

Description

Title of Invention: COMPOUNDS AS CSF1R INHIBITORS

Technical Field

- [0001] The present invention relates to pyrazolopyridine or pyrazolopyrimidine compounds and salts thereof. The present invention also relates to medical use of pyrazolopyridine or pyrazolopyrimidine compounds or salts thereof for treating, preventing, and/or diagnosing diseases associated with colony-stimulating factor-1 receptor (CSF1R). Methods of preparing said compounds or salts thereof are also provided.

Background Art

- [0002] Macrophage colony-stimulating factor-1 receptor (CSF1R) is a member of class III receptor tyrosine kinase family, which also includes FMS-like tyrosine kinase 3 (FLT-3), tyrosine-protein kinase KIT (KIT), and platelet-derived growth factor receptor (PDGFR) α and β . CSF1R is primarily expressed in macrophage lineages including monocytes, tissue macrophages, dendritic cells, Kupffer cells, osteoclasts, and microglia. CSF1R binding CSF-1 or IL-34 in the brain activates signal transduction pathways, such as PI3K/AKT/NF- κ B, PKC/NF- κ B, and ROS/RAS/RAF/MAPK pathways, resulting in the differentiation, survival, proliferation, adhesion, and migration of monocyte/macrophage lineage cells.
- [0003] The phenotype of mice lacking functional CSF1R and ligands includes osteopetrosis, reduced numbers of macrophage and microglia and reduced inflammatory cytokine production, which indicates the diverse functions of CSF1R signaling.
- [0004] CSF1R signaling may also lead to aberrant expression of proinflammatory cytokines, including tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6), which are involved in the exacerbation of various types of cancer, bone disorders, and inflammatory diseases.

Citation List

Non Patent Literature

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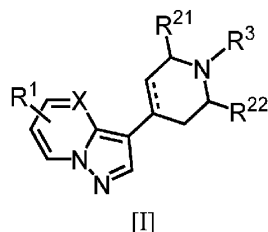
Summary of Invention

Technical Problem

- [0006] It is an object of the present invention to provide a novel pyrazolopyridine or pyrazolopyrimidine compound or a salt thereof useful for treating, preventing and/or diagnosing diseases associated with CSF1R.
- [0007] It is another object of the present invention to provide a medicament having a wide treatment spectrum relating to CSF1R inhibition.

Solution to Problem

- [0008] As a result of exhaustive research aimed at solving the aforementioned problems, the inventors succeeded in synthesizing novel pyrazolopyridine and/or pyrazolopyrimidine compounds.
- [0009] Provided is a compound represented by Formula [I], or a salt thereof:
[Chem.1]



wherein

R¹ is hydrogen, halogen, -CN, -L¹¹-R¹¹ optionally substituted with one or more R¹², or -R¹¹ optionally substituted with one or more R¹²;

L¹¹ is -C₁₋₃ alkylene-, -C₁₋₃ alkylene-C(=O)-, -O-, -O-C₁₋₃ alkylene-, -O-C₁₋₃ alkylene-O-, -OCH₂C(=O)O-, -C(=O)-, -C(=O)NH-, or -NH-C(=O)-;

R¹¹ is

- a) C₁₋₆ alkyl,
- b) C₁₋₆ haloalkyl,
- c) C₃₋₈ cycloalkyl,
- d) a saturated or unsaturated 4- to 10-membered monocyclic, bicyclic, or spiro heterocyclyl;

R¹² is each independently halogen, -OH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl-O-C₁₋₆ alkyl, C₃₋₈ cycloalkyl, a saturated or unsaturated 4- to 10-membered monocyclic, bicyclic, or spiro heterocyclyl optionally substituted with one or more C₁₋₆ alkyl;

R²¹ and R²² are hydrogen, or R²¹ and R²² together with the adjacent heterocyclic form a bridged bicyclic ring;

R³ is -L³¹-R³¹ optionally substituted with one or more R³², or R³¹ optionally substituted with one or more R³²;

L³¹ is -C(=O)-, -C(=O)O-, -C(=O)O-C₁₋₃ alkylene-, -C(=O)-C₁₋₃ alkylene-O-, -C(=O)-C₁₋₃ alkylene-O-C₁₋₃ alkylene-, or -C(=O)NH-C₁₋₃ alkylene-;

R³¹ is

- a) C₁₋₆ alkyl,
- b) C₁₋₆ haloalkyl,
- c) C₃₋₈ cycloalkyl,
- d) phenyl, or
- e) a saturated or unsaturated 4- to 10-membered monocyclic, bicyclic, or spiro heterocyclyl;

R³² is each independently halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₃₋₈ cycloalkyl;

X is CR¹ or N; and a bond:

[Chem.2]

is single or double bond.

[0010] Also provided are pharmaceutical compositions comprising a compound of Formula [I], or a salt thereof, and a pharmaceutically acceptable carrier or excipient.

[0011] Also provided are therapeutic, preventative, and/or diagnostic agents for a disease caused by CSF1R comprising a compound of Formula [I], or a salt thereof.

- [0012] Also provided are methods for treating, preventing, and/or diagnosing a disease caused by CSF1R, which comprise administering to a human in need thereof an effective amount of a compound of Formula [I], or a salt thereof.
- [0013] Also provided is a compound of Formula [I], or a salt thereof, for use in the treatment, prevention, and/or diagnosis of a disease caused by CSF1R.
- [0014] Also provided is use of a compound of Formula [I], or a salt thereof, in the manufacture of a medicament for treating, preventing, and/or diagnosing a disease caused by CSF1R.
- [0015] Also provided are processes for preparing a compound of Formula [I], or a salt thereof, and novel intermediates of use in the preparation of a compound of Formula [I], or a salt thereof.

Description of Embodiments

- [0016] The phrases and terms used in this specification are explained in detail below.
- [0017] In the present specification, the term “halogen” is fluorine, chlorine, bromine, or iodine. It is preferably fluorine, chlorine, or bromine, and more preferably fluorine or chlorine.
- [0018] In the present specification, the term “C₁₋₆ alkyl” is a linear or a branched alkyl having 1 to 6 carbon atoms (C₁₋₆), and specific examples thereof include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, 3-methylpentyl, and the like. “C₁₋₆ alkyl” also includes C₁₋₆ alkyl having deuterium atoms substituted for 1 to 3 hydrogen atoms, and specific examples include methyl-d₁, methyl-d₂, methyl-d₃, ethyl-d₅, and the like.
- [0019] In the present specification, the term “C₁₋₆ haloalkyl” is a linear or a branched alkyl having 1 to 6 carbon atoms (C₁₋₆) with 1 to 4 halogens, preferably 1 to 3 halogens, and specific examples thereof include fluoromethyl, chloromethyl, bromomethyl, iodomethyl, difluoromethyl, dichloromethyl, dibromomethyl, trifluoromethyl, trichloromethyl, 2-fluoroethyl, 2-chloroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 1,1,2,2-tetrafluoroethyl, 3-chloropropyl, 2,3-dichloropropyl, 4,4,4-trichlorobutyl, 4-fluorobutyl, 5-chloropentyl, 3-chloro-2-methylpropyl, 5-bromohexyl, 5,6-dibromohexyl, and the like.
- [0020] In the present specification, the term “C₁₋₃ alkylene” is a linear or a branched alkylene having 1 to 3 carbon atoms (C₁₋₃). Specific examples thereof include methylene, ethylene, 1-methylethylene, 2-methylethylene, trimethylene, methylenemethylene, ethylenemethylene, dimethylenemethylene, and the like. “C₁₋₃ alkylene” also includes C₁₋₃ alkylene in which 1 to 3 hydrogen atoms are replaced with deuterium atoms.
- [0021] In the present specification, the term “C₁₋₆ alkylene” is a linear or a branched alkylene having 1 to 6 carbon atoms (C₁₋₆). Specific examples thereof include methylene,

ethylene, 1-methylethylene, 2-methylethylene, trimethylene, methylmethylene, ethylmethylene, dimethylmethylene, 2,2-dimethylethylene, 2-methyltrimethylene, 2,2-dimethyltrimethylene, 1-methyltrimethylene, and the like. "C₁₋₆ alkylene" also includes C₁₋₆ alkylene in which 1 to 6 hydrogen atoms are substituted with deuterium atoms.

