H NMR (400 MHz, CDCl_3): δ 1.83-2.00 (m, 6H), 2.49 (t, J = 4 Hz, 4H), 2.54-2.63 (m, 1H), 2.90 (d, J = 10.8 Hz, 2H), 3.52 (q, J = 6.8 Hz, 1H), 3.69 (s, 2H), 3.73 (t, J = 4.4 Hz, 4H), 4.66-4.71 (m, 4H), 6.70 (s, 1H), 7.22 (d, J = 5.6 Hz, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H), 8.38 (d, J = 5.6 Hz, 1H), 8.92 (br s, 1H)
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[0425]

Example A66: ethyl 1-[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]piperidine-4-carboxylate

[0426]



[0427]

Step I: ethyl 1-[4-[1-(benzenesulfonyl)-2-(morpholinomethyl)pyrrolo[3,2-c]pyridin-4-

yl]phenyl]piperidine-4-carboxylate (**A-1**):

A mixture of **Intermediate 2-XVII** (0.2 g, 0.51 mmol), **Intermediate 1-VI** (0.192 g, 0.61 mmol) and K_2CO_3 (0.212 g, 1.53 mmol) in dioxane/water (6 mL, ratio: 4:1) was degassed in a stream of argon for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.06 g, 0.051 mmol), and the reaction mixture was again degassed for additional 30 minutes. After stirring at 90°C for 18 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (15 mL), followed by extraction with ethyl acetate (15 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, followed by preparative TLC purification to give the desired product **A-1** (0.250 g, 67%) as a greenish solid; LCMS: m/z 589.1 [$M^+ + 1$].

[0428]

Step II: ethyl 1-[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]piperidine-4-carboxylate (**Example A66**)

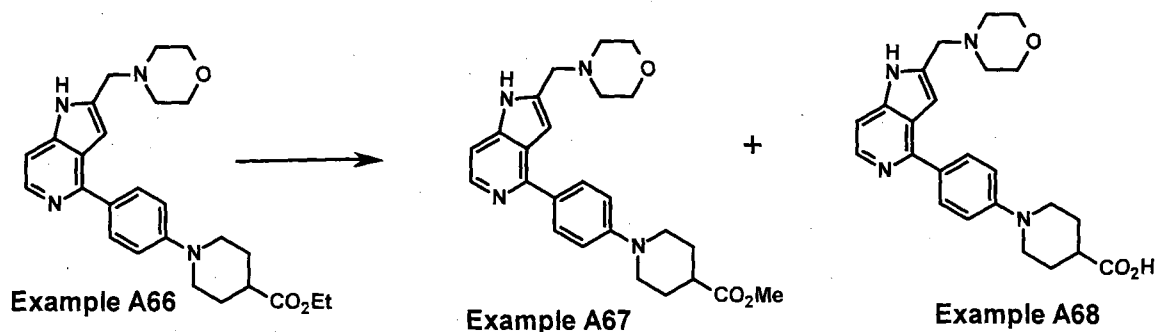
A stirred solution of **A-1** (0.24 g, 0.35 mmol) in 1,4-dioxane (8 mL) was treated with sodium tert-butoxide (0.103 g, 1.07 mmol) under argon atmosphere. After stirring at 90°C for 8 hours, the excess solvent was removed in vacuo. The obtained residue was dissolved in ethyl acetate (25 mL), and the solution was washed successively with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The desired crude compound **Example A66** obtained as a yellow solid (0.22 g) was used in the next step without purification; LCMS: m/z 225.1 [$M^+ / 2 + 1$].

[0429]

Example A67: methyl 1-[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]piperidine-4-carboxylate and

Example A68: 1-[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]piperidine-4-carboxylic acid

[0430]



[0431]

LiOH H₂O (0.206 g, 4.910 mmol) was added to a stirred solution of **Example A66** (0.22 g, 0.491 mmol) in a mixture of THF:MeOH:H₂O (3:2:1 ratio, 5 mL) at room temperature, and the reaction mixture was stirred for 18 hours. The volatiles were concentrated under reduced pressure, and the obtained residue was neutralized to pH 7 using aqueous 1N HCl, and the reaction mixture was concentrated to dryness. The resulting solid was suspended in 10% MeOH in DCM (100 mL), and the suspension was filtered. The filtrate was concentrated in vacuo to give the mixture of crude desired acid **Example A68** as a pale brown solid (0.025 g, 12%) and transesterification product **Example A67** (formed due to solvent methanol used during the hydrolysis reaction) (0.036 g, 16%) as a yellow solid.

Example A67:LCMS: m/z 435.3 [$M^+ + 1$]

¹H NMR (400 MHz, CD₃OD): δ 1.78-1.86 (m, 2H), 1.97-2.01 (m, 2H), 2.30-2.35 (m, 1H), 2.45-2.55 (m, 4H), 2.87 (t, $J = 11.2$ Hz, 2H), 3.67 (t, $J = 4.4$ Hz, 4H), 3.74 (s, 2H), 3.85-3.89 (m, 2H), 3.93 (s, 3H), 6.82 (s, 1H), 7.13 (d, $J = 8.8$ Hz, 2H), 7.48 (d, $J = 6.0$ Hz, 1H), 7.76 (d, $J = 8.8$ Hz, 2H), 8.17 (d, $J = 6.0$ Hz, 1H)

Example A68:LCMS: m/z 421.3 [$M^+ + 1$]

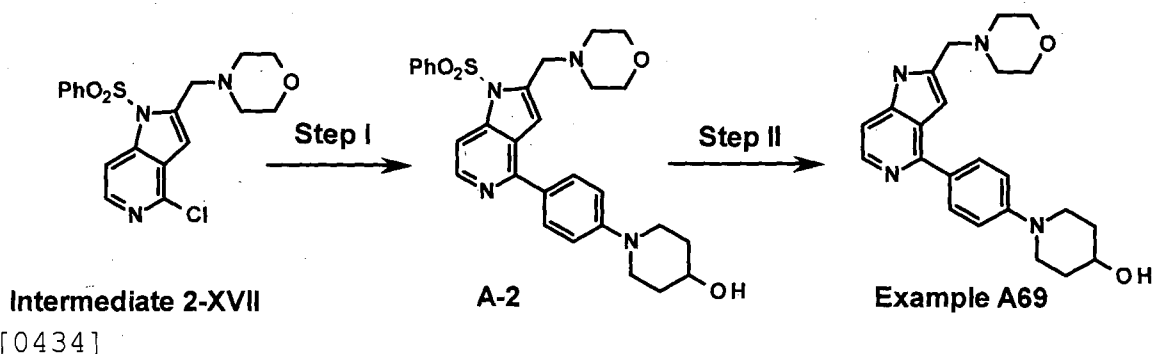
¹H NMR (400 MHz, CD₃OD): δ 1.78-1.81 (m, 2H), 1.99-2.01 (m, 3H), 2.45-2.52 (m, 4H), 2.97 (t, $J = 11$ Hz, 2H), 3.71 (t, $J = 4.6$ Hz, 4H), 3.78 (s, 2H), 3.94 (d, $J = 12.6$ Hz, 2H), 6.95 (s, 1H), 7.18 (d, $J = 8.8$ Hz, 2H), 7.58 (d, $J = 6.8$ Hz, 1H), 7.80 (d, J

= 8.8 Hz, 2H), 8.13 (d, J = 6.8 Hz, 1H)

[0432]

Example A69: 1-[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]piperidin-4-ol

5 [0433]



Step I: 1-[4-[1-(benzenesulfonyl)-2-(morpholinomethyl)pyrrolo[3,2-c]pyridin-4-yl]phenyl]piperidin-4-ol (**A-2**)

10 4-ol (**A-2**)

A mixture of **Intermediate 2-XVII** (0.18 g, 0.46 mmol), **Intermediate 1-V** (0.195 g, 0.64 mmol) and K_2CO_3 (0.191 g, 1.38 mmol) in 4:1 mixture of dioxane/water (6 mL) was degassed in a stream of argon for 30 minutes. To the mixture was added

15 tetrakis(triphenylphosphine)palladium(0) (0.053 g, 0.046 mmol), and the reaction mixture was again degassed for additional 30 minutes. After stirring at 90°C for 18 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (15 mL), followed by extraction with ethyl

20 acetate (15 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, followed by preparative TLC purification to give the desired product **A-2** (0.14 g, 57%) as a yellow solid; LCMS: m/z 533.1 [$M^+ + 1$].

25 [0435]

Step II: 1-[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]piperidin-4-ol (**Example A69**)

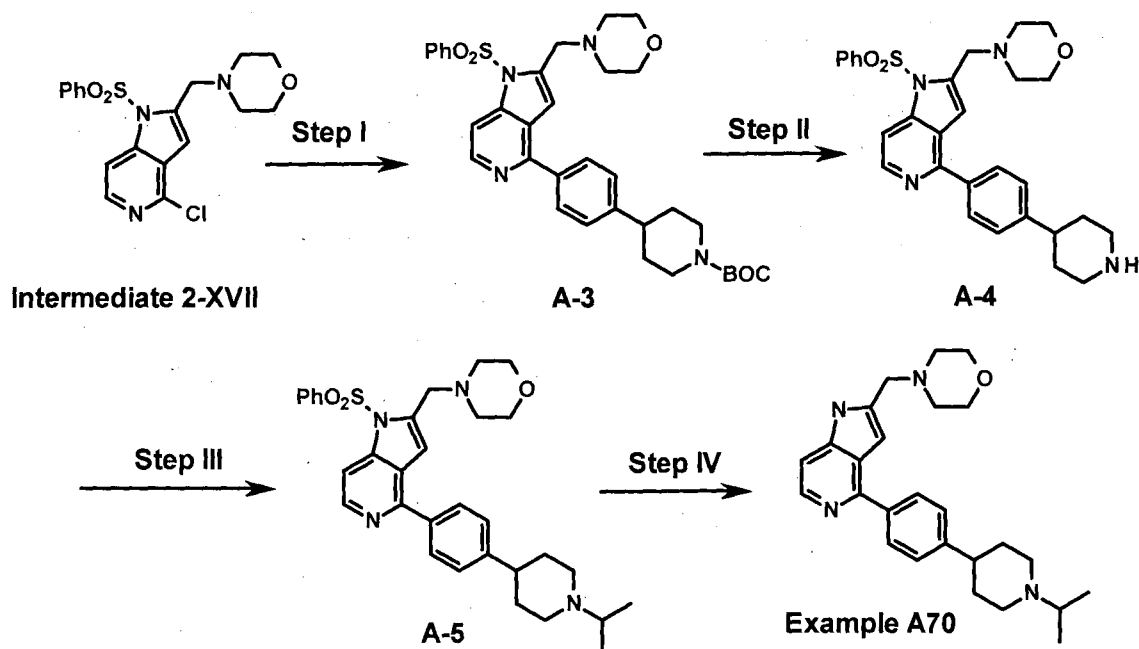
A stirred solution of **A-2** (0.13 g, 0.24 mmol) in 1,4-dioxane (6 mL) was treated with sodium tert-butoxide (0.070 g, 0.73 mmol) under argon atmosphere. After stirring at 90°C for

30 0.73 mmol) under argon atmosphere. After stirring at 90°C for

8 hours, the excess solvent was removed in vacuo. The obtained residue was dissolved in ethyl acetate (25 mL), and the solution was washed successively with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by HPLC to give the desired product **Example A69** (0.035 g, 36%) as a dark yellow solid; LCMS: m/z 393.3 [M⁺+1].
¹H NMR (400 MHz, CD₃OD): δ 1.60-1.68 (m, 2H), 1.93-2.00 (m, 5H), 2.48-2.60 (m, 4H), 3.06 (t, J = 10 Hz, 2H), 3.70-3.85 (m, 6H), 6.82 (s, 1H), 7.16 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 6.4 Hz, 1H), 7.79 (d, J = 8.8 Hz, 2H), 8.13 (d, J = 6.0 Hz, 1H)
 [0436]

Example A70: 4-[[4-[4-(1-isopropyl-4-piperidyl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine

15 [0437]



[0438]

Step I: tert-butyl 4-[4-[1-(benzenesulfonylmethyl)-2-(morpholinomethyl)pyrrolo[3,2-c]pyridin-4-yl]phenyl]piperidine-1-carboxylate (**A-3**)

A mixture of **Intermediate 2-XVII** (0.40 g, 1.02 mmol), **Intermediate 1-IX** (0.475 g, 1.22 mmol) and K₂CO₃ (0.424 g, 3.06 mmol) in 4:1 mixture of dioxane/water (16 mL) was degassed in

a stream of argon for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium(0) (0.118 g, 0.102 mmol), and the reaction mixture was again degassed for additional 30 minutes. After stirring at 90°C for 18 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (25 mL), followed by extraction with ethyl acetate (25 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure, followed by preparative TLC purification to give the desired product **A-3** (0.425 g, 67%) as a white solid; LCMS: *m/z* 617.1 [M⁺+1].
[0439]

Step II: 4-[[1-(benzenesulfonyl)-4-[4-(4-piperidyl)phenyl]pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine
(**A-4**)

To a solution of **A-3** (0.425 g, 0.688 mmol) in methanol (5 mL) at 0°C was added 4 M HCl in diethyl ether (5 mL). After stirring at room temperature for 6 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (2 mL), and pH was adjusted to ~8 using saturated aqueous NaHCO₃ solution (3 mL). The resulting solution was evaporated to dryness, and the obtained residue was diluted with 5% MeOH in dichloromethane (20 mL), and inorganic substance was removed by filtration. The filtrate was concentrated to give the crude desired product **A-4** (0.35 g, 98%) as a white solid. The obtained crude product was used for next step without purification.
[0440]

Step III: 4-[[1-(benzenesulfonyl)-4-[4-(1-isopropyl-4-piperidyl)phenyl]pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine
(**A-5**)

To a solution of **A-4** (0.20 g, 0.38 mmol) and acetone (0.247 g, 0.3 mL, 4.26 mmol) in a mixture of dichloroethane and methanol (2:1, 10 mL) were added a drop of acetic acid and powdered 4Å molecular sieves (0.5 g). The reaction mixture was

stirred for 3 hours at room temperature. Sodium cyanoborohydride (0.317 g, 5.03 mmol) was added thereto, and the mixture was stirred overnight. After completion of reaction (monitored by TLC), the resulting solid was removed
5 by filtration, and the filtrate was diluted with water (10 mL) and ethyl acetate (25 mL). The layers were separated, and the organic layer was washed with saturated aqueous sodium bicarbonate solution (15 mL) and brine (15 mL), dried over anhydrous Na₂SO₄, and concentrated in vacuum to give the
10 desired crude product **A-5** (0.13 g, 60%) as a white solid. The obtained crude product was used in the next step without purification LCMS: *m/z* 559.2 [M⁺+1].

[0441]

Step IV: 4-[[4-[4-(1-isopropyl-4-piperidyl)phenyl]-1H-
15 pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine (**Example A70**)

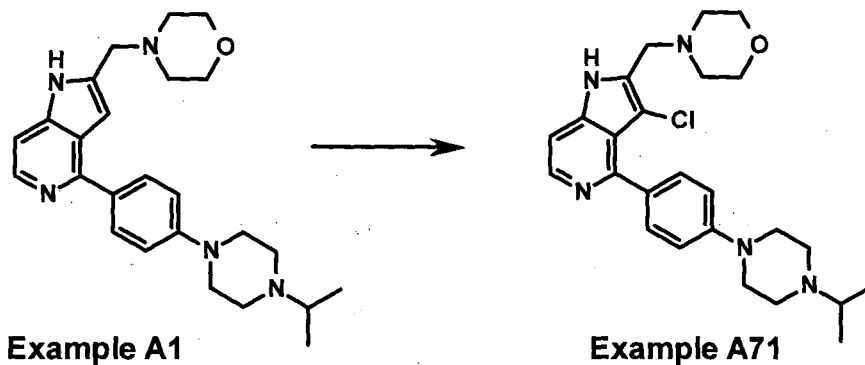
A stirred solution of **A-5** (0.13 g, 0.23 mmol) in 1,4-dioxane (6 mL) was treated with sodium tert-butoxide (0.067 g, 0.69 mmol) under argon atmosphere. After stirring at 90°C for 8 hours, the excess solvent was removed in vacuo. The obtained
20 residue was dissolved in ethyl acetate (25 mL), and the solution was washed successively with water (10 mL) and brine (10 mL), and dried over anhydrous Na₂SO₄. The organic layer was concentrated under reduced pressure. The obtained residue was purified by preparative HPLC to give the desired compound
25 **Example A70** (0.034 g, 24%) as a white solid; LCMS: *m/z* 419.2 [M⁺+1].

¹H NMR (400 MHz, CD₃OD): δ 1.15 (d, *J* = 6.8 Hz, 6H), 1.84-1.97 (m, 4H), 2.43 (t, *J* = 11 Hz, 2H), 2.51 (t, *J* = 4.6 Hz, 4H), 2.66-2.67 (m, 1H), 2.84 (quin, *J* = 6.6 Hz, 1H), 3.10 (d, *J* =
30 12 Hz, 2H), 3.70 (t, *J* = 5.2 Hz, 6H), 6.64 (s, 1H), 7.33 (d, *J* = 6 Hz, 1H), 7.42 (d, *J* = 8 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 2H), 8.16 (d, *J* = 5.6 Hz, 1H)

[0442]

Example A71: 4-[[3-chloro-4-[4-(4-isopropylpiperazin-1-
35 yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine

[0443]



[0444]

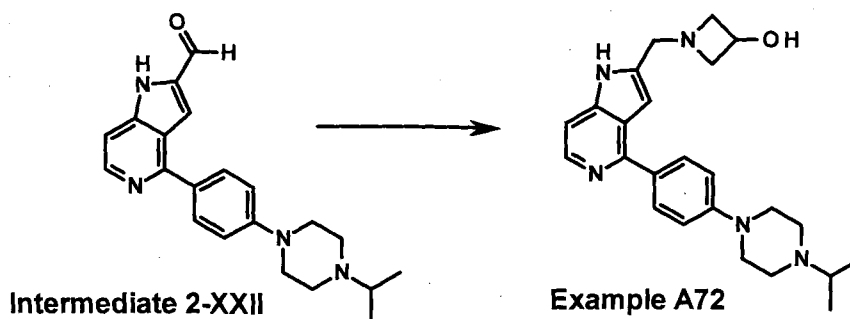
To a solution of **Example A1** (0.10 g, 0.23 mmol) in
 5 anhydrous DMF (2.3 mL) was added N-chlorosuccinamide (0.038 g,
 0.29 mmol) at room temperature. The reaction mixture was
 stirred at room temperature for 16 hours. The excess solvent
 was removed in vacuo, and the obtained residue was diluted
 with ice water, followed by extraction with ethyl acetate (20
 10 mL x 3). The combined organic layers were washed with brine
 (25 mL), dried over anhydrous Na₂SO₄ and concentrated under
 reduced pressure. The obtained residue was purified by
 preparative TLC using 10% methanol in dichloromethane to give
 the desired product **Example A71** (0.037 g, 35%) as a yellow
 15 solid; LCMS: *m/z* 454.3 [*M*⁺ + 1].