[0022] In the present specification, the term "C₃₋₈ cycloalkyl" is a saturated or partially unsaturated carbocyclyl having 3 to 8 carbon atoms, and includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexanyl, cycloheptanyl, cyclooctanyl, and the like.

[0023] In the present specification, the term "saturated or unsaturated 4- to 10-membered monocyclic, bicyclic, or spiro heterocyclyl" comprises at least one heteroatom selected from the group consisting of nitrogen, oxygen, and sulfur atoms and may be partially unsaturated. The heterocyclyl includes a bridged heterocyclyl. Specific examples include a saturated or unsaturated 4- to 6-membered monocyclic heterocyclyl containing 1 to 2 nitrogen atoms as a ring-constituting heteroatom, a saturated or unsaturated 4- to 6-membered monocyclic heterocyclyl containing 1 oxygen atom as ring-constituting heteroatom, a saturated or unsaturated 5- to 6-membered monocyclic heterocyclyl containing 1 to 2 nitrogen atoms and 1 oxygen atom as ring-constituting heteroatom, an unsaturated 5-membered monocyclic heterocyclyl containing 1 to 2 nitrogen atoms and 1 sulfur atom as ring-constituting heteroatom, a saturated or unsaturated 7- to 9-membered bicyclic heterocyclyl containing 2 to 3 nitrogen atoms as ring-constituting heteroatom, a saturated or unsaturated 7- to 9-membered bicyclic heterocyclyl containing 1 to 2 nitrogen atoms and 1 oxygen atom as ring-constituting heteroatom, a saturated or unsaturated 9-membered bicyclic heterocyclyl containing 1 nitrogen atom, 1 oxygen atom and 1 sulfur atom as ring-constituting heteroatom, a saturated or unsaturated 6- to 10-membered bicyclic heterocyclyl containing 1 oxygen atom as ring-constituting heteroatom, a saturated 7-membered spiro heterocyclyl containing 1 to 2 nitrogen atoms as ring-constituting heteroatom, a saturated 7- to 8-membered spiro heterocyclyl containing 1 nitrogen atom and 1 oxygen atom as ring-constituting heteroatom, and a saturated 6- to 10-membered spiro heterocyclyl containing 2 nitrogen atoms as ring-constituting heteroatom.

[0024] In the present specification, a saturated or unsaturated 4- to 6-membered monocyclic heterocyclyl containing 1 to 2 nitrogen atoms as a ring-constituting heteroatom specifically includes azetidiny, piperidiny, pyrazoly, pyrimidiny, pyrroly, imidazoly, pyridiny, tetrahydropyridiny, pyraziny, pyridaziny, pyrrolidiny, imidazolidiny, pyrazolidiny, and piperaziny.

[0025] In the present specification, a saturated or unsaturated 4- to 6-membered monocyclic heterocyclyl containing 1 oxygen atom as a ring-constituting heteroatom specifically includes oxetany, pyranly, furany, tetrahydropyranly, and tetrahydrofuranly.

- [0026] In the present specification, a saturated or unsaturated 5- to 6-membered monocyclic heterocyclyl containing 1 to 2 nitrogen atom and 1 oxygen atom as a ring-constituting heteroatom specifically includes oxazole, isoxazole, oxadiazole, and morpholine.
- [0027] In the present specification, an unsaturated 5-membered monocyclic heterocyclyl containing 1 to 2 nitrogen atoms and 1 sulfur atom as a ring-constituting heteroatom specifically includes thiazolyl, thiazolinyl (dihydrothiazolyl), thiadiazolyl, isothiazolyl, and thiazolidinyl.
- [0028] In the present specification, a saturated or unsaturated 7- to 9-membered bicyclic heterocyclyl containing 2 to 3 nitrogen atoms as a ring-constituting heteroatom specifically includes pyrrolidinopyrrolidinyl, benzoimidazolyl, dihydrobenzoimidazolyl, indazolyl, indazolyl (dihydroindazolyl), benzotriazolyl, imidazopyridinyl, imidazopyrazinyl, tetrahydroimidazopyrazinyl, pyrazolopyridinyl, tetrahydropyrindolyl, benzoazepinyl, tetrahydrobenzoazepinyl, pyrrolopyrrolyl, and hexahydropyrrolopyrrolyl.
- [0029] In the present specification, a saturated or unsaturated 7- to 9-membered bicyclic heterocyclyl containing 1 to 2 nitrogen atoms and 1 oxygen atom as a ring-constituting heteroatom specifically includes benzoxazolyl, dihydrobenzoxazolyl, oxazabicycloheptanyl, tetrahydrofuropyrrolyl, benzoxadiazolyl, benzoisoxazolyl, benzoxazinyl, dihydrobenzoxazinyl, dihydroimidazooxazinyl, dihydropyrazolooxazinyl, furopyridinyl, furopyrrolyl, benzoxazepinyl, and tetrahydrobenzoxazepinyl.
- [0030] In the present specification, a saturated or unsaturated 9-membered bicyclic heterocyclyl containing 1 nitrogen atom, 1 oxygen atom and 1 sulfur atom as a ring-constituting heteroatom specifically includes pyrano[4,3-d]thiazolyl, and dihydropyrano[4,3-d]thiazolyl.
- [0031] In the present specification, a saturated or unsaturated 6- to 10-membered bicyclic heterocyclyl containing 1 oxygen atom as a ring-constituting heteroatom specifically includes 2-oxabicyclo[2.1.1]hexanyl.
- [0032] In the present specification, a saturated 7-membered spiro heterocyclyl containing 1 to 2 nitrogen atoms as a ring-constituting heteroatom specifically includes 2-azaspiro[3.3]heptanyl and 2,6-diazaspiro[3.3]heptanyl.
- [0033] In the present specification, a saturated 7- to 8-membered spiro heterocyclyl containing 1 nitrogen atom and 1 oxygen atom as a ring-constituting heteroatom specifically includes 2-oxa-6-azaspiro[3.3]heptanyl and oxazaspirooctanyl.
- [0034] In the present specification, a saturated 6- to 10-membered spiro heterocyclyl containing 2 nitrogen atoms as a ring-constituting heteroatom specifically includes 2,6-diazaspiro[3.3]heptanyl.
- [0035] In the present specification, the bridged bicyclic ring formed with R²¹, R²², and the adjacent heterocyclyl includes 7- to 8-membered bicyclic ring, and specific examples

thereof include azabicyclooctane, preferably azabicyclo[3.2.1]octane.