¹HNMR (400 MHz, CDCl₃): δ 1.14 (d, *J* = 6.8 Hz, 6H), 2.53 (t, *J*
 = 4.4 Hz, 4H), 2.77 (m, 5H), 3.35 (bs, 4H), 3.73 (m, 6H), 7.01
 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 5.8 Hz, 1H), 7.61 (d, *J* =
 8.8 Hz, 2H), 8.37 (d, *J* = 5.9 Hz, 1H), 8.89 (br s, 1H)

20 [0445]

Example A72: 1-[[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1H-
 pyrrolo[3,2-c]pyridin-2-yl]methyl]azetidin-3-ol

[0446]



[0447]

To a solution of **Intermediate 2-XXII** (0.130 g, 0.373 mmol) in MeOH:DCE (2:4, 5 mL) were added azetidin-3-ol (0.136 g, 1.86 mmol), a drop of acetic acid and activated 4Å powdered molecular sieves (0.5 g) successively. After stirring for 4 hours at room temperature, sodium cyanoborohydride (0.234 g, 3.75 mmol) was added thereto, and the mixture was stirred for 16 hours. The reaction mixture was filtered through a celite pad, and washed with EtOAc (25 mL), and the filtrate was taken into water (10 mL), and the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by preparative TLC using 12% MeOH in dichloromethane to give the desired product **Example A72** (0.04 g, 26%) as a yellow Solid; LCMS: *m/z* 406.3 [*M*⁺+1].

¹H NMR (400 MHz, CDCl₃): δ 1.06 (dd, *J* = 5.8 Hz, 6H), 2.53 (t, *J* = 9.6 Hz, 1H), 2.61–2.75 (m, 4H), 3.02–3.22 (m, 4H), 3.23–3.40 (m, 4H), 3.72–3.78 (m, 2H), 4.44 (t, *J* = 5.8, 1H), 6.64 (s, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 4.8 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 8.19 (d, *J* = 4.8 Hz, 1H)

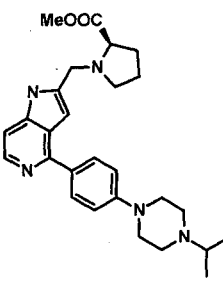
[0448]

The following compound **Example A73** as given in Table 14 was prepared in the same manner as **Example A72**.

[0449]

Table 14

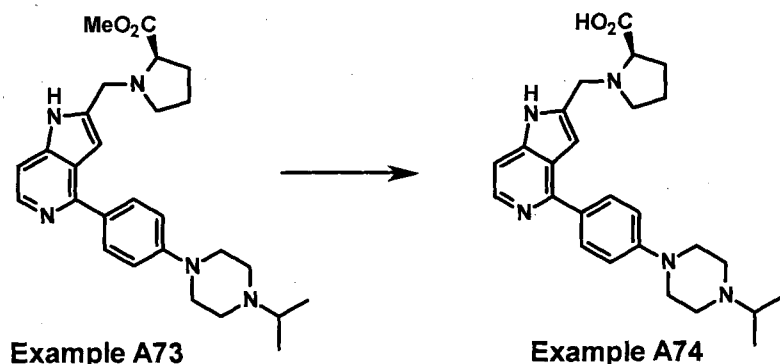
Ex.No.	IUPAC name	Structure	Int. from which	Analytical data
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			prepared	
A73	methyl (2R)-1-[[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]pyrrolidine-2-carboxylate		2-XXII	LCMS: m/z 462.3 $[M^+ + 1]$ ^1H NMR (400 MHz, CDCl_3): δ 1.12 (d, J = 6.8 Hz, 6H), 1.85-1.88 (m, 3H), 2.17-2.30 (m, 1H), 2.42-2.52 (m, 1H), 2.73 (t, J = 5.2 Hz, 5H), 3.06-3.12 (m, 1H), 3.32-3.37 (m, 5H), 3.66 (s, 3H), 3.77 (d, J = 14 Hz, 1H), 4.04 (d, J = 14 Hz, 1H), 6.62 (s, 1H), 7.04 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 5.6 Hz, 1H), 7.91 (d, J = 8.8 Hz, 2H), 8.31 (d, J = 6 Hz, 1H), 9.60 (br s, 1H)

[0450]

Example A74: (2R)-1-[[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]pyrrolidine-2-carboxylic acid

5 [0451]



[0452]

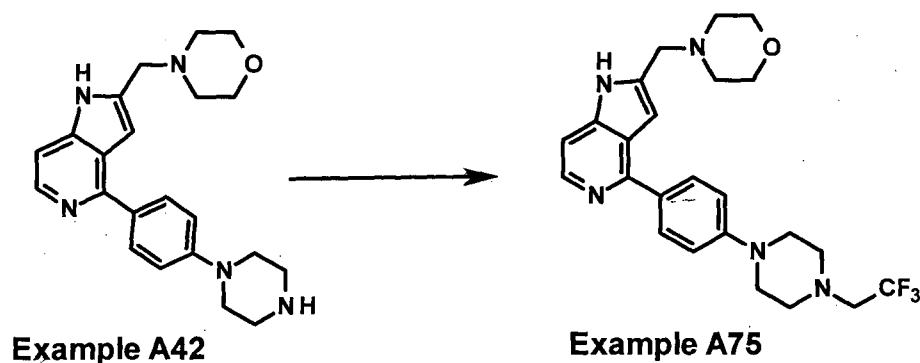
A stirred solution of **Example A73** (0.032 g, 0.072 mmol) in THF:MeOH:H₂O (3:2:1 ratio, 2.5 mL) was treated with LiOH H₂O (0.0036 g, 0.086 mmol) at room temperature, and the mixture was stirred for 16 hours. The volatiles were concentrated under reduced pressure to give a lithium salt of the desired product **Example A74** (0.025 g, 74%) as a yellow solid; LCMS: m/z 448.3 [$M^+ + 1$].

¹H NMR (400 MHz, CD₃OD): δ 1.14 (d, J = 6.4 Hz, 6H), 1.71-1.91 (m, 3H), 2.12-2.23 (m, 2H), 2.69-2.77 (m, 5H), 2.87-2.91 (m, 1H), 3.00 (t, J = 8.2 Hz, 1H), 3.29-3.34 (m, 4H), 3.45 (d, J = 13.6 Hz, 1H), 4.17 (d, J = 13.2 Hz, 1H), 6.59 (s, 1H), 7.11 (d, J = 9.2 Hz, 2H), 7.26 (d, J = 6 Hz, 1H), 7.79 (d, J = 8.8 Hz, 2H), 8.10 (d, J = 6 Hz, 1H)

[0453]

Example A75: 4-[[4-[4-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine

[0454]



20

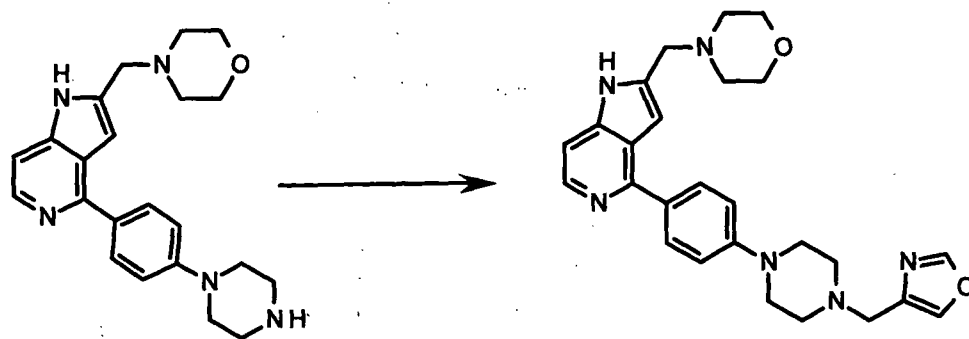
[0455]

To an ice cold solution of **Example A42** (0.05 g, 0.132 mmol) and N,N-diisopropylethylamine (0.025 g, 0.198 mmol) in

dichloromethane (1.5 mL) was added 2,2,2-trifluoroethyl trifluoromethanesulfonate (23 μ L, 0.158 mmol) at room temperature. After stirring at room temperature for 18 hours, the reaction mixture was diluted with water (10 mL) and
 5 dichloromethane (20 mL). The organic layer was separated, washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by preparative TLC using 10% MeOH in dichloromethane to give the desired product **Example A75** (0.031 g, 51%) as a
 10 light yellow solid; LCMS: m/z 460.2 [$\text{M}^+ + 1$].

^1H NMR (400 MHz, CDCl_3): δ 2.49 (t, $J = 4.4$ Hz, 4H), 2.86 (t, $J = 5.2$ Hz, 4H), 3.06 (q, $J = 9.6$ Hz, 2H), 3.32 (t, $J = 4.8$ Hz, 4H), 3.69 (s, 2H), 3.72 (t, $J = 4.8$ Hz, 4H), 6.71 (s, 1H), 7.03 (d, $J = 8.4$ Hz, 2H), 7.21 (d, $J = 6$ Hz, 1H), 7.92 (d, $J =$
 15 8.4 Hz, 2H), 8.34 (d, $J = 5.6$ Hz, 1H), 9.10 (br. s, 1H)
 [0456]

Example A76: 4-[[4-[4-[4-(oxazol-4-ylmethyl)piperazin-1-yl]phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine
 [0457]



Example A42

Example A76

[0458]

A mixture of **Example A42** (0.100 g, 0.264 mmol), oxazol-4-ylmethyl methanesulfonate hydrochloride salt (0.093 g, 0.66 mmol) and K_2CO_3 (0.128 g, 0.092 mmol) in DMF (3 mL) was heated
 25 at 60°C for 18 hours. The excess solvent was removed under reduced pressure, and the obtained residue was diluted with ice water (10 mL) and EtOAc (20 mL). The organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4 and

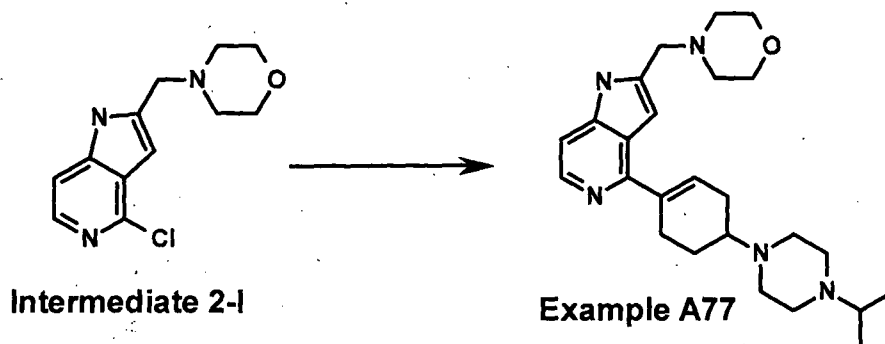
concentrated under reduced pressure. The obtained residue was purified using preparative TLC (solvent system: 10% MeOH in dichloromethane) to give the desired product **Example A76** (0.023 g, 19%) as a yellow solid; LCMS: m/z 459.3 [$M^+ + 1$].

¹H NMR (400 MHz, CDCl₃): δ 2.45–2.58 (m, 4H), 2.68–2.75 (m, 4H), 3.28–3.40 (m, 4H), 3.59 (s, 2H), 3.69–3.72 (m, 6H), 6.72 (s, 1H), 7.03 (d, J = 8.4 Hz, 2H), 7.23 (s, 1H), 7.62 (s, 1H), 7.88 (s, 1H), 7.92 (d, J = 8.4 Hz, 2H), 8.33 (d, J = 6 Hz, 1H), 9.30 (br. s, 1H)

[0459]

Example A77: 4-[[4-[4-(4-isopropylpiperazin-1-yl)cyclohexen-1-yl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine

[0460]



[0461]

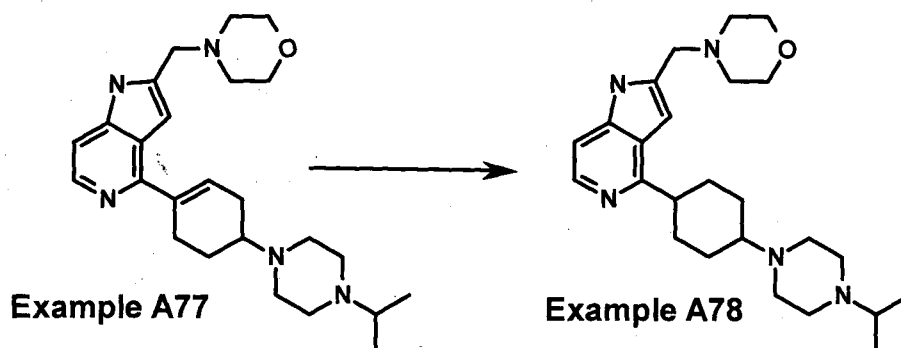
A stirred solution of **Intermediate 2-I** (0.10 g, 0.39 mmol), **Intermediate 1-XXVIII** (0.26 g, 0.79 mmol) and K₂CO₃ (0.16 g, 1.19 mmol) in a mixture of dioxane/water (4:1, 5 mL) was degassed in a stream of argon for 15 minutes. To this mixture was added Pd(PPh₃)₄ (0.046 g, 0.039 mmol), and the reaction mixture was again degassed for additional 15 minutes. After stirring at 100°C for 18 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (20 mL), followed by extraction with ethyl acetate (25 mL x 3). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by preparative TLC to give the desired product **Example A77** (0.085 g, 50%) as a yellow solid; LCMS: m/z 212.7 [$M^+ / 2 + 1$].

¹H NMR (400 MHz, CDCl₃): δ 1.10 (d, J = 6.4 Hz, 6H), 2.17-2.23 (m, 1H), 2.28-2.40 (m, 1H), 2.48 (t, J = 4.4 Hz, 5H), 2.60-2.88 (m, 12H), 2.91-2.99 (m, 1H), 3.66 (s, 2H), 3.72 (t, J = 4.4 Hz, 4H), 6.40 (t, J = 2.0 Hz, 1H), 6.56 (s, 1H), 7.11 (d, J = 5.6 Hz, 1H), 8.24 (d, J = 6.0 Hz, 1H), 8.46 (bs, 1H)

[0462]

Example A78: 4-[[4-[4-(4-isopropylpiperazin-1-yl)cyclohexyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine

[0463]



10

[0464]

To a stirred solution of **Example A77** (0.085 g, 0.2 mmol) in EtOAc (3 mL) was added Pd/C (0.017 g, 20% W/W). The flask was evacuated and filled with hydrogen gas (this procedure was repeated twice). The reaction mixture was then stirred for 18 hours under hydrogen atmosphere. After completion of reaction, the reaction mixture was filtered through a celite pad. The obtained filtrate was concentrated under reduced pressure to give the desired product **Example A78** (0.06 g, 70 %) as a yellow oil. LCMS: *m/z* 213.7 [*M*⁺/2+1].

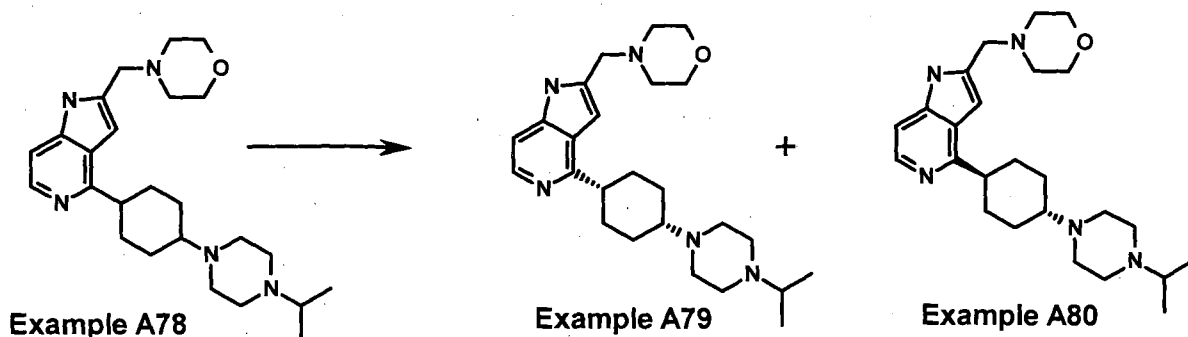
20

[0465]

Examples A79 and A80: *Cis* and *trans*-4-[[4-[4-(4-isopropylpiperazin-1-yl)cyclohexyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine

25

[0466]



[0467]

Example A78 (0.06 g, 0.14 mmol) was dissolved in a mixture of methanol:dichloromethane (9:1, 0.7 mL). 41 μ L of this solution was loaded onto a 150 x 21.2 mm 5 μ phenomenex Gem column and eluted with a mobile phase comprising of acetonitrile:water (6:4; modified with 0.05% Triethylamine) at a flow rate of 16 mL/min. **Example A79** was collected between 2.5 minutes and 3.2 minutes, while **Example A80** was collected between 3.6 minutes and 4.5 minutes. 17 such injections were carried out and the pooled fractions were concentrated under reduced pressure to give the desired products **Example A79** (0.015 g, 0.035 mmol) and **Example A80** (0.022, 0.051 mmol) as white solids. **Examples A79** and **A80** were subjected to hydrochloride salt formation by following procedure:

To a solution of **Example A79** (0.015 g, 0.035 mmol) in dichloromethane (3 mL) was added 4M HCl in dioxane (1 mL) drop wise over 10 minutes. The obtained white precipitate was stirred at ambient temperature for 1 hour, the volatiles were removed by evaporation, and the obtained solid was dried under vacuum to give a 4HCl salt of **Example A79** (0.015 g, 0.035 mmol) as a white solid; LCMS: m/z 426.2 [$M^+ + 1$].

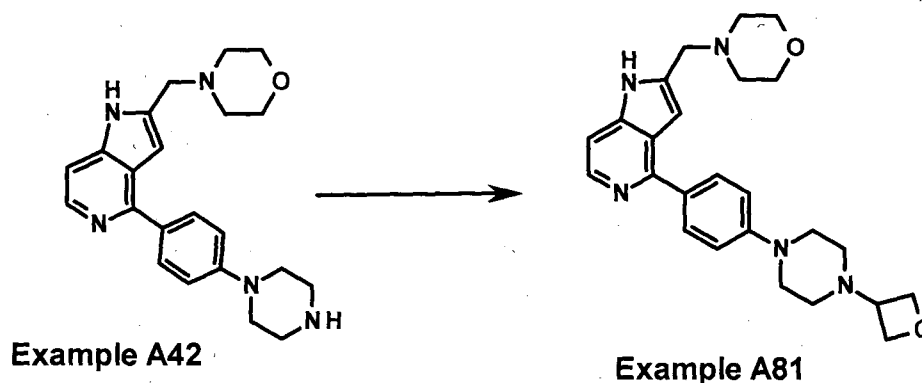
^1H NMR (400 MHz, DMSO): δ 1.31 (d, J = 6.8 Hz, 6H), 1.72-1.77 (m, 2H), 2.05-2.18 (m, 4H), 2.28-2.39 (m, 2H), 3.10-3.19 (m, 2H), 3.61-3.86 (m, 15H, merged in residual solvent peak), 4.09-4.20 (m, 2H), 4.52-4.71 (m, 2H), 7.45 (s, 1H), 7.90 (s, 1H), 8.30 (s, 1H), 11.95 (bs, 1H), 12.25 (bs, 1H), 13.20 (bs, 1H), 15.05 (bs, 1H)

A tetrahydrochloride salt of **Example A80** (0.022, 0.051

mmol) was obtained in a similar manner as **Example A79**; LCMS: m/z 426.2 $[M^+ + 1]$.