- [0036] As used herein, the term “C₁₋₁₈ alkanesulfonyl” is a linear or branched alkanesulfonyl having 1 to 18 carbon atoms (C₁₋₁₈), and specific examples thereof include methane-sulfonyl, 1-propanesulfonyl, 2-propanesulfonyl, butanesulfonyl, cyclohexanesulfonyl, dodecanesulfonyl, octadecanesulfonyl, and the like.
- [0037] As used herein, the term “lower alkanesulfonyloxy” is a linear or branched alkanesulfonyloxy having 1 to 6 carbon atoms (C₁₋₆), and specific examples thereof include methanesulfonyloxy, ethanesulfonyloxy, 1-propanesulfonyloxy, 2-propanesulfonyloxy, 1-butanefulfonyloxy, 3-butanefulfonyloxy, 1-pentanesulfonyloxy, 1-hexanesulfonyloxy, and the like.
- [0038] As used herein, the term “arylsulfonyloxy” is phenylsulfonyloxy, naphthylsulfonyloxy, and the like, that is optionally substituted with 1 to 3 groups selected from the group consisting of a linear or branched alkyl having 1 to 6 carbon atoms (C₁₋₆), a linear or branched alkoxy having 1 to 6 carbon atoms (C₁₋₆), nitro, and halogen, on the benzene or naphthalene ring. Specific examples of phenylsulfonyloxy optionally having substituent(s) include phenylsulfonyloxy, 4-methylphenylsulfonyloxy, 2-methylphenylsulfonyloxy, 4-nitrophenylsulfonyloxy, 4-methoxyphenylsulfonyloxy, 2-nitrophenylsulfonyloxy, 3-chlorophenylsulfonyloxy, and the like. Specific examples of naphthylsulfonyloxy include α -naphthylsulfonyloxy, β -naphthylsulfonyloxy, and the like.
- [0039] As used herein, the term “aralkylsulfonyloxy” is a linear or branched alkanesulfonyloxy having 1 to 6 carbon atoms (C₁₋₆) that is substituted with phenyl optionally substituted with 1 to 3 groups selected from the group consisting of a linear or branched alkyl having 1 to 6 carbon atoms (C₁₋₆), a linear or branched alkoxy having 1 to 6 carbon atoms (C₁₋₆), nitro, and halogen on the benzene ring; or a linear or branched alkanesulfonyloxy having 1 to 6 carbon atoms (C₁₋₆) that is substituted with naphthyl, and the like. Specific examples of alkanesulfonyloxy substituted with phenyl include benzylsulfonyloxy, 2-phenylethylsulfonyloxy, 4-phenylbutylsulfonyloxy, 4-methylbenzylsulfonyloxy, 2-methylbenzylsulfonyloxy, 4-nitrobenzylsulfonyloxy, 4-methoxybenzylsulfonyloxy, 3-chlorobenzylsulfonyloxy, and the like. Specific examples of alkanesulfonyloxy substituted with naphthyl include α -naphthylmethylsulfonyloxy, β -naphthylmethylsulfonyloxy, and the like.
- [0040] Specific examples of the term “perhaloalkanesulfonyloxy” used herein include trifluoromethanesulfonyloxy and the like.
- [0041] Specific examples of the term “sulfonio” used herein include dimethylsulfonio, diethylsulfonio, dipropylsulfonio, di-(2-cyanoethyl)sulfonio, di-(2-nitroethyl)sulfonio, di-(aminoethyl)sulfonio, di-(2-methylaminoethyl)sulfonio, di-(2-dimethylaminoethyl)sulfonio, di-(2-hydroxyethyl)sulfonio, di-

(3-hydroxypropyl)sulfonio, di-(2-methoxyethyl)sulfonio, di-(2-carbamoylethyl)sulfonio, di-(2-carbamoylethyl)sulfonio, di-(2-carboxyethyl)sulfonio, di-(2-methoxycarbonylethyl)sulfonio, diphenylsulfonio, and the like.

[0042] In the present specification, the term “solvent” may be an inert solvent in a reaction described herein, and examples thereof include water, ethers (e.g., dioxane, tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, cyclopentyl methyl ether, diethylene glycol dimethyl ether, and ethylene glycol dimethyl ether), hydrocarbons, halogenated hydrocarbons (e.g., methylene chloride, chloroform, 1,2-dichloroethane, and carbon tetrachloride), aromatic hydrocarbons (e.g., benzene, toluene, and xylene), alcohols (e.g., methanol, ethanol, and isopropanol), esters, ketones, amides, nitriles, sulfoxides, and polar solvents (e.g., N,N-dimethylformamide (DMF), N-methylpyrrolidone (NMP), dimethyl sulfoxide (DMSO), hexamethylphosphoric triamide, and acetonitrile). These solvents may be used alone or as a mixture of any two or more of them with optional ratios. Examples of “hydrocarbons” herein include, for example, aliphatic hydrocarbons such as hexane and pentane; alicyclic hydrocarbons such as cyclopentane and cyclohexane; and aromatic hydrocarbons such as benzene and toluene. Examples of “alcohols” herein include, for example, methanol, ethanol, 2-propanol, propanol, and tert-butanol. Examples of “ethers” herein include, for example, chained ethers such as diethyl ether, diisopropyl ether, dibutyl ether, dimethoxyethane, and diphenyl ether; and circular ethers such as 1,4-dioxane and tetrahydrofuran. Examples of “esters” herein include, for example, ethyl acetate and ethyl propionate. Examples of “ketones” herein include, for example, acetone, methyl ethyl ketone, and methyl isobutyl ketone. Examples of “amides” herein include, for example, N,N-dimethylformamide, N,N-dimethylacetamide, and N-methyl-2-pyrrolidone. Examples of “nitriles” herein include, for example, acetonitrile and propionitrile. Examples of “sulfoxides” herein include, for example, dimethyl sulfoxide.

[0043] In the present specification, the term “catalyst” to be used in reduction reactions is not particularly limited to examples used herein, but specific examples thereof include palladium on carbon (Pd/C), platinum on carbon (Pt/C), platinum oxide (PtO₂), and the like.

[0044] In the present specification, the term “halogenating agent” is not particularly limited to examples used herein, but specific examples thereof include fluorinating agents, chlorinating agents, brominating agents, and iodinating agents, such as potassium fluoride, tetrabutylammonium fluoride, (diethylamino)sulfur trifluoride, phosphorus oxychloride, phosphorus trichloride, phosphorus pentachloride, thionyl chloride, oxalyl chloride, trichlorophosphoric acid, bromine, phosphorus oxybromide, phosphorus tribromide, iodine, sodium iodide, N-chlorosuccinimide, N-bromosuccinimide, N-

iodosuccinimide, and the like.

[0045] In the present specification, the term “acid” is not particularly limited to examples used herein, but includes an inorganic acid, an organic acid, and the like. Examples of the “inorganic acid” include hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid, phosphoric acid, and the like. Examples of the “organic acid” include acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, and the like. These acids may be used alone or as a mixture of any two or more of them.

[0046] In the present specification, the term “base” is not particularly limited to examples used herein, but includes an inorganic base, an organic base, and the like. Examples of the “inorganic base” include alkali metal hydroxides (e.g., lithium hydroxide, sodium hydroxide, potassium hydroxide, and cesium hydroxide), alkaline earth metal hydroxides (e.g., magnesium hydroxide, calcium hydroxide, and barium hydroxide), alkali metal carbonates (e.g., lithium carbonate, sodium carbonate, potassium carbonate, and cesium carbonate), alkaline earth metal carbonates (e.g., magnesium carbonate, calcium carbonate, and barium carbonate), alkali metal carboxylates (e.g., sodium acetate, potassium acetate, and sodium butyrate), alkali metal hydrogen carbonates (e.g., sodium hydrogen carbonate, potassium hydrogen carbonate, and cesium hydrogen carbonate), alkali metal phosphates (e.g., sodium phosphate, potassium phosphate, and cerium phosphate), alkaline earth metal phosphates (e.g., magnesium phosphate and calcium phosphate), alkali metal alkoxides (e.g., sodium methoxide, sodium ethoxide, sodium tert-butoxide, and potassium tert-butoxide), alkali metal hydride (e.g., sodium hydride, potassium hydride, and cesium hydride), and the like. Examples of the “organic base” include aromatic amines (e.g., pyridine and lutidine), trialkylamines (e.g., trimethylamine, triethylamine, tripropylamine, tributylamine, N,N-diisopropylethylamine (DIPEA)), cyclohexyldimethylamine, 4-dimethylaminopyridine (DMAP), N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, tetramethylethylenediamine, tetramethylpropylenediamine, picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), dialkylamine (e.g., diethylamine and diisopropylamine), metal amides (e.g., lithium diisopropylamide and lithium hexamethyldisilazide), metal alkoxides (e.g., sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide, and sodium phenoxide), and the like. These bases may be used alone or as a mixture of any two or more of them. The organic base herein is preferably DMAP or TEA.

[0047] In the present specification, the term “palladium catalyst” is not particularly limited to examples used herein, and examples thereof include tetravalent palladium catalysts

such as sodium hexachloropalladium (IV) acid tetrahydrate and potassium hexachloropalladium (IV) acid; divalent palladium catalysts such as [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane adduct ($\text{PdCl}_2(\text{dppf}) \cdot \text{DCM}$), (2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium (II) methanesulfonate (XPhos Pd G3), palladium (II) chloride, palladium (II) bromide, palladium (II) acetate, palladium (II) acetylacetonate, dichlorobis(benzonitrile)palladium (II), dichlorobis(acetonitrile)palladium (II), dichlorobis(triphenylphosphine)palladium (II), dichlorotetraammine palladium (II), dichloro(cycloocta-1,5-diene)palladium (II), and palladium (II) trifluoroacetate; and zerovalent palladium catalysts such as tris(dibenzylideneacetone)dipalladium (0) ($\text{Pd}_2(\text{dba})_3$), tris(dibenzylideneacetone)dipalladium (0)-chloroform complex, and tetrakis(triphenylphosphine)palladium (0) ($\text{Pd}(\text{PPh}_3)_4$). These palladium compounds may be used alone or as a mixture of any two or more of them.

- [0048] In the present specification, the term “leaving group” is not particularly limited to examples used herein, and examples thereof include halogen (e.g., fluorine, chlorine, bromine, and iodine), C_{1-18} alkylsulfonyl, alkylsulfonyloxy (e.g., methylsulfonyloxy, ethylsulfonyloxy, and trifluoromethylsulfonyloxy), phenyloxy (e.g., 4-nitrophenyloxy), arylsulfonyloxy (e.g., benzenesulfonyloxy, p-toluenesulfonyloxy, 2,4,6-trimethylbenzenesulfonyloxy, 2-nitrobenzenesulfonyloxy, and 4-nitrobenzenesulfonyloxy), aralkylsulfonyloxy, perhaloalkanesulfonyloxy, sulfonio, toluenesulfoxy, nitrophenylcarbonate, imidazolecarbonate, and the like.
- [0049] Various substituents in the compound represented by Formula [I] (herein also referred to as “Compound [I]”) are explained below.
- [0050] In one embodiment of Compound [I], R^1 is hydrogen, halogen, -CN, or $-\text{L}^{11}-\text{R}^{11}$ optionally substituted with one or more R^{12} . Preferably, R^1 may be $-\text{L}^{11}-\text{R}^{11}$ optionally substituted with one or more R^{12} .
- [0051] In another embodiment of Compound [I], R^1 is hydrogen, halogen, cyano, C_{1-6} alkyl, C_{1-6} alkyl-O- optionally substituted with one or more deuteriums, OH or C_{1-6} alkyl-O-, C_{1-6} alkyl-OC(=O)CH₂O-, C_{1-6} haloalkyl-O-, C_{1-6} haloalkyl-O- C_{1-6} alkylene-, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-O-, C_{3-8} cycloalkyl- C_{1-6} alkylene-O- optionally substituted with halogen, C_{1-6} alkyl or C_{1-6} haloalkyl, C_{3-8} cycloalkyl-C(=O)-, C_{3-8} cycloalkyl-NH-C(=O)-, azetidiny optionally substituted with halogen, azetidiny- C_{1-6} alkylene-O- optionally substituted with oxetanyl, azetidiny-O- optionally substituted with oxetanyl, piperidiny optionally substituted with oxetanyl, morpholino, morpholino- C_{1-6} alkylene, morpholino- C_{1-6} alkylene-O-, morpholino-C(=O)- C_{1-6} alkylene, pyrazolyl optionally substituted with C_{1-6} alkyl, C_{1-6} deuterated alkyl, C_{1-6} alkyl-O- C_{1-6} alkylene, C_{3-8} cycloalkyl, thiazolyl optionally substituted with C_{1-6} haloalkyl or diazaspiroheptyl

optionally substituted with C₁₋₆ alkyl, thiadiazolyl optionally substituted with C₁₋₆ alkyl, oxetanyl-C₁₋₆ alkylene-O- optionally substituted with halogen or C₁₋₆ alkyl, tetrahydrofuranlyl, tetrahydropyranlyl, tetrahydroimidazo[1,2-a]pyrazinyl, dihydroimidazo[2,1-c][1,4]oxazinyl, dihydropyrano[4,3-d]thiazolyl, dihydropyrazolo[5,1-c][1,4]oxazinyl, hexahydropyrrolo[3,4-c]pyrrolyl, tetrahydrofuro[3,4-c]pyrrolyl, 2-oxabicyclo[2.1.1]hexanyl-C₁₋₆ alkylene-O-, 2-azaspiro[3.3]heptanyl optionally substituted with halogen, 2-oxa-6-azaspiro[3.3]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl-C(=O)-, or 2-azaspiro[3.3]heptanyl-C₁₋₆ alkylene-O- optionally substituted with halogen.

[0052] In still another embodiment of Compound [I], R¹ is hydrogen, fluoro, chloro, cyano, isopropyl, methoxy, methoxy-d₃, difluoromethoxy, ethoxy, 2-methoxyethoxy, 2-methoxy-2-oxoethoxy, 2,2-difluoroethoxy, 2-(difluoromethoxy)ethoxy, 2-(trifluoromethoxy)ethoxy, 2-hydroxy-2-methylpropoxy, 2-methoxy-2-methylpropoxy, 2,2-difluoropropoxy, 3,3-difluoropropoxy, 3,3,3-trifluoropropoxy, cyclopropyl, cyclopropoxy, cyclopropylmethoxy, cyclopropanecarbonyl, cyclopropylcarbonyl, (1-fluorocyclopropyl)methoxy, (2,2-difluorocyclopropyl)methoxy, 2-(3,3-difluorocyclobutyl)ethoxy, (2,2-difluoro-1-methylcyclopropyl)methoxy, (1-(difluoromethyl)cyclopropyl)methoxy, (1-(trifluoromethyl)cyclopropyl)methoxy, azetidin-1-yl, 3,3-difluoroazetidin-1-yl, (1-(oxetan-3-yl)azetidin-3-yl)oxy, (1-(oxetan-3-yl)azetidin-3-yl)methoxy, 1-methyl-1H-pyrazol-4-yl, 1-(methyl-d₃)-1H-pyrazol-4-yl, 1-(2-methoxyethyl)-1H-pyrazol-4-yl, 1,3,5-trimethyl-1H-pyrazol-4-yl, 1-cyclopropyl-1H-pyrazol-4-yl, 1-cyclopropyl-3,5-dimethyl-1H-pyrazol-4-yl, 3,5-dimethyl-1-(methyl-d₃)-1H-pyrazol-4-yl, 1-(oxetan-3-yl)piperidin-4-yl, (1-methylpiperidin-4-yl)oxy, (oxetan-3-yl)methoxy, (3-fluoro-oxetan-3-yl)methoxy, (3-methyloxetan-3-yl)methoxy, morpholino, morpholinomethyl, 2-morpholino-2-oxoethyl, 2-morpholinoethoxy, 2-morpholinoethyl, thiazol-4-yl, thiazol-5-yl, (trifluoromethyl)thiazol-4-yl, 1,2,4-thiadiazol-5-yl, 3-methyl-1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-2-yl, tetrahydro-2H-pyran-4-yl, tetrahydrofuran-3-yl, 7-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-2-yl, 5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, 6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-3-yl, 5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-2-yl, 6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-yl, ((1s,4s)-2-oxabicyclo[2.1.1]hexan-1-yl)methoxy, tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl, 2-oxa-6-azaspiro[3.3]heptan-6-yl, 2-oxa-6-azaspiro[3.3]heptane-6-carbonyl, 6,6-difluoro-2-azaspiro[3.3]heptan-2-yl, 2-(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)ethoxy, or