^1H NMR (400 MHz, DMSO): δ 1.33 (d, J = 6.4 Hz, 6H), 1.85-1.99 (m, 4H), 2.30-2.46 (m, 2H), 3.10-3.29 (m, 3H), 3.66-4.05 (m, 16 H, merged in residual solvent peak), 3.90-4.05 (m, 2H), 4.52-4.66 (m, 2H), 7.53 (s, 1H), 7.91 (s, 1H), 8.34 (s, 1H), 10.50 (bs, 1H), 12.00 (bs, 1H), 13.22 (bs, 1H), 14.80 (bs, 1H) [0468]

Example A81: 4-[[4-[4-[4-(oxetan-3-yl)piperazin-1-yl]phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine [0469]



[0470]

To a solution of **Example A42** (0.22 g, 0.583 mmol) and oxetan-3-one (0.21 g, 2.91 mmol) in MeOH (5 mL) were added ZnCl_2 (0.4 g, 2.91 mmol) and activated 4Å powdered molecular sieves (0.4 g) at room temperature. After stirring for 2 hours at room temperature, sodium cyanoborohydride (0.183 g, 2.91 mmol) was added thereto at 0°C, and the reaction mixture was stirred for 4 hours at room temperature. The reaction mixture was filtered through a celite pad, and washed with EtOAc (25 mL), and the filtrate was taken into water (20 mL) and saturated aqueous NaHCO_3 solution (10 mL), and the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by preparative TLC using 10% MeOH in dichloromethane to give the desired product **Example A81** (0.180

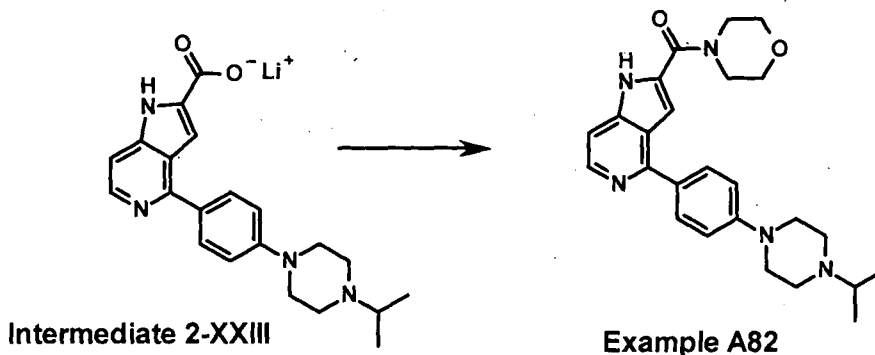
g, 71%) as an off white solid; LCMS: m/z 434.3 [$M^+ + 1$].

^1H NMR (400 MHz, CDCl_3): δ 2.51 (t, $J = 4.8$ Hz, 8H), 3.37 (t, $J = 5.2$ Hz, 4H), 3.56 (quin. 1H), 3.71-3.75 (m, 6H), 4.65-4.73 (m, 4H), 6.78 (s, 1H), 7.05 (d, $J = 8.8$ Hz, 2H), 7.35 (d, $J = 6.4$ Hz, 1H), 7.93 (d, $J = 8.8$ Hz, 2H), 8.26 (d, $J = 6.4$ Hz, 1H), 9.81 (br. s, 1H)

[0471]

Example A82: [4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]-morpholino-methanone

10 [0472]



[0473]

To a solution of **Intermediate 2-XXIII** (0.140 g, 0.385 mmol), N,N -diisopropylethylamine (0.163 mL, 0.964 mmol) and morpholine (0.083 mL, 0.964 mmol) in DMF (2 mL) were added EDC HCl (0.110 g, 0.587 mmol) followed by HOBt (0.026 g, 0.192 mmol) at room temperature. After 18 hours, the reaction mixture was diluted with EtOAc (15 mL) and water (15 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by preparative HPLC using 10% MeOH in dichloromethane to give the desired product **Example A82** (0.016 g, 9%) as a yellow solid; LCMS: m/z 434.3 [$M^+ + 1$].

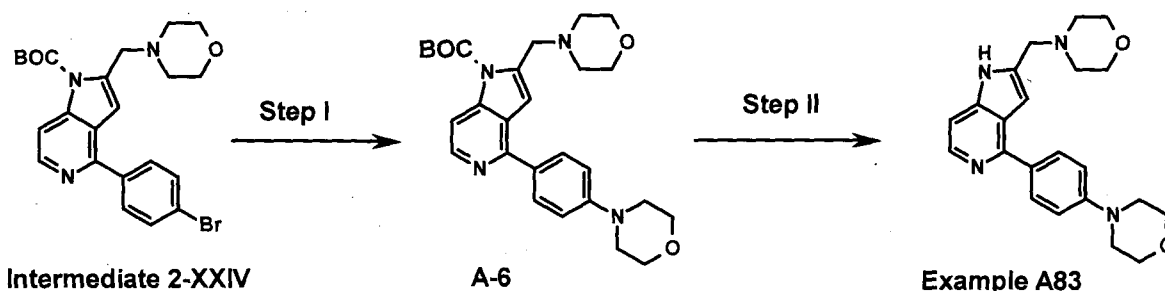
^1H NMR (400 MHz, CD_3OD): δ 1.15 (d, $J = 6.4$ Hz, 6H), 2.73-2.78 (m, 5H), 3.30-3.35 (m, 4H), 3.74 (d, $J = 4.4$ Hz, 4H), 3.80-3.90 (m, 4H), 7.06 (s, 1H), 7.13 (d, $J = 9.2$ Hz, 2H), 7.37 (d, $J = 8$ Hz, 1H), 7.80 (d, $J = 8.4$ Hz, 2H), 8.24 (d, $J = 6$ Hz,

1H)

[0474]

Example A83: 4-[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]morpholine

5 [0475]



[0476]

Step I: tert-butyl 2-(morpholinomethyl)-4-(4-morpholinophenyl)pyrrolo[3,2-c]pyridine-1-carboxylate (**A-6**)

10 A solution of **Intermediate 2-XXIV** (0.17 g, 0.36 mmol), morpholine (0.078 g, 0.90 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.013 g, 0.021 mmol) and Cs₂CO₃ (0.176 g, 0.54 mmol) in anhydrous 1,4-dioxane (2.5 mL) was degassed under a stream of argon for 15 minutes. Tris

15 (dibenzylideneacetone)dipalladium(0) (0.07 g, 0.007 mmol) was added thereto, and degassing was continued for another 15 minutes. The reaction mixture was heated to 100°C for 24 hours. The reaction mixture was cooled to room temperature and diluted with water (10 mL) and EtOAc (15 mL). The organic

20 layer was separated, and the aqueous layer was back extracted with EtOAc (15 mL X 2). The combined organic layers were washed with brine (15 mL) and dried over anhydrous Na₂SO₄. The obtained residue after evaporation of solvent was purified by preparative TLC (solvent system: 5% MeOH in dichloromethane)

25 to give the desired product **A-6** (0.080 g, 46%) as a white solid. LCMS: *m/z* 479.2 [M⁺+1].

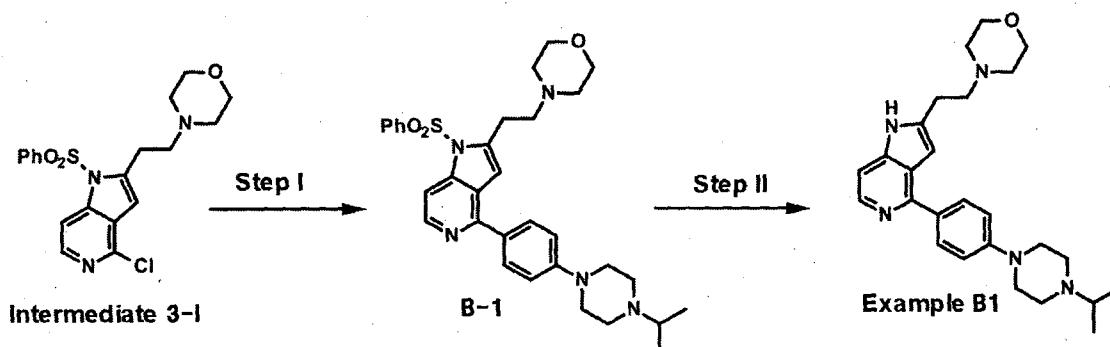
[0477]

Step II: 4-[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]morpholine (**Example A83**)

30 A solution of **A-6** (0.08 g, 0.167 mmol) in diethyl ether

(2 mL) was treated with 2 M HCl in diethyl ether (1 mL) at 0°C. After 2 hours, the reaction mixture was evaporated and pH was adjusted to ~7 using saturated aqueous NaHCO₃ solution. The resulting mixture was evaporated to dryness (product is water soluble). The obtained residue was taken into 20% MeOH in dichloromethane (25 mL), and the mixture was filtered. The filtrate was evaporated to give the desired product **Example A83** (0.02 g, 32 %) as a yellow solid; LCMS: *m/z* 379.3 [*M*⁺+1]. ¹HNMR (400 MHz, CDCl₃): δ 2.50 (t, *J* = 4.4 Hz, 4H), 3.26 (t, *J* = 4.8 Hz, 4H), 3.69 (s, 2H), 3.72 (t, *J* = 4.4 Hz, 4H), 3.89 (t, *J* = 4.8 Hz, 4H), 6.71 (s, 1H), 7.04 (d, *J* = 9.2 Hz, 2H), 7.22 (d, *J* = 5.6 Hz, 1H), 7.95 (d, *J* = 8.8 Hz, 2H), 8.35 (d, *J* = 6.0 Hz, 1H), 9.19 (bs, 1H) [0478]

Example B1: 4-[2-[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine [0479]



Step I: 4-[2-[1-(benzenesulfonyl)-4-[4-(4-isopropylpiperazin-1-yl)phenyl]pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine (**B-1**) [0480]

A mixture of **Intermediate 3-I** (0.166 g, 0.40 mmol), 1-isopropyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine (**Intermediate 1-II**) (0.175 g, 0.53 mmol) and K₂CO₃ (0.17 g, 1.22 mmol) in dioxane/water (4:1, 5 mL) was degassed in a stream of argon for 15 minutes. To this mixture was added 1,1-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (0.005 g, 0.0061 mmol), and the reaction mixture was again degassed for additional 15 [0481]

minutes. After stirring at 100°C for 18 hours, the volatiles were removed by evaporation, and the obtained crude reaction mixture was diluted with water (20 mL), followed by extraction with ethyl acetate (25 mL x 3). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na₂SO₄, concentrated in vacuo, followed by preparative TLC purification to give the desired product **B-1** (0.152 g, 66%) as a brown solid; LCMS: *m/z* 574.2 [*M*⁺ +1].

[0481]

10 Step II: 4-[2-[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine (**Example B1**)

A stirred solution of **B-1** (0.15 g, 0.26 mmol) in 1,4-dioxane (5 mL) was treated with sodium *tert*-butoxide (0.075 g, 0.784 mmol) under argon atmosphere. After stirring at 90°C for 8 hours, the excess solvent was removed in vacuo. The obtained residue was dissolved in ethyl acetate (25 mL), and the solution was washed successively with water (10 mL) and brine (10 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. The obtained residue (0.14 g) was purified by preparative TLC to give the desired compound **Example B1** (0.076 g, 67%) as a pale yellow solid; LCMS: *m/z* 434.4 [*M*⁺ +1].

¹HNMR (400 MHz, CDCl₃): 1.13 (d, *J* = 6.4 Hz, 6H), 2.60 - 2.62 (m, 4H), 2.73 - 2.79 (m, 7H), 2.99 (t, *J* = 5.6 Hz, 2H), 3.34 (t, *J* = 4.8 Hz, 4H), 3.83 (t, *J* = 4.8 Hz, 4H), 6.57 (s, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 6 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 8.31 (d, *J* = 5.2 Hz, 1H), 10.39 (br s, 1H)

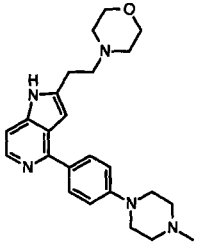
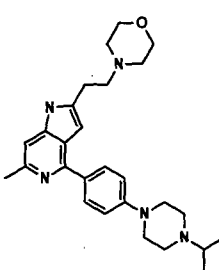
[0482]

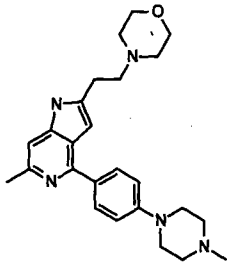
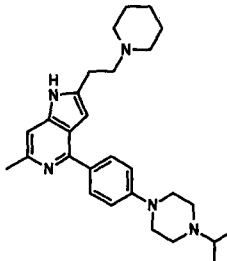
The following compounds **Examples B2-B5** as shown in Table 15 were prepared from the corresponding intermediates in the same manner as **Example B1**.

[0483]

Table 15:

Ex.No.	IUPAC name	Structure	Int. from which prepared	Analytical data
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B2	4-[2-[4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine		3-I and 1-I	LCMS: m/z 406.3 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3): δ 2.37 (s, 3H), 2.60-2.63 (m, 8H), 2.75 (t, J = 6 Hz, 2H), 2.98 (t, J = 6 Hz, 2H), 3.31 (t, J = 4.4 Hz, 4H), 3.84 (t, J = 4 Hz, 4H), 6.54 (s, 1H), 7.05 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 6 Hz, 1H), 7.92 (d, J = 8.8 Hz, 2H), 8.32 (d, J = 5.6 Hz, 1H), 10.9 (s, 1H)
B3	4-[2-[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-6-methyl-1H-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine		3-II and 1-II	LCMS: m/z 448.3 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3): δ 1.11 (d, J = 6.3 Hz, 6H), 2.58-2.62 (m, 4H), 2.66 (s, 3H), 2.70-2.75 (m, 7H), 2.93 (t, J = 5.9 Hz, 2H), 3.29 (t, J = 4.9 Hz, 4H), 3.82 (t, J = 4.9 Hz, 4H), 6.46 (s, 1H),

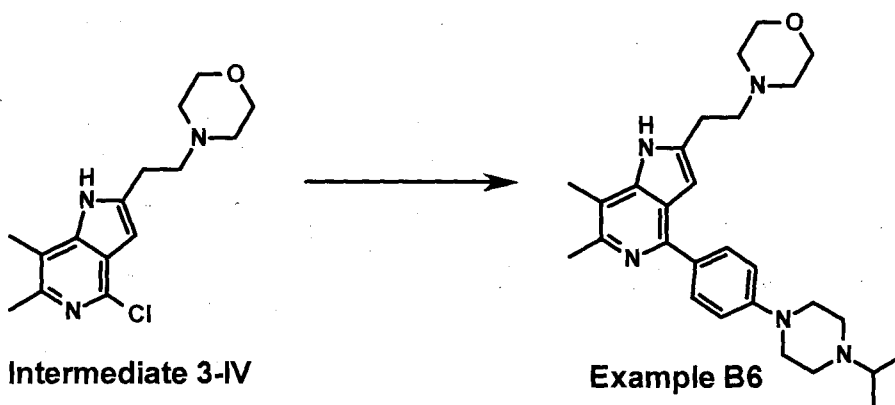
				7.07 (s, 1H), 7.30 (d, J = 8.8 Hz, 2H), 7.89 (d, J = 8.8 Hz, 2H), 9.82 (bs, 1H)
B4	4-[2-[6-methyl-4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine		3-II and 1-I	LCMS: m/z 420.3 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3): δ 2.38 (s, 3H), 2.57-2.65 (m, 8H), 2.74-2.80 (m, 5H), 2.96 (t, J = 5.6 Hz, 2H), 3.30 (t, J = 4.8 Hz, 4H), 3.82 (t, J = 4.4 Hz, 4H), 6.49 (s, 1H), 7.02 (d, J = 8.8 Hz, 2H), 7.07 (s, 1H), 7.91 (d, J = 8.8 Hz, 2H), 10.40 (bs, 1H)
B5	4-[4-(4-isopropylpiperazin-1-yl)phenyl]-6-methyl-2-[2-(1-piperidyl)ethyl]-1H-pyrrolo[3,2-c]pyridine		3-III and 1-II	LCMS: m/z 446.3 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3): δ 1.11 (d, J = 6.4 Hz, 6H), 1.70-1.80 (m, 4H), 2.20-2.45 (m, 3H), 2.50-2.63 (m, 5H), 2.65-2.78 (m, 8H), 2.95 (t, J =

				6.0 Hz, 2H), 3.29 (t, J = 4.4 Hz, 4H), 6.44 (s, 1H) 7.00-7.04 (m, 3H), 7.89 (d, J = 8.4 Hz, 2H), 10.40 (bs, 1H)
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[0484]

Example B6: 4-[2-[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-6,7-dimethyl-1H-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine

[0485]



5

[0486]

A mixture of **Intermediate 3-IV** (0.200 g, 0.68 mmol), **Intermediate 1-II** (0.337 g, 1.02 mmol) and K_2CO_3 (0.282 g, 2.04 mmol) in 4:1 mixture of dioxane/water (5 mL) was degassed in a stream of argon for 30 minutes. To the mixture was added $PdCl_2(dppf)$ DCM (0.008 g, 0.010 mmol), and the reaction mixture was again degassed for additional 30 minutes. After stirring at 90°C for 18 hours, the reaction mixture was diluted with water (10 mL), followed by extraction with ethyl acetate (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using 5-10% MeOH in dichloromethane to give the desired product **Example B6** (0.16 g, 51%) as a light yellow solid; LCMS: m/z 462.4 $[M^+ + 1]$.

20

1H NMR (400 MHz, $CDCl_3$): δ 1.11 (d, J = 6.4 Hz, 6H), 2.40 (s, 3H),

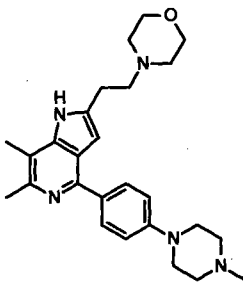
2.61-2.64 (m, 4H), 2.65 (s, 3H), 2.70-2.73 (m, 5H), 2.77 (t, J = 6.0 Hz, 2H), 2.96 (t, J = 6.0 Hz, 2H), 3.28 (t, J = 4.8 Hz, 4H), 3.84 (t, J = 4.4 Hz, 4H), 6.45 (s, 1H), 7.02 (d, J = 8.8 Hz, 2H), 7.88 (d, J = 8.8 Hz, 2H), 10.32 (bs, 1H, -NH)

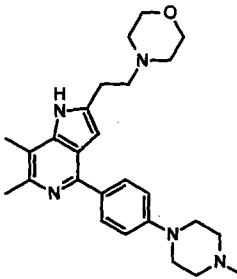
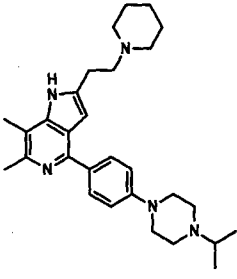
5 [0487]

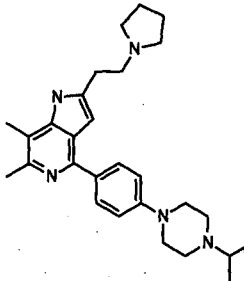
The following compounds **Examples B7-B10** as shown in Table 16 were prepared from their corresponding intermediates in the same manner as **Example B6**.