- 2-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)thiazol-5-yl. Preferably, R¹ may be 2-methoxyethoxy, cyclopropoxy, (1-methylpiperidin-4-yl)oxy, or 2,2-difluoroethoxy.
- [0053] In one embodiment of Compound [I], L¹¹ is methylene, ethylene, methylene-C(=O)-, -O-, -O-methylene, -O-ethylene, -O-ethylene-O-, -OCH₂C(=O)O-, -C(=O)-, -C(=O)NH-, or -NH-C(=O)-.
- [0054] In another embodiment of Compound [I], L¹¹ is -O-, -O-ethylene, -O-ethylene-O-, -C(=O)NH-, or -NH-C(=O)-. Preferably, L¹¹ may be -O- or -O-ethylene-O-.
- [0055] In one embodiment of Compound [I], R¹¹ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, or a saturated 4- to 6-membered monocyclic heterocyclyl.
- [0056] In another embodiment of Compound [I], R¹¹ is methyl, methyl-d₃, ethyl, propyl, isopropyl, isobutyl, difluoromethyl, trifluoromethyl, difluoroethyl, difluoropropyl, trifluoropropyl, cyclopropyl, cyclobutyl, oxetanyl, tetrahydrofuryl, tetrahydropyranyl, azetiziny, piperidiny, morpholino, pyrazolyl, thiazolyl, thiadiazolyl, tetrahydroimidazopyridiny, dihydroimidazooxaziny, dihydropyrazolooxaziny, dihydropyranthiazolyl, hexahydropyrrolopyrrolyl, tetrahydrofuropyrrolyl, oxabicyclohexanyl, azaspiroheptanyl, or oxoazaspiroheptanyl.
- [0057] In still another embodiment of Compound [I], R¹¹ is methyl, methyl-d₃, ethyl, propyl, isopropyl, isobutyl, difluoromethyl, trifluoromethyl, difluoroethyl, difluoropropyl, trifluoropropyl, cyclopropyl, cyclobutyl, azetidin-1-yl, azetidin-3-yl, 1H-pyrazol-4-yl, piperidin-4-yl, oxetan-3-yl, pyrimidin-2-yl, morpholino, thiazol-4-yl, thiazol-5-yl, 1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-2-yl, tetrahydro-2H-pyran-4-yl, tetrahydrofuran-3-yl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-2-yl, hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, 6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-3-yl, 5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-2-yl, 6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-yl, (1s,4s)-2-oxabicyclo[2.1.1]hexan-1-yl, tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl, 2-oxa-6-azaspiro[3.3]heptan-6-yl, 2-oxa-6-azaspiro[3.3]heptane-6-yl, or 2-azaspiro[3.3]heptan-2-yl.
- [0058] In still another embodiment of Compound [I], R¹¹ is methyl, cyclopropyl, difluoroethyl, pyrazolyl, tetrahydrofuranyl, thiazolyl, piperidiny, tetrahydropyranyl, morpholino, tetrahydrofuropyrrolyl, hexahydropyrrolopyrrolyl, azaspiroheptanyl, or oxazaspiroheptanyl.
- [0059] In one embodiment of Compound [I], R¹² is halogen, -OH, C₁₋₆ alkyl optionally substituted with one or more deuteriums, C₁₋₆ haloalkyl, C₁₋₆ alkoxy-C₁₋₆ alkyl, C₃₋₈ cycloalkyl, a saturated 6- to 10-membered spiro heterocyclyl containing 2 nitrogen atoms as ring-constituting heteroatom optionally substituted with C₁₋₆ alkyl. Preferably, R¹² may be halogen, C₁₋₆ alkyl optionally substituted with one or more deuteriums, or C₁₋₆ haloalkyl.
- [0060] In another embodiment of Compound [I], R¹² is fluoro, methyl, methyl-d₃, difluo-

romethyl, trifluoromethyl, methoxyethyl, cyclopropyl, -OH, oxetanyl, or diazaspiroheptanyl optionally substituted with methyl.

[0061] In still another embodiment of Compound [I], R¹² is fluoro, methyl, methyl-d₃, or cyclopropyl.

[0062] In one embodiment of Compound [I], R³ is -L³¹-R³¹ optionally substituted with one or more R³².

[0063] In another embodiment of Compound [I], R³ is C₁₋₆ haloalkyl-O-C(=O)-, C₃₋₈ cycloalkyl-O-C(=O)- optionally substituted with halogen, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl-C₁₋₆ alkylene-O-C(=O)- optionally substituted with C₁₋₆ alkyl, benzyloxy, phenyl-CH₂OCH₂-C(=O)- optionally substituted with C₁₋₆ alkyl, phenoxy-C₁₋₆ alkylene-C(=O)- optionally substituted with C₁₋₆ alkyl, phenyl-C₁₋₃ alkylene-NH-C(=O)-, azetidiny-C(=O)- optionally substituted with halogen or C₁₋₆ haloalkyl, oxazolyl-C₁₋₆ alkylene-O-C(=O)- optionally substituted with C₁₋₆ alkyl, oxadiazolyl optionally substituted with C₁₋₆ alkyl, oxadiazolyl-O-C(=O)- optionally substituted with C₃₋₈ cycloalkyl, thiazolyl-C₁₋₆ alkylene-O-C(=O)- optionally substituted with C₁₋₆ haloalkyl, pyrimidinyl optionally substituted with C₁₋₆ alkyl, tetrahydrofuranyl-C₁₋₆ alkylene-O-C(=O)-, oxazabicycloheptanyl-C(=O)-, or oxazaspirooctanyl-C(=O)-.

[0064] In one embodiment of Compound [I], L³¹ is -C(=O)-, -C(=O)O-, or -C(=O)O-C₁₋₃ alkylene-. Preferably, L³¹ may be -C(=O)-, -C(=O)O-, or -C(=O)O-methylene-.

[0065] In one embodiment of Compound [I], R³¹ is methyl, tert-butyl, cyclopropyl, cyclobutyl, cyclohexyl, phenyl, oxazolyl, thiazolyl, oxadiazole, pyrimidinyl, tetrahydrofuranyl, azetidiny, diazaspirooctanyl, oxazaspirooctanyl, or oxazatricyclooctane. Preferably, R³¹ may be tert-butyl, cyclopropyl, oxazolyl, thiazolyl, or azetidiny. More preferably, R³¹ may be cyclopropyl, oxazolyl, thiazolyl, or azetidiny. Still more preferably, R³¹ may be cyclopropyl, oxazolyl, or thiazolyl.

[0066] In another embodiment of Compound [I], R³¹ is methyl, cyclopropyl, cyclobutyl, cyclohexyl, or phenyl.