[0488]

10 Table 16:

Ex.No	IUPAC name	Structure	Int. from which prepared	Analytical Data
B7	4-[2-[6,7-dimethyl-4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine		3-IV and 1-I	LCMS: m/z 434.4 [M ⁺ +1] ¹ HNMR (400 MHz, CDCl ₃): δ 2.36 (s, 3H), 2.40 (s, 3H), 2.5-2.63 (m, 8H), 2.66 (s, 3H), 2.77 (t, J = 6.0 Hz, 2H), 2.96 (t, J = 6.0 Hz, 2H), 3.28 (t, J = 4.8 Hz, 4H), 3.84 (t, J = 4.4 Hz, 4H), 6.46 (s, 1H), 7.02 (d, J = 8.8 Hz, 2H), 7.89 (d, J = 8.4 Hz, 2H), 10.30 (bs, 1H)

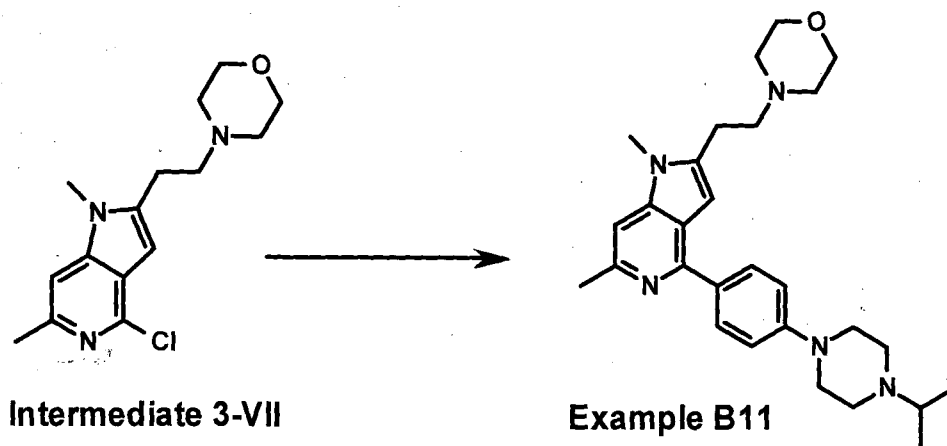
B8	4-[2-[4-[4-(4-ethylpiperazin-1-yl)phenyl]-6,7-dimethyl-1H-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine		3-IV and 1-IV	LCMS: m/z 448.4 ($M^+ + 1$) ^1H NMR (400 MHz, CDCl_3): δ 1.14 (t, $J = 7.2$ Hz, 3H), 2.39 (s, 3H), 2.46-2.52 (m, 2H), 2.61-2.64 (m, 8H), 2.65 (s, 3H), 2.77 (t, $J = 6.0$ Hz, 2H), 2.96 (t, $J = 6.0$ Hz, 2H), 3.30 (t, $J = 4.8$ Hz, 4H), 3.84 (t, $J = 4.4$ Hz, 4H), 6.46 (s, 1H), 7.02 (d, $J = 8.8$ Hz, 2H), 7.88 (d, $J = 8.8$ Hz, 2H), 10.39 (bs, 1H, -NH)
B9	4-[4-(4-isopropylpiperazin-1-yl)phenyl]-6,7-dimethyl-2-[2-(1-piperidyl)ethyl]-1H-pyrrolo[3,2-c]pyridine		3-V and 1-II	LCMS: m/z 460.4 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3): δ 1.10 (d, $J = 6.4$ Hz, 6H), 1.55-1.57 (m, 2H), 1.69-1.73 (m, 4H), 2.40 (s, 3H), 2.52-2.62 (m, 4H), 2.64 (s, 3H), 2.68-2.76 (m, 7H), 2.93 (t,

				$J = 6.0 \text{ Hz, 2H}$), $3.27 \text{ (t, } J = 4.8 \text{ Hz, 4H)}$, 6.42 (s, 1H) , $7.02 \text{ (d, } J = 8.8 \text{ Hz, 2H)}$, $7.88 \text{ (d, } J = 8.8 \text{ Hz, 2H)}$, $10.81 \text{ (bs, 1H, -NH)}$.
B10	4-[4-(4-isopropylpiperazin-1-yl)phenyl]-6,7-dimethyl-2-(2-pyrrolidin-1-ylethyl)-1H-pyrrolo[3,2-c]pyridine		3-VI and 1-II	LCMS: m/z 446.3 $[M^+ + 1]$ $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 1.10 (d, $J = 6.4 \text{ Hz, 6H}$), 1.89-1.91 (m, 4H), 2.36 (s, 3H), 2.64 (s, 3H), 2.68-2.76 (m, 9H), 2.88 (t, $J = 6.4 \text{ Hz, 2H}$), 2.97 (t, $J = 6.4 \text{ Hz, 2H}$), 3.28 (t, $J = 4.4 \text{ Hz, 4H}$), 6.44 (s, 1H), 7.02 (d, $J = 8.8 \text{ Hz, 2H}$), 7.88 (d, $J = 8.8 \text{ Hz, 2H}$), 10.42 (bs, 1H, -NH)

[0489]

Example B11: 4-[2-[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1,6-dimethyl-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine

[0490]



[0491]

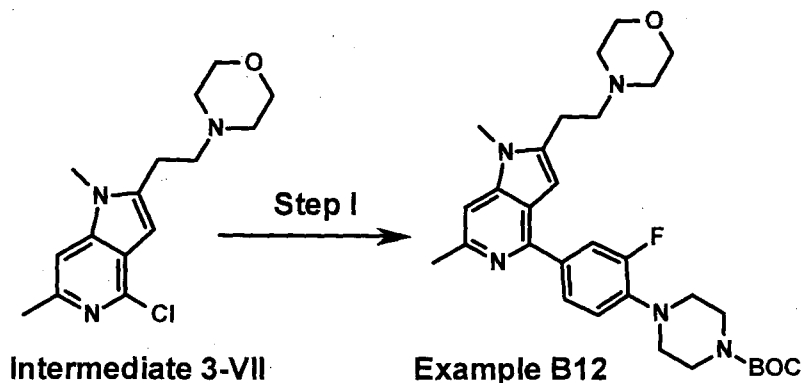
A mixture of **Intermediate 3-VII** (11.2 g, 38.12 mmol), **Intermediate 1-II** (15.09 g, 45.74 mmol) and K_2CO_3 (15.7 g, 114.36 mmol) in 4:1 mixture of dioxane/water (100 mL) was degassed in a stream of argon for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium(0) (4.4 g, 3.82 mmol), and the reaction mixture was again degassed for additional 30 minutes. After stirring at 95°C for 18 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (150 mL), followed by extraction with ethyl acetate (250 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using 3% MeOH in dichloromethane to give the desired product **Example B11** (14.4 g, 70%) as a light brown solid; LCMS: m/z 462.3 [$M^+ + 1$].

1H NMR (400 MHz, $CDCl_3$): δ 1.14 (d, J = 6.4 Hz, 6H), 2.55 (t, J = 4.4 Hz, 4H), 2.71–2.85 (m, 10 H), 2.95 (t, J = 7.2 Hz, 2H), 3.33–3.40 (m, 4H), 3.68 (s, 3H), 3.75 (t, J = 4.4 Hz, 4H), 6.52 (s, 1H) 6.95 (s, 1H), 7.05 (d, J = 8.8 Hz, 2H), 7.90 (d, J = 8.8 Hz, 2H)

[0492]

Example B12: tert-butyl 4-[4-[1,6-dimethyl-2-(2-morpholinoethyl)pyrrolo[3,2-c]pyridin-4-yl]-2-fluorophenyl]piperazine-1-carboxylate

[0493]



[0494]

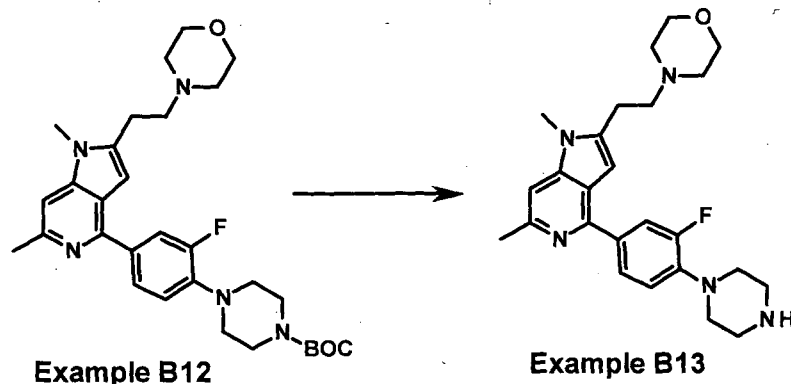
A mixture of **Intermediate 3-VII** (0.2 g, 0.682 mmol),
 5 **Intermediate 1-XX** (0.387 g, 0.954 mmol) and K_2CO_3 (0.282 g, 2.046 mmol) in 4:1 mixture of dioxane/water (5 mL) was degassed in a stream of argon for 30 minutes. To this mixture was added tetrakis(triphenylphosphine)palladium (0.079 g, 0.0682 mmol), and the reaction mixture was again degassed for
 10 additional 15 minutes. After stirring at 95°C for 16 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (15 mL), followed by extraction with ethyl acetate (25 mL x 3). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and
 15 concentrated under reduced pressure. The obtained residue was purified by Combiflash using 4% MeOH in dichloromethane to give the desired product **Example B12** (0.201 g, 55%) as a light brown solid; LCMS: m/z 169.2 ($M^+/2$ -BOC + 1).

1H NMR (400 MHz, DMSO): δ 1.43 (s, 9H), 2.44-2.54 (m, 4H), 2.55
 20 (s, 3H), 2.65 (t, $J = 7.6$ Hz, 2H), 2.94 (t, $J = 7.6$ Hz, 2H), 3.03 (t, $J = 4.8$ Hz, 4H), 3.50-3.51 (m, 4H), 3.59 (t, $J = 4.4$ Hz, 4H), 3.69 (s, 3H), 6.56 (s, 1H), 7.16 (app. t, $J = 8.8$ Hz, 1H), 7.24 (s, 1H), 7.72 (dd, $J = 2$ Hz, $J = 14$ Hz, 1H), 7.77 (dd, $J = 1.6$ Hz, $J = 10.4$ Hz, 1H)

25 [0495]

Example B13: 4-[2-[4-(3-fluoro-4-(piperazin-1-yl)-phenyl)-1,6-dimethyl-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine

[0496]



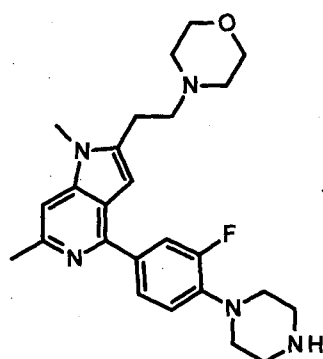
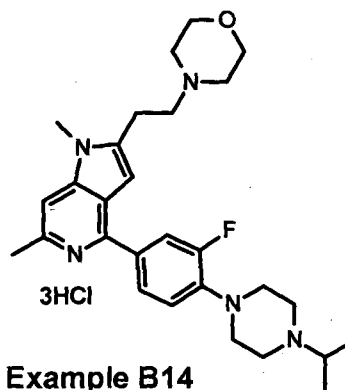
[0497]

To a solution of **Example B12** (0.200 g, 0.372 mmol) in
 5 1,4-dioxane (2 mL) at 0°C was added 4M HCl in 1,4-dioxane (4
 mL). After stirring at room temperature for 16 hours, the
 volatiles were removed by evaporation, and the obtained
 residue was diluted with water (2 mL) and pH was adjusted to
 ~8 using saturated aqueous NaHCO₃ solution (10 mL). The
 10 resulting solution was evaporated to dryness, and the obtained
 residue was diluted with 5% MeOH in dichloromethane (20 mL)
 and inorganic substance was removed by filtration. The
 filtrate was concentrated to give the desired product **Example**
B13 (0.158 g, 97%) as a white solid. The obtained crude
 15 product was used for next step without purification; LCMS: m/z
 219.6(M⁺/2 +1).

[0498]

Example B14: 4-[2-[4-[3-fluoro-4-(4-isopropylpiperazin-1-
 yl)phenyl]-1,6-dimethyl-pyrrolo[3,2-c]pyridin-2-
 20 yl]ethyl]morpholine

[0499]

**Example B13****Example B14**

[0500]

To a solution of **Example B13** (0.158 g, 0.363 mmol) in a mixture of MeOH:DCE (1:1, 4 mL) were added acetone (0.251 g, 4.33 mmol), a drop of acetic acid and activated 4Å powdered molecular sieves (0.4 g) successively. After stirring for 4 hours at room temperature, sodium cyanoborohydride (0.034 g, 0.542 mmol) was added thereto, and the mixture was stirred for 16 hours. The reaction mixture was filtered through a celite pad, and washed with EtOAc (25 mL), and the filtrate was taken into water (20 mL), and the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by preparative TLC using 10% MeOH in dichloromethane to give the desired product **Example B14** (0.14 g, 80%) as a pale yellow liquid. To the solution of **Example B14** (0.07 g, 0.146 mmol) in dioxane (0.5 mL) was added 4M HCl in dioxane (1 mL) at 0°C. After stirring for 2 hours at room temperature, the volatiles were removed by evaporation, and the obtained solid was dried under vacuum to give a 3HCl salt of **Example B14** (0.055 g, 63%) as a yellow solid; LCMS: *m/z* 480.2 [*M*⁺+1]. ¹HNMR (400 MHz, DMSO): δ 1.35 (d, *J* = 6.4 Hz, 6H), 2.79 (s, 3H), 3.12-3.26 (m, 4H), 3.42-3.46 (m, 4H), 3.49-3.56 (m, signal merged in DMSO, 7H), 3.70 (d, *J* = 12 Hz, 2H), 3.85 (t, *J* = 12 Hz, 2H), 3.91 (s, 3H), 4.00 (d, *J* = 12 Hz, 2H), 6.90 (s, 1H), 7.40 (app. t, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.83 (dd, *J* = 1.6 Hz, *J* = 13.2 Hz, 1H), 7.96 (s, 1H), 11.20 (s, 1H),

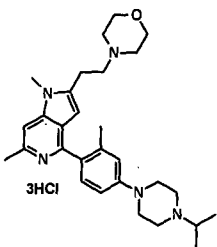
12.00 (s, 1H), 14.30 (s, 1H)

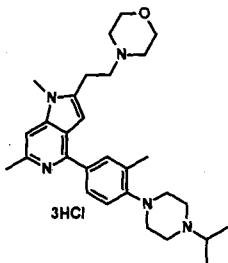
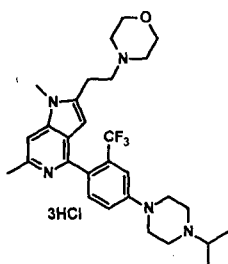
[0501]

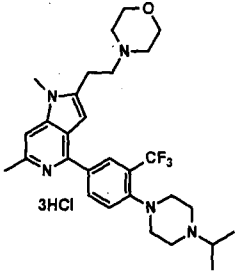
The following compounds **Examples B15-B23** as shown in Table 17 were prepared from their corresponding intermediates in the same manner as in the preparation of **Example B14 from Intermediate 3-VII**.

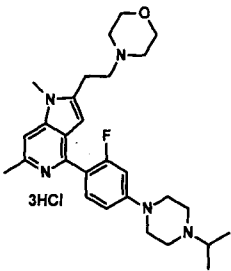
[0502]

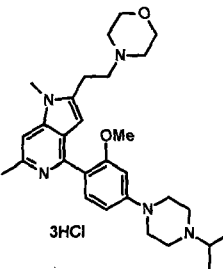
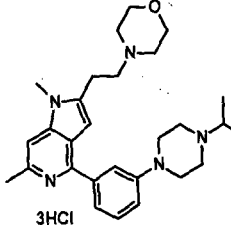
Table 17

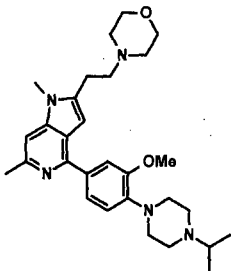
Ex.No.	IUPAC name	Structure	Int. from which prepared	Analytical Data
B15	4-[2-[4-[4-(4-isopropylpiperazin-1-yl)-2-methylphenyl]-1,6-dimethylpyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine		3-VII and 1-XXIV	LCMS: m/z 476.20 [$M^+ + 1$] ^1H NMR (400 MHz, DMSO): δ 1.37 (d, $J = 4$ Hz, 6H), 2.18 (s, 3H), 2.76 (s, 3H), 3.11 (m, 4H), 3.35-3.38 (m, 4H), 3.49-3.56 (m, 7H), 3.81-3.88 (m, 2H), 3.90 (s, 3H) 3.98-4.02 (m, 4H), 6.49 (s, 1H), 7.08 (d, $J = 8.8$ Hz, 1H), 7.13 (s, 1H), 7.39 (d, $J = 8.8$ Hz, 1H), 7.96 (s, 1H), 11.23 (bs, 1H), 11.97 (bs, 1H), 14.23 (bs, 1H)

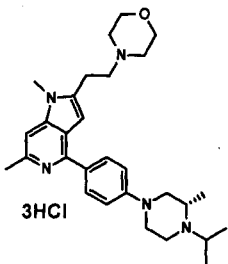
B16	4-[2-[4-[4-(4-isopropylpiperazin-1-yl)-3-methylphenyl]-1,6-dimethylpyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine		3-VII and 1-XXI	LCMS: m/z 476.20 $[M^+ + 1]$ ^1H NMR (400 MHz, DMSO): δ 1.37 (d, $J = 4$ Hz, 6H), 2.42 (s, 3H), 2.78 (s, 3H), 3.10-3.14 (m, 3H), 3.23-3.24 (m, 2H), 3.32-3.38 (m, 4H), 3.45-3.47 (m, 2H), 3.50-3.56 (m, 6H), 3.82-3.88 (m, 2H), 3.91 (s, 3H), 3.99-4.02 (m, 2H), 6.87 (s, 1H), 7.33 (d, $J = 8$ Hz, 1H), 7.75 (d, $J = 8$ Hz, 2H), 7.94 (s, 1H), 11.12 (bs, 1H), 11.98 (bs, 1H), 14.23 (bs, 1H)
B17	4-[2-[4-[4-(4-isopropylpiperazin-1-yl)-2-(trifluoromethyl)phenyl]-1,6-		3-VII and 1-XXV	LCMS: m/z 530.2 $[M^+ + 1]$ ^1H NMR (400 MHz, DMSO): δ 1.35 (d, $J = 4$ Hz, 6H), 2.75 (s, 3H), 3.03-3.22 (m, 5H), 3.38-

	dimethyl- pyrrolo[3,2- c]pyridin-2- yl]ethyl]mor pholine			3.56 (m, 12H), 3.83-3.86 (m, 2H), 3.91 (s, 3H), 3.96-3.98 (m, 2H), 6.41 (s, 1H), 7.49 (d, J = 8 Hz, 1H), 7.54 (s, 1H), 7.59 (d, J = 8.8 Hz, 1H), 8.04 (s, 1H), 11.44 (br.s, 1H), 11.86 (br.s, 1H), 14.85 (br.s, 1H)
B18	4-[2-[4-[4- (4- isopropylpip erazin-1- yl)-3- (trifluorome thyl)phenyl] -1,6- dimethyl- pyrrolo[3,2- c]pyridin-2- yl]ethyl]mor pholine		3-VII and 1-XXII	LCMS: m/z 530.2 [M ⁺ +1] ¹ HNMR (400 MHz, DMSO): δ 1.37 (d, J = 4 Hz, 6H), 2.81 (s, 3H), 3.09-3.16 (m, 4H), 3.23- 3.26 (m, 3H), 3.54-3.611 (m, 9H), 3.68-3.70 (m, 2H), 3.86- 3.93 (m, 4H), 3.99-4.02 (m, 2H), 6.86 (s, 1H), 7.79 (d, J = 8 Hz, 1H), 8.01 (s, 1H), 8.24 (d, J = 8 Hz, 2H), 11.21

				(br.s, 1H), 11.90 (br.s, 1H), 14.60 (br.s, 1H)
B19	4-[2-[4-[2-fluoro-4-(4-isopropylpiperazin-1-yl)phenyl]-1,6-dimethylpyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine		3-VII and 1-XXVII	LCMS: m/z 480.2 [M^++1] ^1H NMR (400 MHz, DMSO): δ 1.34 (d, J = 8.0 Hz, 6H), 2.75 (s, 3H), 3.12 - 3.20 (m, 4H), 3.45 - 3.54 (m, 11H), 3.81 - 3.90 (m, 2H), 3.88 (s, 3H), 4.00 (d, J = 12.0 Hz, 2H), 4.09 (d, J = 12.0 Hz, 2H), 6.64 (s, 1H), 7.10 (d, J = 8.8 Hz, 1H), 7.15-7.19 (d, J = 14.8 Hz, 1H), 7.65 (app. t, J = 8.8 Hz, 1H), 7.95 (s, 1H), 11.10 (br.s, 1H), 12.71 (br.s, 1H), 14.45 (br. s, 1H)

B20	4-[2-[4-[4-(4-isopropylpiperazin-1-yl)-2-methoxyphenyl]-1,6-dimethylpyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine		3-VII and 1-XXVI	LCMS: m/z 492.2 $[M^++1]$ $^1\text{HNMR}$ (400 MHz, DMSO): δ 1.34 (d, J = 8.0 Hz, 6H), 2.73 (s, 3H), 3.12 - 3.21 (m, 4H), 3.45 - 3.50 (m, 11H), 3.86 - 3.95 (m, 8H), 3.99 (d, J = 12.0 Hz, 2H), 4.10 (d, J = 12.0 Hz, 2H), 6.58 (s, 1H), 6.82 - 6.88 (m, 2H), 7.46 (d, J = 12 Hz, 1H), 7.88 (s, 1H), 11.42 (br. s, 1H), 11.95 (br.s, 1H), 14.1 (br.s, 1H)
B21	4-[2-[4-[3-(4-isopropylpiperazin-1-yl)phenyl]-1,6-dimethylpyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine		3-VII and 1-VII	LCMS: m/z 462.2 $[M^++1]$ $^1\text{HNMR}$ (400 MHz, DMSO): δ 1.34 (d, J = 7.2 Hz, 6H), 2.81 (s, 3H), 3.09 - 3.19 (m, 5H), 3.34 - 3.69 (m, 10H), 3.82 - 3.88 (t, J = 2.4

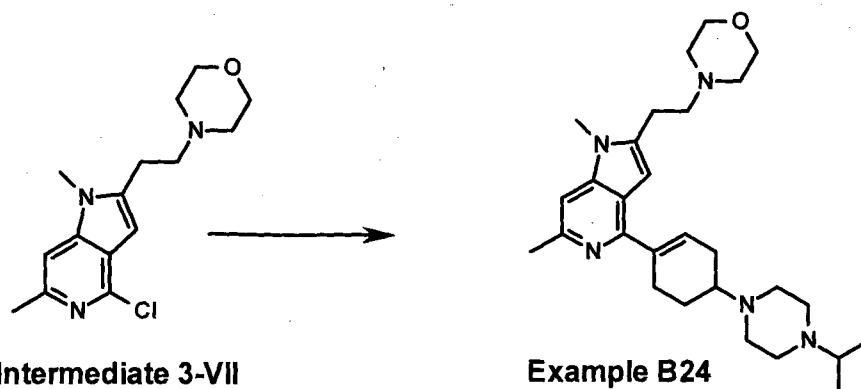
				Hz , 2H), 3.92 (s, 3H), 3.97 - 4.08 (m, 4H), 6.84 (s, 1H), 7.33 - 7.38 (m, 2H), 7.45 - 7.46 (m, 1H), 7.56 - 7.60 (app. t, J = 8.4 Hz, 1H), 7.98 (s, 1H), 11.02 (br.s, 1H), 11.81 (br.s, 1H), 14.45 (br.s, 1H)
B22	4-[2-[4-[4- (4- isopropylpip erazin-1- yl)-3- methoxy- phenyl]-1,6- dimethyl- pyrrolo[3,2- c]pyridin-2- yl]ethyl]mor pholine		3-VII and 1-XXIII	LCMS: m/z 492.2 $[M^+ + 1]$ $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 1.13 (d, J = 6.4 Hz, 6H), 2.54-2.56 (m, 4H), 2.71 (s, 3H), 2.72- 2.75 (m, 2H), 2.76-2.80 (m, 5H), 2.96 (t, J = 7.2 Hz, 2H), 3.19-3.21 (m, 4H), 3.68 (s, 3H), 3.75 (t, J = 4.4 Hz, 4H), 3.97 (s, 3H), 6.52 (s, 1H), 6.98 (s, 1H), 7.05 (d, J = 8.8 Hz, 1H), 7.47-

				7.51 (m, 2H)
B23	4-[2-[4-[4- [(3S)-4- isopropyl-3- methyl- piperazin-1- yl]phenyl]- 1,6- dimethyl- pyrrolo[3,2- c]pyridin-2- yl]ethyl]mor- pholine	 3HCl	3-VII and 1-XXIX	LCMS: m/z 476.2 $[M^+ + 1]$ ^1H NMR (400 MHz, DMSO): δ 1.18 (d, J = 7 Hz, 3H), 1.35- 1.48 (m, 1H), 1.43 (d, 7 Hz, 6H), 2.78 (s, 3H), 3.00-3.20 (m, 3H), 3.25- 3.35 (m, 2H), 3.45-3.60 (m, 6H), 3.65-3.75 (m, 1H), 3.80- 3.95 (m, 6H), 3.95-4.05 (m, 2H), 4.09 (t, J = 11.8 Hz, 2H), 6.87 (s, 1H), 7.31 (d, J = 8.6 Hz, 2H), 7.85 (d, J = 8.6 Hz, 2H), 7.88 (s, 1H), 11.30 (s, 1H), 11.90 (s, 1H), 14.10 (s, 1H)

[0503]

Example B24: 4-[2-[4-[4-(4-isopropylpiperazin-1-yl)cyclohexen-1-yl]-1,6-dimethyl-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine

[0504]



[0505]

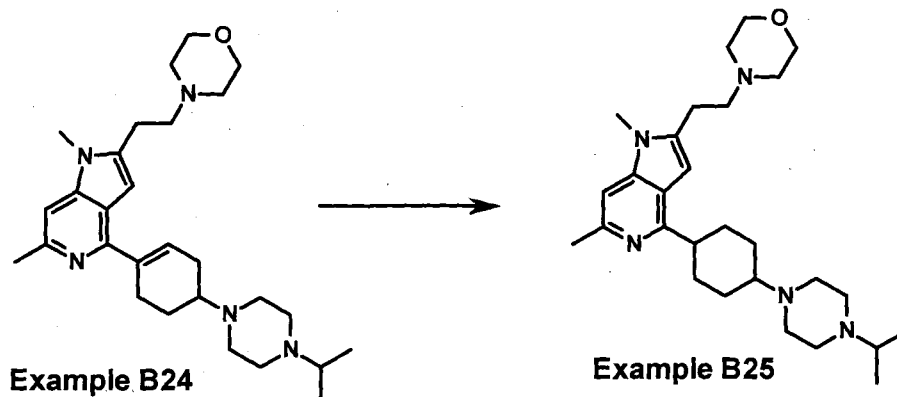
A stirred solution of **Intermediate 3-VII** (0.15 g, 0.51 mmol), **Intermediate 1-XXVIII** (0.34 g, 1.02 mmol) and K_2CO_3 (0.21 g, 1.53 mmol) in a mixture of dioxane/water (4:1, 5 mL) was degassed in a stream of argon for 15 minutes. To this mixture was added $Pd(PPh_3)_4$ (0.06 g, 0.05 mmol), and the reaction mixture was again degassed for additional 15 minutes. After stirring at 100°C for 18 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (20 mL), followed by extraction with ethyl acetate (25 mL x 3). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by preparative TLC to give the desired product **Example B24** (0.12 g, 50%) as a yellow solid; LCMS: m/z 233.7 [$M^+/2+1$].

1H NMR (400 MHz, $CDCl_3$): δ 1.09 (d, $J = 6.4$ Hz, 6H), 2.12-2.21 (m, 1H), 2.26-2.38 (m, 1H), 2.45-2.49 (m, 2H), 2.56 (t, $J = 4.4$ Hz, 4H), 2.62 (s, 3H), 2.62-2.68 (m, 4H), 2.70-2.74 (m, 9H), 2.93 (t, $J = 7.2$ Hz, 3H), 3.63 (s, 3H), 3.75 (t, $J = 4.8$ Hz, 4H), 6.32 (t, $J = 2.8$ Hz, 1H), 6.37 (s, 1H), 6.88 (s, 1H).

[0506]

Example B25: 4-[2-[4-[4-(4-isopropylpiperazin-1-yl)cyclohexyl]-1,6-dimethyl-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine

[0507]



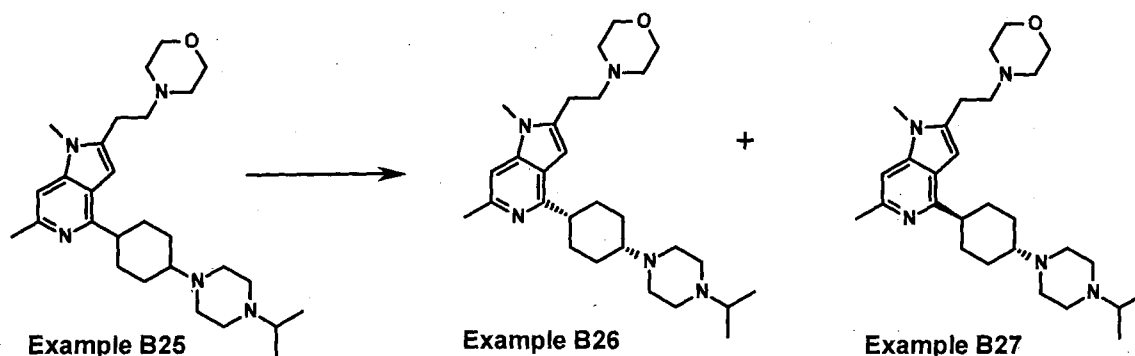
[0508]

To a stirred solution of **Example B24** (0.12 g, 0.25 mmol) in EtOAc (3 mL) was added Pd/C (0.024 g, 20% W/W). The flask was evacuated and filled with hydrogen gas (this procedure was repeated twice). The reaction mixture was then stirred for 18 hours under hydrogen atmosphere. After completion of reaction, the reaction mixture was filtered through a celite pad. The obtained filtrate was concentrated under reduced pressure to give the desired product **Example B25** (0.08 g, 66 %) as a yellow oil; LCMS: m/z 234.7 [$M^+/2+1$].

[0509]

Example B26 and Example B27: *Cis* and *trans*-4-[2-[4-[4-(4-isopropylpiperazin-1-yl)cyclohexyl]-1,6-dimethyl-pyrrolo[3,2-
c]pyridin-2-yl]ethyl]morpholine

[0510]



[0511]

Example B25 (0.08 g, 0.17 mmol) was dissolved in a mixture of methanol:dichloromethane (9:1, 2 mL). 83 μ L of this solution was loaded onto a 150 x 21.2 mm 5 μ phenomenex Gem

column and eluted with a mobile phase comprising of acetonitrile:water (6:4; modified with 0.05% Triethylamine) at a flow rate of 16 mL/min. **Example B26** was collected between 3.0 minute and 4.0 minute time points, while **Example B27** was collected between 4.3 minute and 5.6 minute time points. 24 such injections were carried out and the pooled fractions were concentrated under reduced pressure to give the desired products **Example B26** (0.03 g, 0.064 mmol) and **Example B27** (0.05, 0.10 mmol). **Examples B26** and **B27** were subjected to hydrochloride salt formation by following procedure:

To a solution of **Example B26** (0.03 g, 0.064 mmol) in dichloromethane (3 mL) was added 4M HCl in dioxane (1 mL) drop wise over 10 minutes. The resulting white precipitate was stirred at ambient temperature for 1 hour. The volatiles were removed by evaporation, and the solid obtained was dried under vacuum to give a 4HCl salt of **Example B26** (0.030 g, 0.064 mmol) as a white solid; LCMS: m/z 468.3 [$M^+ + 1$].

^1H NMR (400 MHz, DMSO- d_6): δ 1.31 (d, $J = 6.4$ Hz, 6H), 1.68-1.82 (m, 2H), 2.01-2.09 (m, 2H), 2.15-2.28 (m, 2H), 2.30-2.39 (m, 2H), 2.74 (s, 3H), 3.13-3.22 (m, 2H), 3.40-3.49 (m, 3H), 3.52-3.62 (m, 8H), 3.70-3.73 (m, 5H, merged in residual solvent peak), 3.85 (s, 3H), 3.87-3.90 (m, 3H), 4.00-4.05 (m, 2H), 7.11 (s, 1H), 7.84 (s, 1H), 11.90 (bs, 1H), 12.02 (bs, 1H), 12.38 (bs, 1H), 14.42 (bs, 1H)

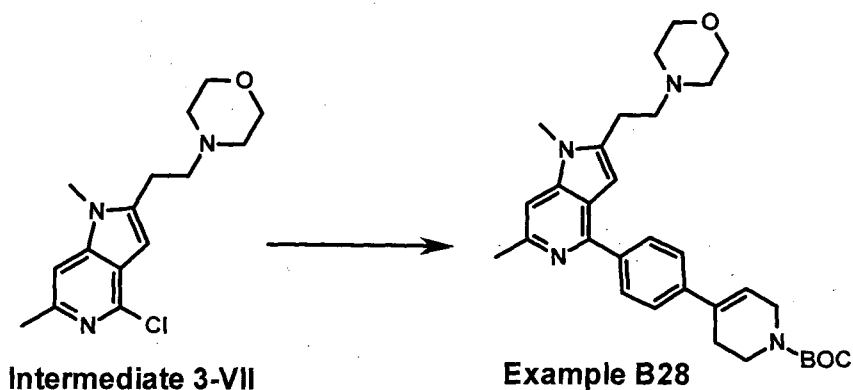
[0512]

A tetrahydrochloride salt of **Example B27** (0.050, 0.10 mmol) was prepared in a similar manner as **Example B26**; LCMS: m/z 468.3 [$M^+ + 1$].

^1H NMR (400 MHz, DMSO- d_6): δ 1.34 (d, $J = 6.4$ Hz, 6H), 1.78-1.90 (m, 4H), 2.41-2.49 (m, 3H), 2.79 (s, 3H), 3.12-3.25 (m, 2H), 3.40-3.45 (m, 2H), 3.52-3.62 (m, 12 H, merged in solvent residual peak), 3.86 (s, 3H), 3.89-3.99 (m, 4H), 4.01-4.05 (m, 2H), 4.12-4.18 (m, 2H), 7.20 (s, 1H), 7.85 (s, 1H), 10.42 (bs, 1H), 11.88 (bs, 1H), 12.00 (bs, 1H), 14.20 (bs, 1H)

[0513]

Example B28: tert-butyl 4-[4-[1,6-dimethyl-2-(2-morpholinoethyl)pyrrolo[3,2-c]pyridin-4-yl]phenyl]-3,6-dihydro-2H-pyridine-1-carboxylate
[0514]



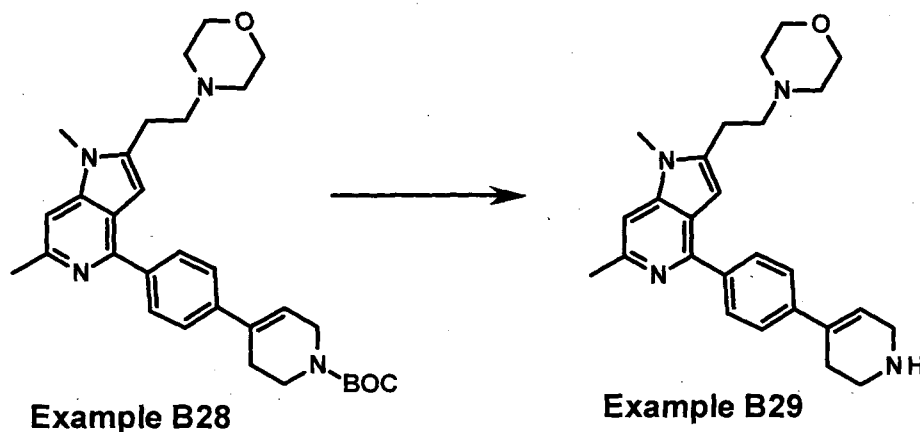
[0515]

A mixture of **Intermediate 3-VII** (0.15 g, 0.511 mmol), **Intermediate 1-VIII** (0.236 g, 0.614 mmol) and K_2CO_3 (0.211 g, 1.53 mmol) in 4:1 mixture of dioxane/water (4 mL) was degassed in a stream of argon for 30 minutes. To this mixture was added tetrakis(triphenylphosphine)palladium(0) (0.059 g, 0.0511 mmol) and the reaction mixture was again degassed for additional 15 minutes. After stirring at 95°C for 16 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (15 mL), followed by extraction with ethyl acetate (25 mL x 3). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by Combiflash using 4% MeOH in dichloromethane as eluent to give the desired product **Example B28** (0.19 g, 72%) as a brown solid.

[0516]

Example B29: 4-[2-[1,6-dimethyl-4-[4-(1,2,3,6-tetrahydropyridin-4-yl)phenyl]pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine

[0517]



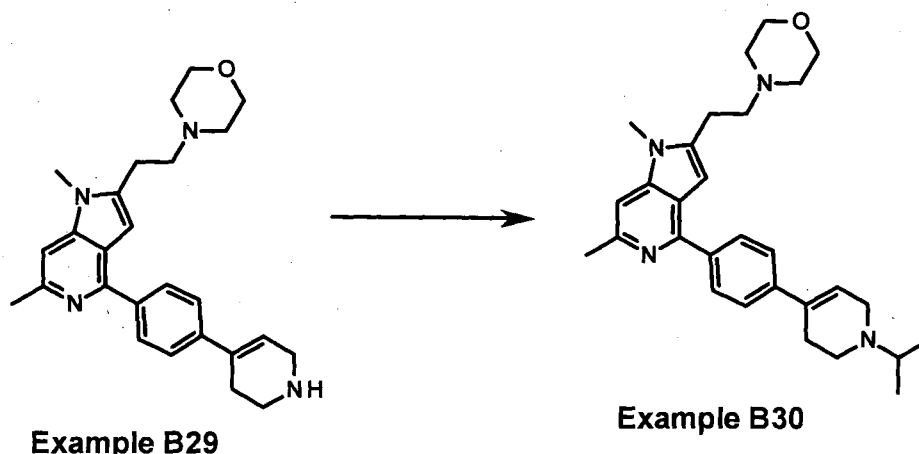
[0518]

To a solution of **Example B28** (0.19 g, 0.368 mmol) in 1,4-dioxane (2 mL) at 0°C was added 4M HCl in 1,4-dioxane (3 mL).
 5 After stirring at room temperature for 16 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (2 mL) and pH was adjusted to ~8 using saturated aqueous NaHCO₃ solution (10 mL). The resulting solution was evaporated to dryness, and the obtained residue
 10 was diluted with 5% MeOH in dichloromethane (20 mL) and inorganic substance was removed by filtration. The filtrate was concentrated to give the desired product **Example B29** (0.13 g, 85%) as an off white solid. The obtained crude product was used for next step without purification; LCMS: m/z 417.3 ($M^+ + 1$).