[0067] In one embodiment of Compound [I], R³² is fluoro, methyl, ethyl, cyclopropyl, difluoromethyl, or trifluoromethyl.

[0068] In one embodiment of Compound [I], X is CH or N.

[0069] In the present specification, the options and preferred embodiments for the different features of the compound, method and composition of the present invention as presented include all possible combinations of the options and preferred embodiments for these different features as long as they are consistent combinations.

[0070] Methods for manufacturing Compound [I] are explained below. Compound [I] may be manufactured, but is not limited thereto, based on the methods described in the General syntheses and Examples below. Unless otherwise specified, reaction temperatures may be optionally adjusted depending on reactants, solvents, and other

conditions used in each reaction herein.

[0071] An alkylation reaction, hydrolysis reaction, amination reaction, esterification reaction, amidation reaction etherification reaction, nucleophilic substitution reaction, addition reaction, oxidation reaction, reduction reaction, and the like in the General syntheses may be performed in accordance with any known methods. Examples of such methods include the methods described in Experimental Chemistry (Fifth Edition, edited by The Chemical Society of Japan, Maruzen Co., Ltd.); Organic Functional Group Preparations Second Edition, Academic Press, Inc., 1989; Comprehensive Organic Transformations, VCH Publishers, Inc., 1989; and P.G.M. Wuts and T.W. Greene, Greene's Protective Groups in Organic Synthesis (Fourth Edition, 2006), and the like.

[0072] In addition to the definitions described above, examples of a condensation agent used herein include, for example:

T3P; HATU; DCC; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide; N,N-diisopropylethylamine; WSC or a hydrochloride salt thereof; N,N'-carbonylbis(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene, 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphoryl chloride; phosphorus trichloride; diphenylphosphoryl azide; thionyl chloride; oxalyl chloride; alkyl haloformate such as ethyl chloroformate and isopropyl chloroformate; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide inner salt; benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; and so-called Vilsmeier agents prepared by reactions of DMF with thionyl chloride, phosgene, trichloromethyl chloroformate, or phosphorus oxychloride.

[0073] In addition to a condensation agent, a condensation accelerator may be added.

Examples of a condensation accelerator used herein include, for example,

1-hydroxybenzotriazole (HOBt), N-hydroxysuccinimide (HOSu), 1-hydroxy-7-azabenzotriazole (HOAt), and hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine (HOOBt).

[0074] Examples of a "protecting group of hydroxy" used herein include, but not limited to, any protecting groups of hydroxy used in the field of synthetic organic chemistry, and include, for example, alkyl groups (e.g., methyl, ethyl, isopropyl, tert-butyl, trifluoromethyl, hydroxymethyl, 2-hydroxyethyl, acetylmethyl); alkenyl groups (e.g., ethenyl, 1-propenyl, 2-propenyl, 1-methyl-2-propenyl); alkynyl groups (e.g., ethynyl, 1-propynyl, 2-propynyl, 1-methyl-2-propynyl); formyl; alkyl (alkenyl) carbonyl groups

(e.g., acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxyacetyl, acryloyl, propioloyl, methacryloyl, crotonoyl, isocrotonoyl, (E)-2-methyl-2-butenoyl); aryl-carbonyl groups (e.g., benzoyl, α -naphthoyl, β -naphthoyl, 2-bromobenzoyl, 4-chlorobenzoyl, 2,4,6-trimethylbenzoyl, 4-toluoyl, 4-anisoyl, 4-nitrobenzoyl, 2-nitrobenzoyl, 2-(methoxycarbonyl)benzoyl, 4-phenylbenzoyl); alkoxycarbonyl groups (e.g., methoxycarbonyl, tert-butoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl, 9-fluorenylmethyloxycarbonyl); tetrahydro (thio) pyranyl (furanyl) groups (e.g., tetrahydropyran-2-yl, 3-bromotetrahydropyran-2-yl, 4-methoxytetrahydropyran-4-yl, tetrahydrothiopyran-2-yl, 4-methoxytetrahydrothiopyran-4-yl, tetrahydrofuran-2-yl, tetrahydrothiofuran-2-yl); silyl groups (e.g., trimethylsilyl, triethylsilyl, isopropyl dimethylsilyl, tert-butyl dimethyl silyl, methyl diisopropyl silyl, methyl di-tert-butylsilyl, triisopropylsilyl, diphenylmethyl silyl, diphenylbutyl silyl, diphenylisopropyl silyl, phenyldiisopropyl silyl); alkoxymethyl groups (e.g., methoxymethyl, 1,1-dimethyl-1-methoxymethyl, ethoxymethyl, propoxymethyl, isopropoxymethyl, butoxymethyl, tert-butoxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl); alkoxyethyl groups (e.g., 1-ethoxyethyl, 1-(isopropoxy)ethyl); halogenated ethyl groups (e.g., 2,2,2-trichloroethyl); aralkyl groups (e.g., benzyl, α -naphthylmethyl, β -naphthylmethyl, diphenylmethyl, triphenylmethyl, α -naphthyl diphenylmethyl, 9-anthrylmethyl, 4-methylbenzyl, 2,4,6-trimethylbenzyl, 3,4,5-trimethylbenzyl, 4-methoxybenzyl, 4-methoxyphenyldiphenylmethyl, 2-nitrobenzyl, 4-nitrobenzyl, 4-chlorobenzyl, 4-bromobenzyl, 4-cyanobenzyl); alkenyloxycarbonyl groups (e.g., vinyloxycarbonyl, allyloxycarbonyl); and aralkyloxycarbonyl groups (e.g., benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl).

[0075] Examples of a "protecting group of carboxy" used herein include, but not limited to, any protecting groups of carboxy used in the field of synthetic organic chemistry, and include, for example, the "alkyl groups", "alkenyl groups", "alkynyl groups", "aralkyl groups", and "silyl groups" as above listed in the examples of the "protecting group of hydroxy" and similar groups thereof.

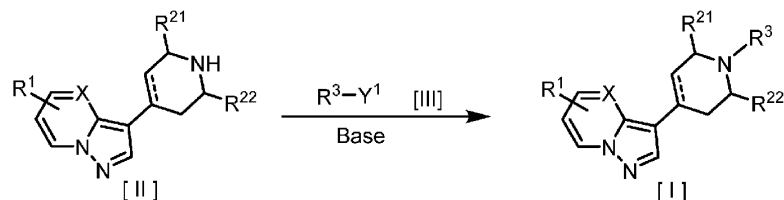
[0076] Examples of a "protecting group of amino" used herein include, but not limited to, any protecting groups of amino used in the field of synthetic organic chemistry, and include, for example, the "alkyl (alkenyl) carbonyl groups", "arylcarbonyl groups", "alkoxycarbonyl groups", "silyl groups", "aralkyl groups", "alkenyloxycarbonyl groups", and "aralkyloxycarbonyl groups" as above listed in the "protecting group of hydroxy" and similar groups thereof.

[0077] The reaction temperature in each step in the General syntheses herein typically

ranges from -80 to 150°C. The reaction time in each step typically ranges from 0.1 to 200 hours.

[0078] General synthesis 1

[Chem.3]



In the above scheme, Y¹ is a leaving group such as, halogens (e.g. chlorine and bromine), and phenyloxy groups (e.g. 4-nitro-phenyloxy group) and the other symbols are as defined for Compound [I] above.