15 [0519]

Example B30: 4-[2-[4-[4-(1-isopropyl-3,6-dihydro-2H-pyridin-4-yl)phenyl]-1,6-dimethyl-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine

[0520]



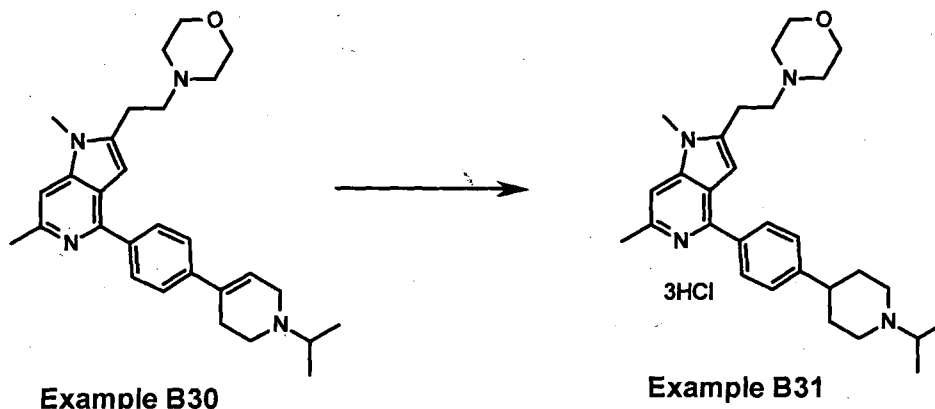
[0521]

To a solution of **Example B29** (0.13 g, 0.310 mmol) in a mixture of MeOH:DCE (1:1, 4 mL) were added acetone (0.904 g, 1.50 mmol), a drop of acetic acid and activated 4Å powdered molecular sieves (0.25 g) successively. After stirring for 4 hours at room temperature, sodium cyanoborohydride (0.096 g, 1.50 mmol) was added thereto, and the mixture was stirred for 16 hours. The reaction mixture was filtered through a celite pad, and washed with EtOAc (20 mL), and the filtrate was taken into water (20 mL), and the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified by preparative TLC using 3% MeOH in dichloromethane as eluent to give the desired product **Example B30** (0.07 g, 48%) as a white solid; LCMS: *m/z* 230.2 [M⁺/2+1].

[0522]

Example B31: 4-[2-[4-[4-(1-isopropyl-4-piperidyl)phenyl]-1,6-dimethyl-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine

[0523]



[0524]

To a stirred solution of **Example B30** (0.07 g, 0.15 mmol) in EtOAc (3 mL) was added Pd/C (0.02 g, 20% W/W). The flask was evacuated and filled with hydrogen gas (this procedure was repeated twice). The reaction mixture was then stirred for 18 hours under hydrogen atmosphere. After completion of reaction, the reaction mixture was filtered through a celite pad. The obtained residue after the evaporation of filtrate was purified using preparative TLC (mobile phase 10% MeOH:DCM) to give the desired product **Example B31** (0.04 g) as a white solid.

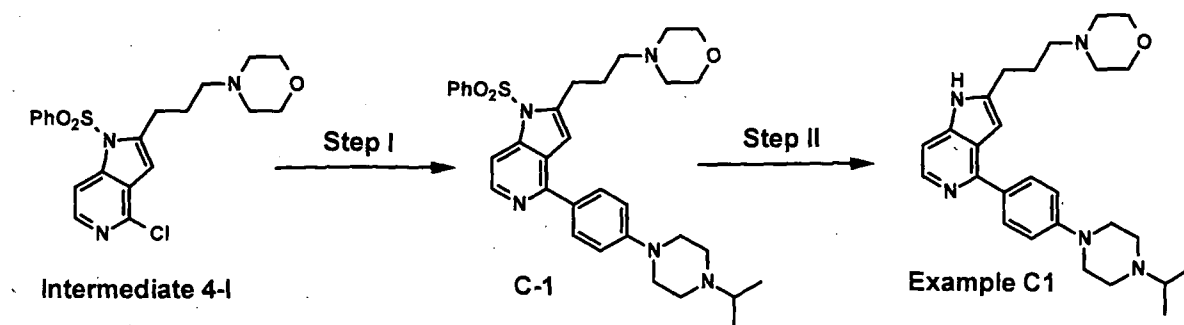
To a solution of **Example B31** (0.04 g, 0.146 mmol) in dioxane (0.5 mL) was added 4M HCl in dioxane (3 mL) at 0°C. After stirring for 2 hours at room temperature, the volatiles were removed by evaporation, and the obtained solid was dried under vacuum to give a 3HCl salt of **Example B31** (0.05 g, 57%) as an off white solid; LCMS: m/z 461.2 $[M^+ + 1]$.

^1H NMR (400 MHz, DMSO): δ 1.33 (d, J = 6.4 Hz, 6H), 2.03 (d, J = 12.4 Hz, 2H), 2.30 – 2.41 (m, 3H), 2.79 (s, 3H), 3.01 – 3.20 (m, 5H), 3.30 – 3.56 (m, 8H), 3.82 (t, J = 12.4 Hz, 2H), 3.91 (s, 3H), 4.01 (d, J = 11.2 Hz, 2H), 6.87 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8 Hz, 2H), 7.97 (s, 1H), 10.81 (br.s, 1H), 11.71 (br.s, 1H), 14.41 (bs, 1H)

[0525]

Example C1: 4-[3-[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]propyl]morpholine

[0526]



[0527]

Step I: 4-[3-[1-(benzenesulfonyl)-4-[4-(4-isopropylpiperazin-1-yl)phenyl]pyrrolo[3,2-c]pyridin-2-yl]propyl]morpholine (**C-1**)

5 A mixture of **Intermediate 4-I** (0.120 g, 0.285 mmol), **Intermediate 1-II** (0.122 g, 0.371 mmol) and K_2CO_3 (0.118 g, 0.857 mmol) in a mixture of dioxane/water (4:1, 5 mL) was degassed in a stream of argon for 15 minutes. To this mixture was added tetrakis(triphenylphosphine)palladium(0) (0.033 g, 10 0.0285 mmol), and the reaction mixture was again degassed for additional 15 minutes. After stirring at 90°C for 18 hours, the volatiles were removed by evaporation, and the obtained residue was diluted with water (20 mL), followed by extraction with ethyl acetate (25 mL x 3). The combined organic layers 15 were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by preparative TLC (8% MeOH in dichloromethane) to give the desired product **C-1** (0.135 g, 80%) as a brown solid; LCMS: m/z 420.0 [$M^+ + 1$].

20 [0528]

Step II: 4-[3-[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]propyl]morpholine (**Example C1**)

A stirred solution of **C-1** (0.135 g, 0.230 mmol) in 1,4-dioxane (2.5 mL) was treated with sodium tert-butoxide (0.132 25 g, 1.38 mmol) under argon atmosphere. After stirring at 70°C for 18 hours, the excess solvent was removed in vacuo. The obtained residue was dissolved in ethyl acetate (25 mL). The organic layer was washed successively with water (10 mL) and brine (10 mL) and dried over anhydrous Na_2SO_4 and concentrated

under reduced pressure. The obtained residue was purified by preparative TLC to give the desired compound **Example C1** (0.076 g, 73%) as a pale brown solid; LCMS: m/z 448.3 [$M^+ + 1$].

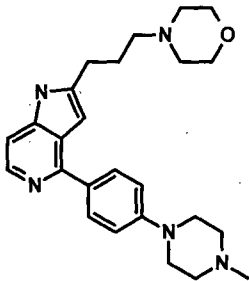
^1H NMR (400 MHz, CDCl_3): δ 1.13 (d, $J = 6.8$ Hz, 6H), 1.92 (quin. 2H), 2.49-2.53 (m, 6H), 2.72 (t, $J = 4.8$ Hz, 4H), 2.73-2.77 (m, 1H), 2.92 (t, $J = 6$ Hz, 2H), 3.32 (t, $J = 5.6$ Hz, 4H), 3.82 (t, $J = 4.4$ Hz, 4H), 6.54 (s, 1H), 7.04 (d, $J = 8.8$ Hz, 2H), 7.16 (d, $J = 5.6$ Hz, 1H), 7.93 (d, $J = 8.8$ Hz, 2H), 8.31 (d, $J = 6$ Hz, 1H), 10.70 (br. s, 1H)

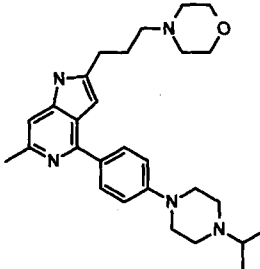
10 [0529]

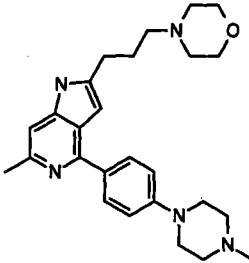
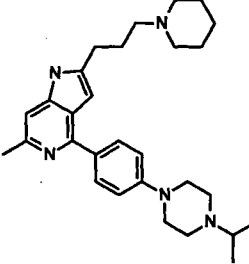
The following compounds **Examples C2-C5** as shown in Table 18 were prepared from their corresponding intermediates in the same manner as **Example C1**.

[0530]

15 Table 18:

Ex.No	IUPAC name	Structure	Int. from which prepared	Analytical Data
C2	4-[3-[4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]propyl]morpholine		4-I and 1-I	LCMS: m/z 420.4 [$M^+ + 1$] ^1H NMR (400 MHz, CDCl_3): δ 1.92 (quin. 2H), 2.37 (s, 3H), 2.50-2.54 (m, 6H), 2.60 (t, $J = 5.2$ Hz, 4H), 2.93 (t, $J = 6.4$ Hz, 2H), 3.32 (t, $J = 5.2$ Hz, 4H), 3.82 (t, $J = 4.4$ Hz, 4H), 6.54 (s, 1H), 7.04 (d, J

				= 8.8 Hz, 2H), 7.16 (d, J = 5.6 Hz, 1H), 7.93 (d, J = 8.8 Hz, 2H), 8.31 (d, J = 5.6 Hz, 1H), 10.72 (br. s, 1H)
C3	4-[3-[4-[4- (4- isopropylpip erazin-1- yl)phenyl]- 6-methyl-1H- pyrrolo[3,2- c]pyridin-2- yl]propyl]mo rpholine		4-II and 1-II	LCMS: m/z 462.3 [M ⁺ +1] ¹ H NMR (400 MHz, CDCl ₃): δ 1.10 (d, J = 6 Hz, 6H), 1.89 (quin., 2H), 2.48-2.53 (m, 6H), 2.68 (s, 3H), 2.69-2.73, (m, 5H), 2.88 (t, J = 4.8 Hz, 2H), 3.29-3.31 (m, 4H), 3.81- 3.83 (m, 4H), 6.54 (s, 1H), 6.99 (s, 1H), 7.02 (d, J = 8 Hz, 2H), 7.89 (d, J = 8 Hz, 2H), 10.40 (br. s, 1H)

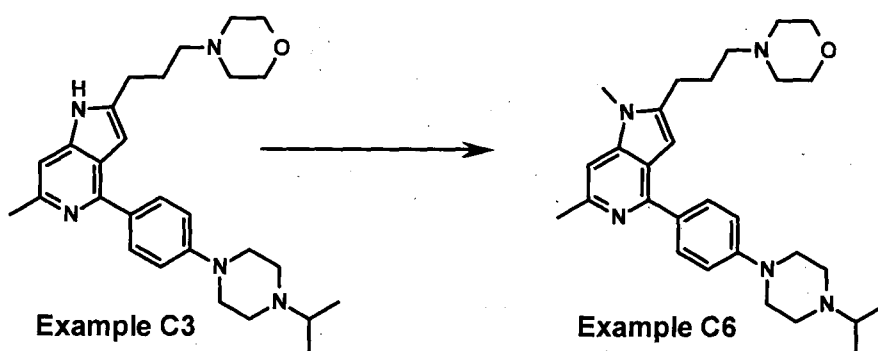
C4	4-[3-[6-methyl-4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]propyl]morpholine		4-II and 1-I	LCMS: m/z 434.3 [$M^+ + 1$] 1H NMR (400 MHz, $CDCl_3$): δ 1.89 (quin., 2H), 2.37 (s, 3H), 2.47-2.53 (m, 6H), 2.62 (t, $J = 4.8$ Hz, 4H), 2.66 (s, 3H), 2.88 (t, $J = 6.8$ Hz, 2H), 3.30 (t, $J = 4.8$ Hz, 4H), 3.82 (t, $J = 4.8$ Hz, 4H), 6.44 (s, 1H), 6.98 (s, 1H), 7.03 (d, $J = 8.8$ Hz, 2H), 7.89 (d, $J = 8.8$ Hz, 2H), 10.25 (br. s, 1H)
C5	4-[4-(4-isopropylpiperazin-1-yl)phenyl]-6-methyl-2-[3-(1-piperidyl)propyl]-1H-pyrrolo[3,2-c]pyridine		4-III and 1-II	LCMS: m/z 460.3 [$M^+ + 1$] 1H NMR (400 MHz, $CDCl_3$): δ 1.11 (d, $J = 6.4$ Hz, 6H), 1.50 - 1.82 (m, 10H), 1.95-1.99 (m, 2H), 2.56 (t, $J = 12$ Hz, 2H), 2.71 - 2.76 (m, 8H), 2.92 - 2.95 (t, $J = 6$

				Hz , 2H), 3.29 - 3.31 (t, J = 10 Hz, 4H), 6.44 (s, 1H), 7.00-7.08 (m, 3H), 7.90 (d, J = 8.8 Hz, 2H)
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[0531]

Example C6: 4-[3-[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-1,6-dimethyl-pyrrolo[3,2-c]pyridin-2-yl]propyl]morpholine

[0532]



5

[0533]

NaOtBu (0.537 g, 5.60 mmol) was added to a solution of **Example C3** (0.52 g, 1.12 mmol) in 1,4-dioxane (5 mL) at room temperature. After stirring for 15 minutes, methyl

10 benzenesulfonate (0.193 g, 1.12 mmol) was added thereto, and stirring was continued for 3 hours. The reaction mixture was diluted with EtOAc (30 mL) and water (10 mL). The organic layer was separated, dried over Na₂SO₄ and concentrated under reduced pressure. The obtained residue was purified using

15 preparative HPLC to give the desired product **Example C6** (0.178 g) as a pale yellow liquid. The obtained liquid product was taken into dioxane (0.5 mL), and 4M HCl in dioxane (1.5 mL) was added thereto at 0°C. After 3 hours at room temperature, the volatiles were removed by evaporation, and the obtained

20 solid was dried under vacuum to give a 3HCl salt of **Example C6** (0.198 g, 30%) as a dark yellow solid; LCMS: *m/z* 476.6 [M⁺+1].

¹H NMR (400 MHz, DMSO-D₆): 1.32 (d, J = 6.8 Hz, 6H), 2.19

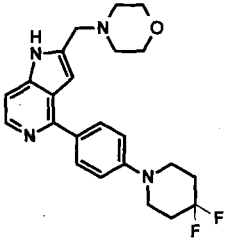
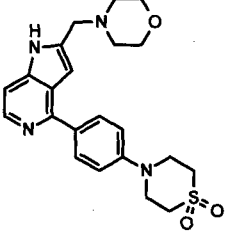
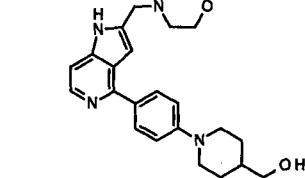
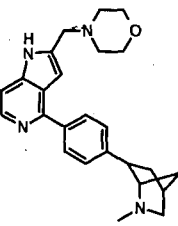
(quin., 2H), 2.75 (s, 3H), 2.94 (t, J = 7.6 Hz, 2H), 3.01-3.04 (m, 2H), 3.12-3.15 (m, 5H), 3.35-3.41 (m, 4H), 3.50-3.54 (m, 4H), 3.81-3.86 (m, 2H), 3.84 (s, 3H), 4.05-4.41 (m, 2H), 6.84 (s, 1H), 7.27 (d, J = 8.8 Hz, 2H), 7.83-7.86 (m, 3H), 11.10 (br.s, 1H), 11.50 (br.s, 1H), 14.05 (br.s, 1H).

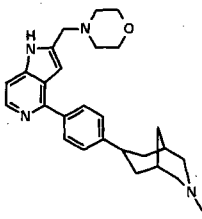
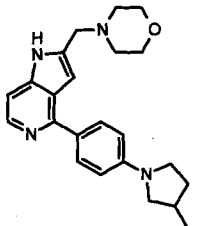
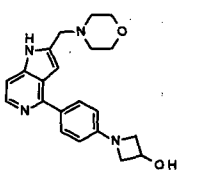
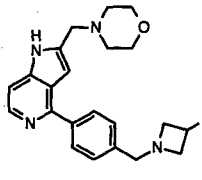
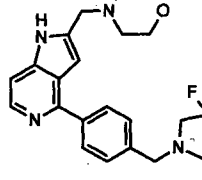
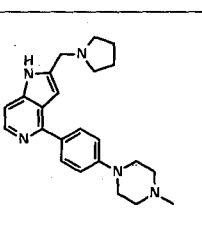
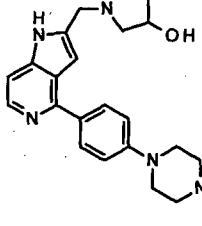
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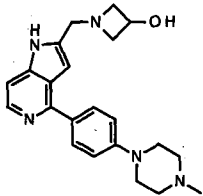
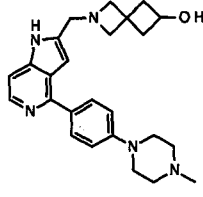
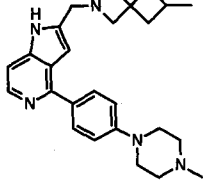
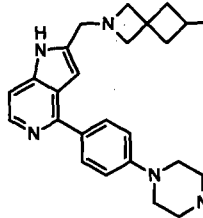
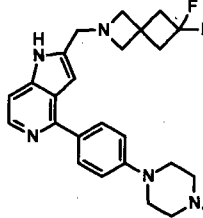
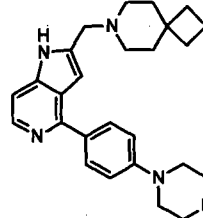
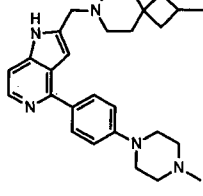
The following compounds as shown in Table 19 can also be prepared according to Schemes 1-13 or in the same manner as in the above mentioned Examples.

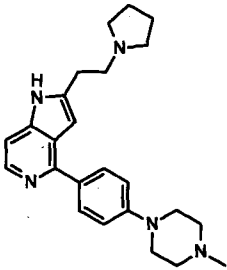
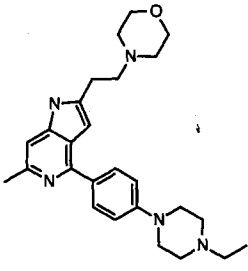
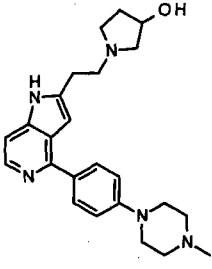
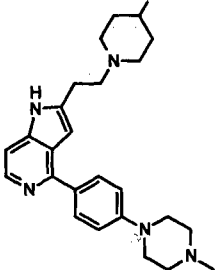
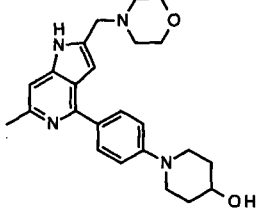
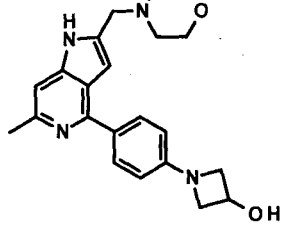
10 [0535]

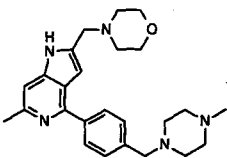
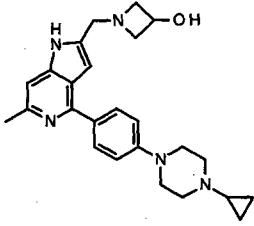
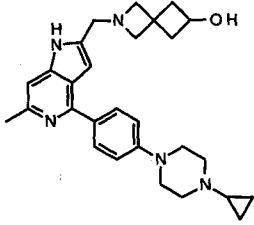
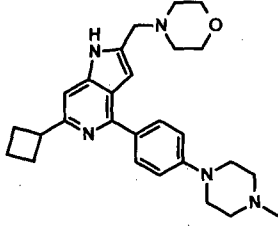
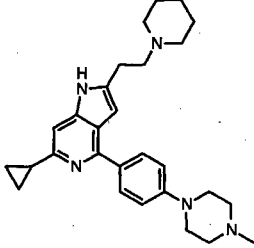
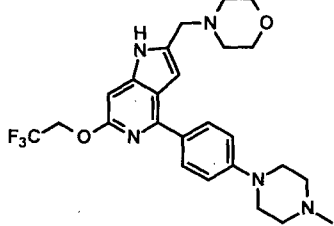
Table 19

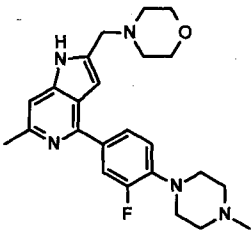
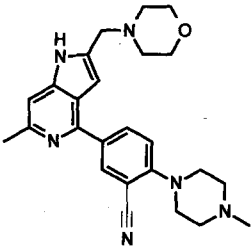
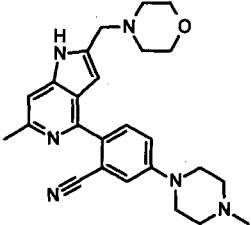
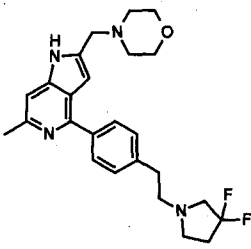
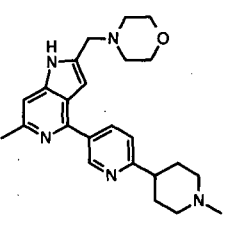
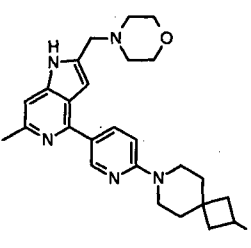
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	4-[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]-thiomorpholine 1,1-dioxide
	[1-[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]-4-piperidyl]methanol
	4-[[4-[4-(3-methyl-3-azabicyclo[2.2.1]heptan-5-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine

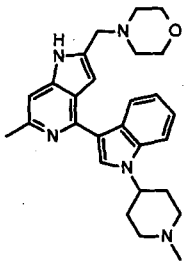
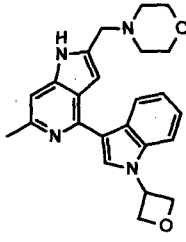
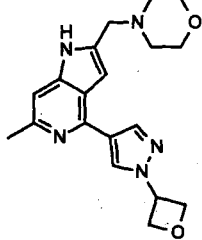
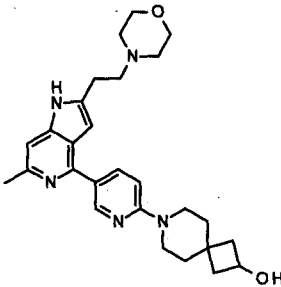
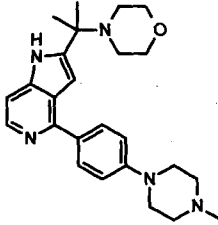
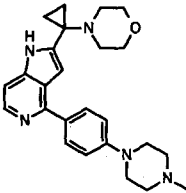
	4-[[4-[4-(3-methyl-3-azabicyclo[3.3.1]nonan-7-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine
	4-[[4-[4-(3-methylpyrrolidin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine
	1-[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]azetidin-3-ol
	1-[[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]methyl]azetidin-3-ol
	4-[[4-[4-[(3,3-difluoropyrrolidin-1-yl)methyl]phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine
	4-[4-(4-methylpiperazin-1-yl)phenyl]-2-(pyrrolidin-1-ylmethyl)-1H-pyrrolo[3,2-c]pyridine
	1-[[4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]pyrrolidin-3-ol

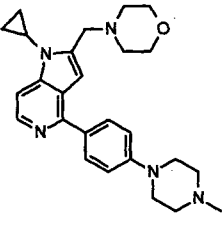
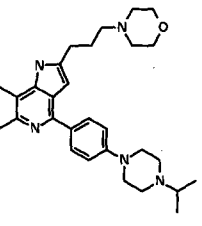
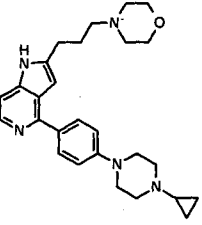
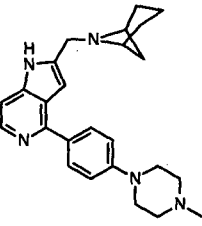
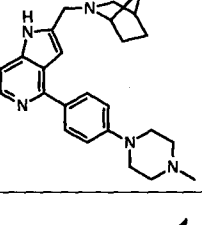
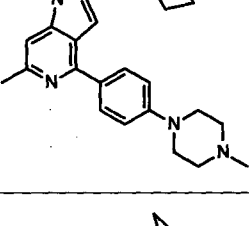
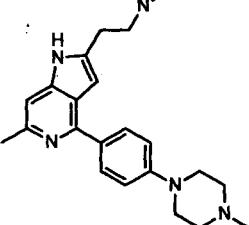
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	2-[(2-methyl-6-azaspiro[3.3]heptan-6-yl)methyl]-4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridine
	2-[(2-fluoro-6-azaspiro[3.3]heptan-6-yl)methyl]-4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridine
	2-[(2,2-difluoro-6-azaspiro[3.3]heptan-6-yl)methyl]-4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridine
	7-[[4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]-7-azaspiro[3.5]nonan-2-ol
	2-[(2-methyl-7-azaspiro[3.5]nonan-7-yl)methyl]-4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridine

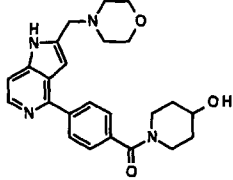
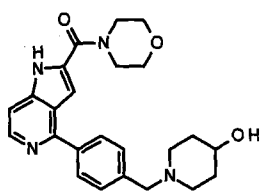
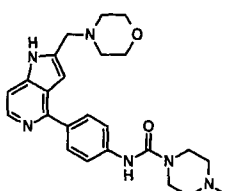
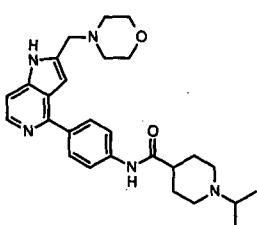
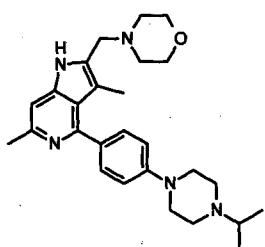
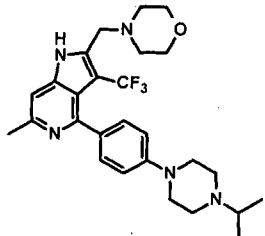
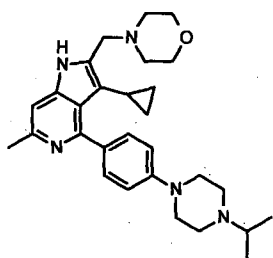
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	1-[2-[4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]ethyl]pyrrolidin-3-ol
	1-[2-[4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]ethyl]piperidin-4-ol
	1-[4-[6-methyl-2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]piperidin-4-ol
	1-[4-[6-methyl-2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]azetidin-3-ol

	4-[[6-methyl-4-[4-[(4-methylpiperazin-1-yl)methyl]phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine
	1-[[4-[4-(4-cyclopropylpiperazin-1-yl)phenyl]-6-methyl-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]azetidin-3-ol
	6-[[4-[4-(4-cyclopropylpiperazin-1-yl)phenyl]-6-methyl-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]-6-azaspiro[3.3]heptan-2-ol
	4-[[6-cyclobutyl-4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine
	6-cyclopropyl-4-[4-(4-methylpiperazin-1-yl)phenyl]-2-[2-(1-piperidyl)ethyl]-1H-pyrrolo[3,2-c]pyridine
	4-[[4-[4-(4-methylpiperazin-1-yl)phenyl]-6-(2,2,2-trifluoroethoxy)-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine

	4-[[4-[3-fluoro-4-(4-methylpiperazin-1-yl)phenyl]-6-methyl-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine
	5-[6-methyl-2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]-2-(4-methylpiperazin-1-yl)benzonitrile
	2-[6-methyl-2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]-5-(4-methylpiperazin-1-yl)benzonitrile
	4-[[4-[4-[2-(3,3-difluoropyrrolidin-1-yl)ethyl]phenyl]-6-methyl-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine
	4-[[6-methyl-4-[6-(1-methyl-4-piperidyl)-3-pyridyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine
	7-[5-[6-methyl-2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]-2-pyridyl]-7-azaspiro[3.5]nonan-2-ol

	4-[[6-methyl-4-[1-(1-methyl-4-piperidyl)indol-3-yl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine
	4-[[6-methyl-4-[1-(oxetan-3-yl)indol-3-yl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine
	4-[[6-methyl-4-[1-(oxetan-3-yl)pyrazol-4-yl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine
	7-[5-[6-methyl-2-(2-morpholinoethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]-2-pyridyl]-7-azaspiro[3.5]nonan-2-ol
	4-[1-methyl-1-[4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine
	4-[1-[4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]cyclopropyl]morpholine

	4-[[1-cyclopropyl-4-[4-(4-methylpiperazin-1-yl)phenyl]pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine
	4-[3-[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-6,7-dimethyl-1H-pyrrolo[3,2-c]pyridin-2-yl]propyl]morpholine
	4-[3-[4-[4-(4-cyclopropylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]propyl]morpholine
	2-(6-azabicyclo[3.1.1]heptan-6-ylmethyl)-4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridine
	2-(3-azabicyclo[2.2.1]heptan-3-ylmethyl)-4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridine
	2-(3-azabicyclo[2.2.1]heptan-3-ylmethyl)-6-methyl-4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridine
	2-[2-(3-azabicyclo[2.2.1]heptan-3-yl)ethyl]-6-methyl-4-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridine

	(4-hydroxy-1-piperidyl)-[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]methanone
	[4-[4-[(4-hydroxy-1-piperidyl)methyl]phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]-morpholino-methanone
	4-methyl-N-[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]piperazine-1-carboxamide
	1-isopropyl-N-[4-[2-(morpholinomethyl)-1H-pyrrolo[3,2-c]pyridin-4-yl]phenyl]piperidine-4-carboxamide
	4-[[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-3,6-dimethyl-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine
	4-[[4-[4-(4-isopropylpiperazin-1-yl)phenyl]-6-methyl-3-(trifluoromethyl)-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine
	4-[[3-cyclopropyl-4-[4-(4-isopropylpiperazin-1-yl)phenyl]-6-methyl-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine

[0536]

Experimental Example 1

hTLR9 antagonism (SEAP inhibition assay) in HEK293 cell lines:

The SEAP reporter gene in HEK-Blue™-hTLR9 cells is placed
5 under the control of the IFN- β minimal promoter fused to five
NF- κ B and AP-1 binding sites. The stimulation with a TLR9
ligand (ODN-2006) activates NF- κ B and AP-1 which induces the
production of SEAP. Levels of SEAP are determined with QUANTI-
Blue™ detection medium that turns purple/blue in the presence
10 of alkaline phosphatase. Decrease in the levels of SEAP
production as indicated by reduction in absorbance at 650nm is
directly co-related with the TLR9 inhibitory activity of the
antagonist (NCE).

HEK-Blue™-hTLR9 cells were maintained in DMEM with 10%
15 FBS, 1% Penicillin/Streptomycin/Amphotericin (complete growth
medium) and 0.2% Normocin. For the assay, cells were
dissociated by washing in 1X PBS and re-suspended in complete
DMEM. Cells were seeded at a density of 20000 cells per well;
(40 μ l per well) in a 384 well assay plate.

20 5 μ l of 10X antagonist (NCE) was added to the cells in
triplicates for each concentration. The plate was incubated
for half an hour at 37°C with 5% CO₂. 5 μ l of agonist (ODN-
2006) was added and the plate was incubated overnight for 18
hours at 37°C with 5% CO₂. 5 μ l of supernatant was transferred
25 to a 384 well reading plate and to this 45 μ l of Quanti-Blue™
detection reagent was added. The plate was then incubated for
an hour at 37°C. SEAP activity in the supernatant was
indicated by change in the pink color of Quanti-Blue™
detection reagent to purple/blue and the absorbance was read
30 at 650 nm in the end point mode.

[0537]

Experimental Example 2

mTLR9 and mTLR7 antagonism (cytokine release assay) in mouse
splenocytes:

35 [0538]

Materials:

Splenocytes isolated from male C57/BL6 mice

TLR7 ligand R0006 (IDT, 5'-

rU*rU*rG*rU*rU*rG*rU*rU*rG*rU*rU*rG*rU*rU*rG*rU*rU-

5 3'), Liposomal transfection reagent - DOTAP (Roche, Cat.

No.11202375001), TLR9 ligand CpG ODN2006 (Sequence:

T*C*G*T*C*G*T*T*T*T*G*T*C*G*T*T*T*T*G*T*C*G*T*T;

*=phosphorothioate)

DMSO (Sigma, D2650), RPMI Powder (Sigma, R6504), Fetal Bovine

10 Serum (Gibco, 10270), Dulbecco's Phosphate Buffered Saline

(Sigma, D1408), 96 well plate (Flat bottom, Costar 3599),

ELISA kit for IL-6 (EBioscience, 88-7064-77 and TNFa

(EBioscience, 88-7346-88), MACS Buffer (AutoMACS Rinsing

Solution (Miltenyl Biotec, 130-091-222) + 0.05% BSA), RBC

15 lysis buffer (0.85% NH4Cl), 40µm cell strainer (BD Falcon,

352340)

[0539]

Method:

A. Isolation of mouse splenocytes

20 Mouse spleen was isolated from C57BL6 mouse and stored in
1X chilled PBS buffer until further processed. Spleen was
transferred to a sterile petriplate and chopped in to 5-6
pieces in presence of MACS buffer (100µl) with the help of
fresh surgical blade and crushed with flat plunger of a
25 sterile syringe. A uniform suspension was prepared by passing
cells through a 40 µm cell strainer. Cells were centrifuged at
450xg for 5 minutes at 4°C, supernatant was discarded and
pellet dislodged gently, resuspended in 2 ml of pre-warmed
(37°C) RBC lysis buffer at room temperature with continuous
30 gentle mixing with 1 ml pipette. Lysis buffer was neutralized
with 12 ml of chilled MACS buffer and cells were passed
through 40 µm cell strainer. Cell suspension was collected in
15 ml MACS buffer and centrifuged at 450xg for 5 minutes at 4°C.
Pellet was resuspended in 15 ml MACS buffer and centrifuged at
35 400xg for 5 minutes. Cells were resuspended in 10 ml of RPMI

complete medium and viability was estimated by Trypan blue method.

Expected yield: 60-70 million cells from single mouse spleen.
[0540]

5 mTLR9 antagonism (IL-6 and TNF- α release assay):

500 μ M stock of CpG ODN-2006 was prepared in sterile, endotoxin-free water. Dilutions of 10x concentrations of NCEs were prepared in incomplete RPMI media, maintaining a final DMSO concentration of 0.3%. NCEs were added in a concentration
10 range of 30 μ M to 1 nM in respective wells of assay plate, assay medium containing 0.3% DMSO were added to control wells. 0.2 million splenocytes were added to all the wells and incubated at 37°C in 5% CO₂ incubator for 30 minutes. 1 μ g/ml of respective agonist was added to all the wells except those
15 were assigned as negative controls and mixed thoroughly. Incomplete RPMI was added to negative control wells and incubated overnight at 37°C/5% CO₂. The plate was centrifuged at 450xg for 5 minutes at room temperature and the supernatant was collected. ELISA was performed as per manufacturer's
20 protocol. S/B Ratio, % Activity and % Inhibition was calculated using MS Excel. IC₅₀ and inhibition curve was generated using Graph Pad Prism.

[0541]

mTLR7 antagonism (IL-6 and TNF- α release assay):

25 1 mg/ml stock of R0006 was prepared in sterile, endotoxin-free water. R0006 stock was diluted 10 fold with DOTAP and incubated for 30 minutes to form liposome complex (100 μ g/ml of R0006). This complex was further diluted 10 fold with incomplete RPMI media (10 μ g/ml of R0006) to achieve the
30 final agonist concentration of 1 μ g/ml. DOTAP alone was diluted 10 fold in incomplete RPMI media. NCEs were added in a concentration range of 30 μ M to 1 nM in respective wells of assay plate, assay medium containing 0.3% DMSO were added to control wells. 0.2 million splenocytes were added to all the
35 wells and incubated at 37°C in 5% CO₂ incubator for 30 minutes.

1 $\mu\text{g/ml}$ of respective agonist was added to all the wells except those were assigned as negative controls and mixed thoroughly. DOTAP was added to negative control wells and incubated overnight at $37^{\circ}\text{C}/5\% \text{CO}_2$. The plate was centrifuged
 5 at $450\times g$ for 5 minutes at room temperature and the supernatant was collected. ELISA was performed as per manufacturer's protocol. S/B Ratio, % Activity and % Inhibition was calculated using MS Excel. IC_{50} and inhibition curve was generated using Graph Pad Prism.