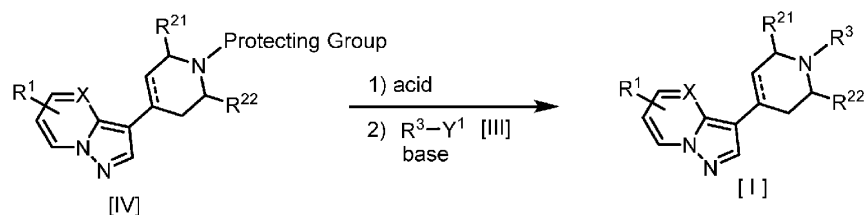
[0079] Compound [I] may be manufactured by the reaction indicated by the above synthetic scheme. Specifically, compound [II] may be reacted with compound [III] having a leaving group (Y¹) in the presence of a base in an inert solvent to give Compound [I].

Any bases that are described above may be used in this reaction, and the base preferably used herein includes organic bases (e.g. trimethylamine, triethylamine and N,N-diisopropylethylamine (DIPEA)).

Any solvents that are described above may be used in this reaction, and the solvent preferably used herein includes inert solvents such as halohydrocarbons (e.g. chloroform and dichloromethane), ethers (e.g. dioxane, and tetrahydrofuran), amides (e.g. N,N-dimethylformamide) and nitriles (e.g. acetonitrile).

[0080] General synthesis 2

[Chem.4]



In the above scheme, Y¹ is a leaving group such as, halogen (e.g. chlorine and bromine), and phenyloxy groups (e.g. 4-nitrophenyloxy group), the protecting group includes alkyl (alkenyl) carbonyl groups, arylcarbonyl groups and alkoxy carbonyl groups (e.g. tert-butoxycarbonyl), and the other symbols are as defined for Compound [I] above.

[0081] Compound [I] may be manufactured by the reaction indicated by the above synthetic scheme. Specifically, compound [IV] may be de-protected in the presence of an acid in

an inert solvent, followed by treatment with compound [III] having a leaving group (Y^1) in the presence of a base in an inert solvent, to give Compound [I].

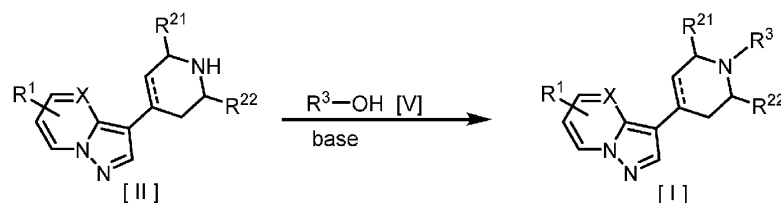
An intermediate compound obtained after the first step may be purified before moving to the second step or be used to the second step without purification.

Any acids that are described above may be used in the first step, and the acid preferably used herein includes inorganic acids (e.g. hydrochloric acid, sulfuric acid and hydrobromic acid) and organic acids (acetic acid, trifluoroacetic acid and p-toluenesulfonic acid).

Any solvents that are described above may be used in the first step, and the solvent preferably used herein includes as halogenated hydrocarbons (e.g. chloroform and dichloromethane), ethers (e.g. dioxane and tetrahydrofuran), and alcohols (e.g. methanol, ethanol and 2-propanol).

The base and inert solvent used in the second step may be chosen from those described in General synthesis 1.

[0082] General synthesis 3
[Chem.5]



In the above scheme, each symbol is as defined for Compound [I] above.

[0083] Compound [I] may be manufactured by the reaction indicated by the above synthetic scheme. Specifically, Compound [I] may be manufactured by reacting compound [II] with compound [V] in an inert solvent in the presence of a base.

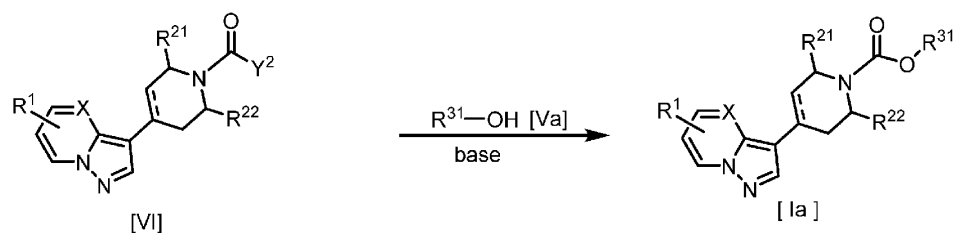
Any condensation agents that are described above may be used in this reaction, and the condensation agents preferably used herein includes HATU, WSC or a hydrochloride salt.

Any bases that are described above may be used in this reaction, and the base preferably used herein includes as an organic base (e.g. trimethylamine, triethylamine and N,N-diisopropylethylamine (DIPEA)).

Any solvents that are described above may be used in this reaction, and the solvent preferably used herein includes as halogenated hydrocarbons (e.g. chloroform and dichloromethane), ethers (e.g. dioxane and tetrahydrofuran), amides (e.g. N,N-dimethylformamide), and nitriles (e.g. acetonitrile).

[0084] General synthesis 4

[Chem.6]



In the above scheme, Y² is a leaving group such as phenyloxy groups (e.g. 4-nitrophenyloxy group), and the other symbols are as defined for Compound [I] above.

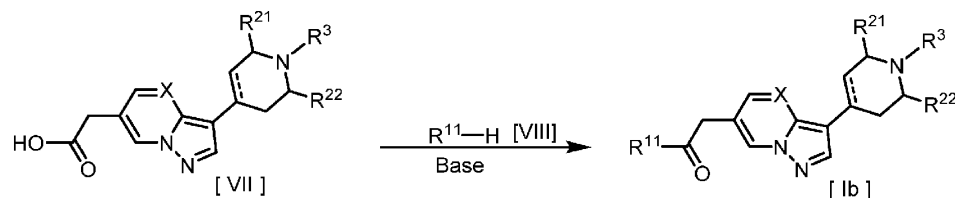
[0085] Compound [Ia] may be manufactured by the reaction indicated by the above synthetic scheme. Specifically, compound [Ia] may be manufactured by reacting compound [VI] with compound [Va] in an inert solvent in the presence of a base.

Any bases that are described above may be used in this reaction, and the base preferably used herein includes alkali metal hydrides (e.g. sodium hydride, and potassium hydride), and metal alkoxides (e.g. sodium tert-butoxide, and potassium tert-butoxide).

Any solvents that are described above may be used in this reaction, and the solvent preferably used herein includes ethers (e.g. dioxane and tetrahydrofuran), and amides (e.g. N,N-dimethylformamide),

[0086] General synthesis 5

[Chem.7]



In the above scheme, each symbol is as defined for Compound [I] above.

[0087] Compound [Ib] may be manufactured by the reaction indicated by the above synthetic scheme. Specifically, compound [Ib] may be manufactured by reacting compound [VII] with compound [VIII] in an inert solvent in the presence of a base.

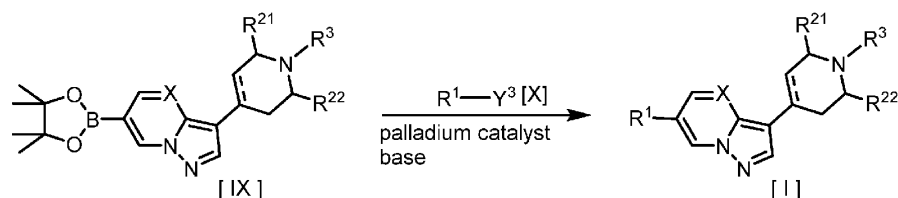
Any condensation agents that are described above may be used in this reaction, and the agents preferably used herein includes agents (e.g. HATU, WSC or a hydrochloride salt).

Any bases that are described above may be used in this reaction, and the base preferably used herein includes as an organic base (e.g. trimethylamine, triethylamine, and N,N-diisopropylethylamine (DIPEA)).