10 hTLR9 %inhibition and mTLR7 and mTLR9, IL-6 and TNF- α release %inhibition at $1 \mu\text{M}$ concentration are given in Table 20 below

[0542]

Table 20:

Example No.	hTLR9 inhibitory activity (% at $1\mu\text{M}$)	mTLR7 inhibitory activity (% at $1 \mu\text{M}$) (IL-6, TNF- α)	mTLR9 inhibitory activity (% at $1 \mu\text{M}$) (IL-6, TNF- α)
A1	100	97, 100	100, 94
A2	100	90, 100	100, 94
A3	100	100, 100	100, 85
A4	100	100, 100	100, 100
A5	100	100, 100	100, 91
A8	100	100, 100	ND, 100
A9	100	ND, 100	ND, 94
A10	29	ND	ND
A11	77.5	ND	ND
A12	100	80, 45	95, 52
A13	100	98, 91	100, 91
A16	100	100, 99	100, 100
A17	100	100, 100	100, 100
A18	100	ND	ND
A19	90	ND	ND

A22	62	ND	ND
A24	95.1	ND, 100	ND, 100
A25	95.2	100, 100	100, 100
A27	96.4	ND	ND
A28	91	88, 100	100, 100
A29	100	97, 82	96, 64
A30	96.7	100, 100	100, 100
A31	66	ND	ND
A32	49	ND	ND
A33	90.4	ND, 83	ND, 85
A34	82	ND, 100	ND, 93
A35	96.3	100, 100	100, 90
A36	96.7	100, 99	ND, 100
A37	100	ND, 100	ND, 100
A38	98.5	100, 100	100, 100
A39	74.3	ND, 100	ND, 100
A40	80	ND, 100	ND, 100
A42	96	34, 9	84, 41
A45	76.1	ND	ND
A46	83.5	ND	ND
A49	91	2, 3	65, 15
A51	100	100, 96	100, 90
A52	84.5	71, 10	100, 29
A53	77	100, 83	100, 80
A54	95.4	ND, 0	ND, 0
A55	96.5	100, 33	96, 59
A56	99.5	ND, 64	ND, 71
A57	96.9	80, 79	100, 34
A58	98	ND	ND
A59	94.7	ND	ND
A60	86	ND, 29	0, 38
A61	89.5	78, 74	100, 45
A62	98.2	ND, 75	ND, 79
A63	93.4	ND, 0	ND, 0

A64	73	13, 4	25, 0
A65	70.5	ND	ND
A67	27.5	ND	ND
A68	21	ND	ND
A69	73.5	ND	ND
A70	100	100, 36	95, 52
A71	86.1	ND	ND
A72	100	0, 14	72, 0
A73	72	ND	ND
A74	89.4	ND, 32	ND, 95
A75	34.9	ND	ND
A76	81.2	ND	ND
A79	100	ND	ND
A80	95.8	18, 16	ND
A81	64	25, 24	37, 20
A82	98	86, 24	100, 52
A83	29.5	ND	ND
B1	100	100, 100	100, 100
B2	100	100, 100	100, 95
B3	100	ND, 100	100, 100
B4	100	ND, 100	ND, 100
B5	78	ND, 100	ND, 100
B6	79.7	100, 100	100, 100
B7	81.6	ND, 100	ND, 100
B8	93.7	ND, 88	ND, 93
B9	95.2	ND	ND
B10	93.1	100, 100	100, 100
B11	80	100, 100	100, 100
B14	88.7	100, 100	ND
B15	93.3	88, 83	ND
B16	91	100, 100	ND
B17	91.5	93, 90	ND
B18	99.3	100, 100	ND
B19	100	100, 100	100, 100

B20	100	70, 57	ND
B21	100	100, 100	100, 100
B22	99.7	100, 100	100, 92
B23	99.2	100, 100	ND
B26	89.9	62, 47	ND
B27	95.8	88, 77	100, 72
B31	99.4	100, 100	100, 92
C1	99.2	ND, 100	ND, 100
C2	100	ND, 100	ND, 100
C3	94.8	100, 100	100, 100
C4	98.7	ND	ND
C5	94.7	100, 97	94, 100
C6	99.1	100, 100	100, 100

ND: Not Determined

[0543]

Experimental Example 3

Mouse Lupus Disease Model:

5 Examples B6 and B11 were tested in well studied mouse model of lupus, lupus-prone MRL *lpr/lpr* mice that develop disease similar to human SLE [J Exp Med., 1978, 148 (5), 1198-1215]. These mice develop spontaneous systemic autoimmunity with both molecular (IFN signature) and clinical (autoantibody
10 production and glomerulonephritis) features similar to human SLE. Anti-dsDNA antibodies are correlated with human SLE and the reduction in anti-dsDNA antibodies is believed to be of potential clinical benefit. Positive TLR7 and/or TLR9 target validation results have been reported for this disease model.

15 [0544]

Mouse Lupus Disease Model Strain:

Female MRL/*lpr* mice were purchased from Jackson Laboratories (USA) which manifest spontaneous lupus disease. Female MRL/*lpr* mice were treated for 9 weeks by oral route
20 once a day with TLR-7/9 antagonists [Examples B6 and B11] at 3, 10 and 30 mg/kg doses. Prednisolone (2 mg/kg, P.O., QD) was used as a positive control during the studies. At the end of

treatment period, animals were sacrificed and blood samples were collected to estimate anti-dsDNA IgG titers using anti-dsDNA IgG ELISA kit, Alpha Diagnostics, USA.

Key findings for **Example B6** in the SLE disease model are as follows.

Mice treated with **Example B6** showed trend towards dose dependent reduction in mean anti-dsDNA IgG titers after 6 weeks of treatment at 3, 10 and 30 mg/kg doses (QD) [Fig. 1A].

Significant reduction in anti-dsDNA IgG was observed with 10 mg/kg once daily oral dose after 9 weeks of treatment [Fig. 1B].

Key findings for **Example B11** in the SLE disease model are as follows.

Mice treated with **Example B11** showed dose dependent reduction in mean anti-dsDNA IgG titers after 6 weeks of treatment at 3, 10 and 30 mg/kg doses (QD), significant at 30 mg/kg dose [QD] [Fig. 2A].

[0545]

Formulation Example 1

20	(1) Compound of Example A1	10.0 g
	(2) Lactose	70.0 g
	(3) Cornstarch	50.0 g
	(4) Soluble starch	7.0 g
	(5) Magnesium stearate	3.0 g

25 After 10.0 g of the compound of Example A1 and 3.0 g of magnesium stearate are granulated in 70 ml aqueous solution of soluble starch (7.0 g as soluble starch) and then dried, and the resulting mixture is mixed with 70.0 g of lactose and 50.0 g of cornstarch (lactose, cornstarch, soluble starch and
30 magnesium stearate are all products in compliance with Japanese Pharmacopoeia 14th Edition). The mixture is compressed to obtain a tablet.

Industrial Applicability

[0546]

35 According to the present invention, the compound having a

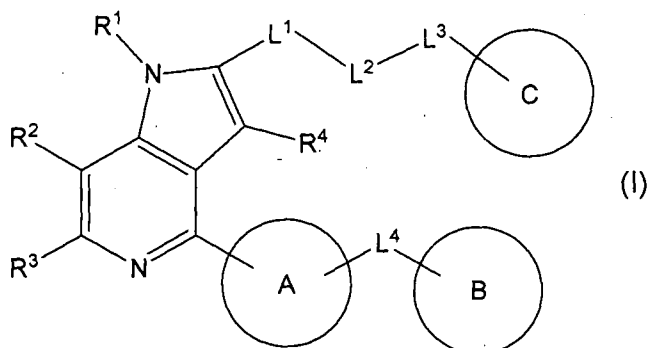
TLR7, TLR9, TLR7/8, TLR7/9 or TLR7/8/9 inhibitory action,
which is useful as an agent for the prophylaxis or treatment
of autoimmune diseases, inflammatory diseases and the like, in
particular, systemic lupus erythematosus, Sjogren's syndrome,
5 rheumatoid arthritis, psoriasis, inflammatory bowel disease
and the like, can be provided.

[0547]

This application is based on patent application No.
3656/DELNP/2013 filed on December 13, 2013 in India, the
10 contents of which are encompassed in full herein.

CLAIMS

1. A compound represented by the formula (I):



5 wherein

- R^1 is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted hydroxy group, an optionally substituted amino group, an optionally substituted sulfanyl group, or an acyl group,
- R^2 , R^3 and R^4 are independently a hydrogen atom or a substituent,
- Ring A is an optionally substituted ring,
- Ring B is an optionally substituted heterocycle,
- Ring C is an optionally substituted 3- to 10-membered
- 15 nitrogen-containing heterocycle,
- L^1 is a bond or a divalent hydrocarbon group,
- L^2 is a bond, -O-, -C(O)-, -NH-C(O)-, -C(O)-NH-, -S-, -SO-, -SO₂-, -SO₂-O-, -O-SO₂- or -CH(CN)-,
- L^3 is a bond or a divalent hydrocarbon group, with the proviso
- 20 that at least one of L^1 , L^2 and L^3 is not a bond, and
- L^4 is a bond or a spacer having 1 to 6 atoms, or a salt thereof.

2. The compound or salt of claim 1, wherein

- 25 R^1 is a hydrogen atom, a C₁₋₁₀ alkyl group or a C₃₋₁₀ cycloalkyl group,
- R^2 is a hydrogen atom or a C₁₋₁₀ alkyl group,
- R^3 is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted hydroxy group,

R⁴ is a hydrogen atom, a halogen atom or an optionally substituted hydrocarbon group,

Ring A is an optionally substituted C₃₋₁₀ cycloalkane, an optionally substituted C₃₋₁₀ cycloalkene, an optionally substituted C₆₋₁₄ aromatic hydrocarbon or an optionally substituted aromatic heterocycle optionally fused with benzene, Ring B is an optionally substituted 3- to 10-membered non-aromatic heterocycle,

Ring C is an optionally substituted 5- or 6- membered nitrogen-containing aromatic heterocycle or an optionally substituted 3- to 10-membered nitrogen-containing non-aromatic heterocycle,

L¹ and L³ are independently

- (1) a bond,
- (2) a C₁₋₁₀ alkylene group, or
- (3) a C₃₋₈ cycloalkylene group,

L² is a bond or -C(O)-, and

L⁴ is a bond, a straight chain C₁₋₆ alkylene group, -X¹-O-X²-, -X¹-C(O)-X²- or -X¹-NH-C(O)-X²-, wherein X¹ and X² are independently a bond or a straight chain C₁₋₅ alkylene group, and the total atom number is 6 or less.

3. 4-[2-[4-[4-(4-Isopropylpiperazin-1-yl)phenyl]-6,7-dimethyl-1H-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine or a salt thereof.

4. 4-[2-[4-[4-(4-Isopropylpiperazin-1-yl)phenyl]-1,6-dimethyl-pyrrolo[3,2-c]pyridin-2-yl]ethyl]morpholine or a salt thereof.

5. 4-[[4-[4-(4-Isopropylpiperazin-1-yl)phenyl]-1H-pyrrolo[3,2-c]pyridin-2-yl]methyl]morpholine or a salt thereof.

6. 4-[4-(4-Isopropylpiperazin-1-yl)phenyl]-2-(1-piperidylmethyl)-1H-pyrrolo[3,2-c]pyridine or a salt thereof.

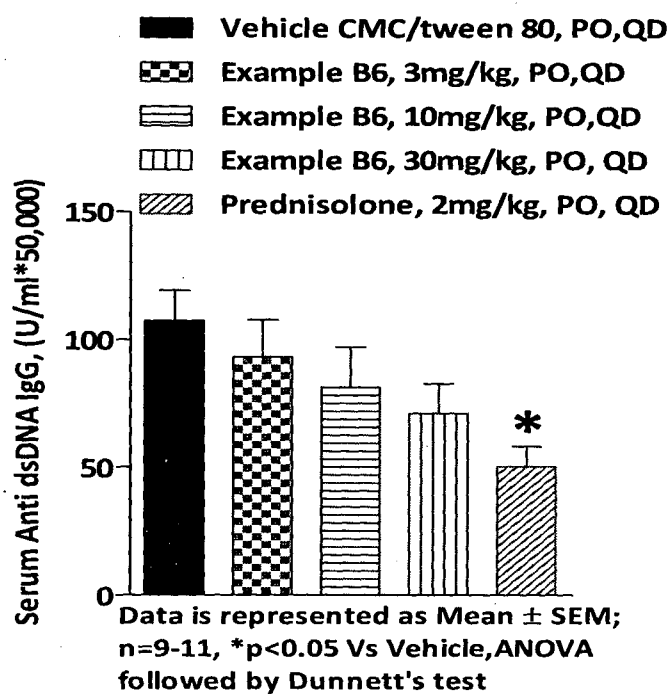
7. A medicament comprising the compound or salt of claim 1.
8. The medicament of claim 7, which is a TLR7, TLR9, TLR7/8, TLR7/9 or TLR7/8/9 inhibitor.
- 5 9. The medicament of claim 7, which is an agent for the prophylaxis or treatment of autoimmune diseases and/or inflammatory diseases.
- 10 10. The medicament of claim 9, wherein the autoimmune diseases and/or inflammatory diseases is selected from systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, psoriasis and inflammatory bowel disease.
- 15 11. The compound or salt of claim 1 for use in the prophylaxis or treatment of autoimmune diseases and/or inflammatory diseases.
12. The compound or salt of claim 11, wherein the autoimmune
20 diseases and/or inflammatory diseases is selected from systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, psoriasis and inflammatory bowel disease.
13. A method of inhibiting TLR7, TLR9, TLR7/8, TLR7/9 or
25 TLR7/8/9 in a mammal, which comprises administering an effective amount of the compound or salt of claim 1 to the mammal.
14. A method for the prophylaxis or treatment of autoimmune
30 diseases and/or inflammatory diseases in a mammal, which comprises administering an effective amount of the compound or salt of claim 1 to the mammal.
15. The method of claim 14, wherein the autoimmune diseases
35 and/or inflammatory diseases is selected from systemic lupus

erythematosus, Sjogren's syndrome, rheumatoid arthritis,
psoriasis and inflammatory bowel disease.

16. Use of the compound or salt of claim 1 for the production
5 of an agent for the prophylaxis or treatment of autoimmune
diseases and/or inflammatory diseases.

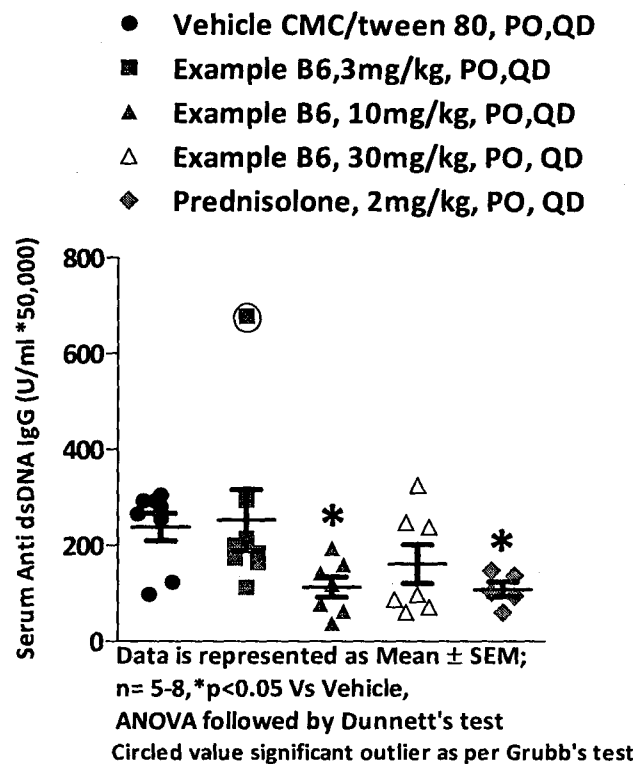
17. Use of claim 16, wherein the autoimmune diseases and/or
inflammatory diseases is selected from systemic lupus
10 erythematosus, Sjogren's syndrome, rheumatoid arthritis,
psoriasis and inflammatory bowel disease.

Fig. 1A: Reduction in anti-dsDNA IgG with Example B6 after 6 weeks of treatment



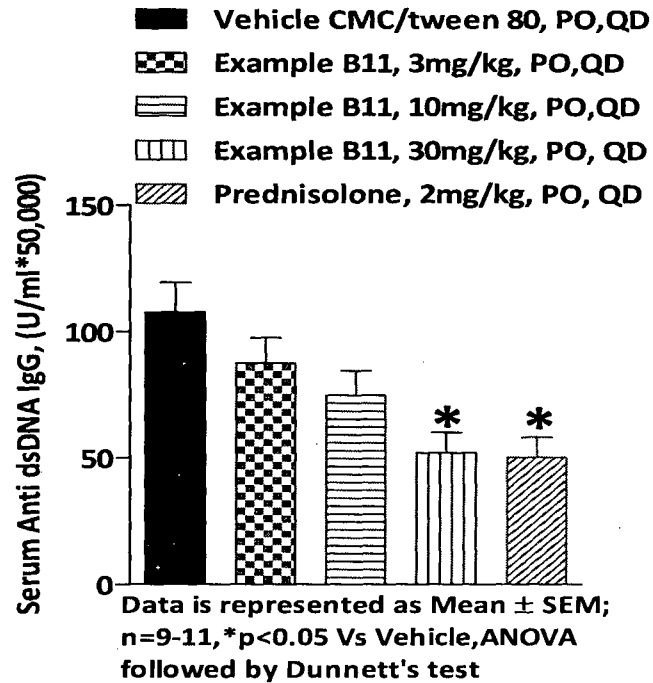
Treatment	Veh.	Ex.B6	Ex.B6	Ex.B6	Pred
Dose[QD; (mg/kg)]	-	3	10	30	2
Duration (weeks)	6	6	6	6	6
Age(Weeks)	16	16	16	16	16
% Reduction	-	13	24	34	53

Fig. 1B: Reduction in anti-dsDNA IgG with Example B6 after 9 weeks of treatment



Treatment	Veh.	Ex. B6	Ex. B6	Ex. B6	Pred
Dose [QD; (mg/kg)]	-	3	10	30	2
Duration (weeks)	9	9	9	9	9
Age (Weeks)	19	19	19	19	19
% Reduction	-	20	52	32	55

Fig. 2A: Reduction in anti-dsDNA IgG with Example B11 after 6 weeks of treatment



Treatment	Veh.	Ex.B11	Ex.B11	Ex.B11	Pred
Dose [QD; (mg/kg)	-	3	10	30	2
Duration (weeks)	6	6	6	6	6
Age (Weeks)	16	16	16	16	16
% Reduction	-	19	30	52	53

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2014/083630

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/04 C07D519/00 A61K31/437 A61P29/00 A61P37/00
A61P17/00 A61P19/00

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 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/167046 A1 (JANUS BIOTHERAPEUTICS INC [US]; LIPFORD GRAYSON B [US]; ZEPP CHARLES M) 6 December 2012 (2012-12-06) cited in the application claims 1-29 -----	1-17
A	WO 2005/007672 A2 (COLEY PHARM GMBH [DE]; COLEY PHARM GROUP INC [US]; LIPFORD GRAYSON B []) 27 January 2005 (2005-01-27) cited in the application claims 1-142 -----	1-17



Further documents are listed in the continuation of Box C.



See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search

12 February 2015

Date of mailing of the international search report

19/02/2015

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Marzi, Elena

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/JP2014/083630

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