Any solvents that are described above may be used in this reaction, and the solvent preferably used herein includes as halogenated hydrocarbons (e.g. chloroform, and dichloromethane), ethers (e.g. dioxane and tetrahydrofuran), amides (e.g. N,N-dimethylformamide) and nitriles (e.g. acetonitrile).

[0088] General synthesis 6

[Chem.8]



In the above scheme, Y^3 is a leaving group such as halogen (e.g. chlorine and bromine) and alkylsulfonyloxy groups (e.g. trifluoromethylsulfonyloxy), and the other symbols are as defined for Compound [I] above.

[0089] Compound [I] may be manufactured by the reaction indicated by the above synthetic scheme. Specifically, compound [I] may be manufactured by Suzuki coupling reaction of a boronic acid ester compound [IX] with compound [X] having a leaving group in an inert solvent in the presence of a base and a palladium catalyst.

Instead of compound [IX], a compound where the boronic acid ester moiety of compound [IX] may be replaced with boronic acid may be used herein.

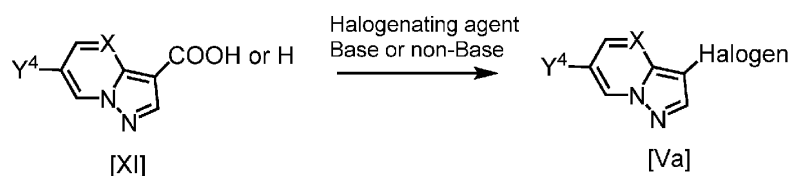
Any bases that are described above may be used in this reaction, and the base preferably used herein includes alkali metal carbonates (e.g. sodium carbonate, potassium carbonate and cesium carbonate) and alkali metal phosphates (e.g. sodium phosphate and potassium phosphate).

Any palladium catalysts that are described above may be used in this reaction, and the palladium catalyst preferably used herein includes $PdCl_2(dppf) \cdot DCM$, XPhos Pd G3, palladium (II) acetate, $Pd_2(dba)_3$ and $Pd(PPh_3)_4$.

Any solvents that are described above may be used in this reaction, and the solvent preferably used herein includes ethers (e.g. dimethoxyethane, 1,4-dioxane and tetrahydrofuran).

[0090] General synthesis 7

[Chem.9]



In the above scheme, Y⁴ is a leaving group such as halogen (e.g. chlorine and bromine) and alkylsulfonyloxy groups (e.g. trifluoromethylsulfonyloxy) or a protecting group of hydroxy such as alkyl groups (e.g. methyl) and aralkyl groups (e.g. benzyl), and X is as defined for Compound [I] above.

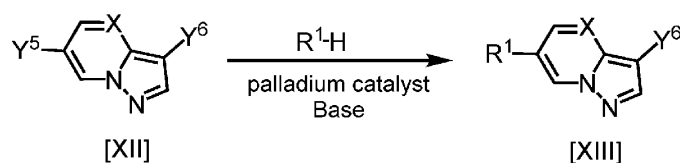
[0091] Intermediate [Va] may be manufactured by the reaction indicated by the above synthetic scheme. Specifically, intermediate [Va] may be manufactured by reacting compound [XI] with a halogenating agent in an inert solvent in the presence or absence of a base.

Any known halogenating agents may be used in this reaction, and the halogenating agent preferably used herein includes N-chlorosuccinimide, N-bromosuccinimide and N-iodosuccinimide.

Any bases that are described above may be used in this reaction, and the base preferably used herein includes alkali metal carbonates (e.g. sodium carbonate, potassium carbonate and cesium carbonate).

Any solvents that are described above may be used in this reaction, and the solvent preferably used herein includes amides (e.g. N,N-dimethylformamide) and nitriles (e.g. acetonitrile).

[0092] General synthesis 8
[Chem.10]



In the above scheme, Y⁵ and Y⁶ are a leaving group such as halogen (e.g. chlorine and bromine) and alkylsulfonyloxy groups (e.g. trifluoromethylsulfonyloxy), and the other symbols are as defined for Compound [I] above.

[0093] Intermediate [XIII] may be manufactured by the reaction indicated by the above synthetic scheme. Specifically, intermediate [XIII] may be manufactured by reacting compound [XII] with R¹-H in an inert solvent in the presence of a base.

Any bases that are described above may be used in this reaction, and the base preferably used herein includes metal alkoxides (e.g. sodium tert-butoxide, and potassium tert-butoxide) and alkali metal carbonates (e.g., sodium carbonate, potassium carbonate, and cesium carbonate).

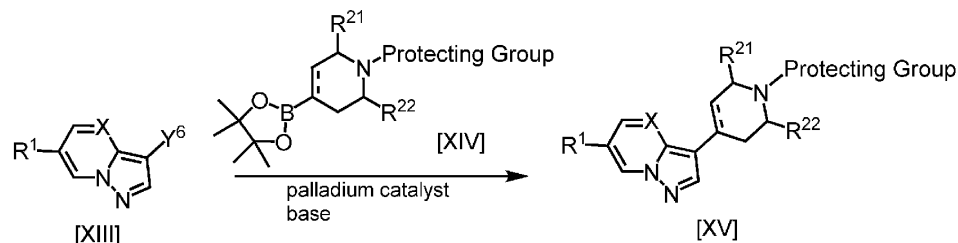
Any palladium catalysts that are described above may be used in this reaction, and the palladium catalyst preferably used herein includes palladium (II) acetate and Pd₂(dba)₃.

Any solvents that are described above may be used in this reaction, and the solvent

preferably used herein includes aromatic hydrocarbons such as benzene and toluene, ethers (e.g. dioxane and tetrahydrofuran) and alcohols (e.g. tert-butanol).

[0094] General synthesis 9

[Chem.11]



In the above scheme, the protecting group includes alkyl (alkenyl) carbonyl groups, arylcarbonyl groups and alkoxycarbonyl groups, and each symbol is as defined above.

[0095] Intermediate [XV] may be manufactured by the reaction indicated by the above synthetic scheme. Specifically, intermediate [XV] may be manufactured by Suzuki coupling reaction of compound [XIII] having a leaving group Y^6 with a boronic acid ester compound [XIV] in an inert solvent in the presence of a base and a palladium catalyst.

Instead of compound [XIV], a compound where the boronic acid ester moiety of compound [XIV] may be replaced with boronic acid may be used herein.

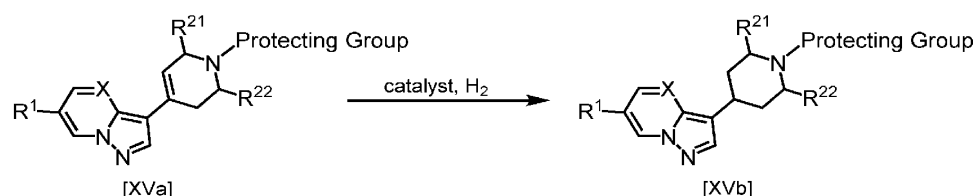
Any bases that are described above may be used in this reaction, and the base preferably used herein includes alkali metal carbonates (e.g. sodium carbonate, potassium carbonate and cesium carbonate) and alkali metal phosphates (e.g. sodium phosphate and potassium phosphate).

Any palladium catalysts that are described above may be used in this reaction, and the palladium catalyst preferably used herein includes $PdCl_2(dppf) \cdot DCM$, XPhos Pd G3, palladium (II) acetate, $Pd_2(dba)_3$ and $Pd(PPh_3)_4$.

Any solvents that are described above may be used in this reaction, and the solvent preferably used herein includes ethers (e.g. dimethoxyethane, 1,4-dioxane and tetrahydrofuran) with or without water.

[0096] General synthesis 10

[Chem.12]



In the above scheme, the protecting group and each symbol are as defined above.

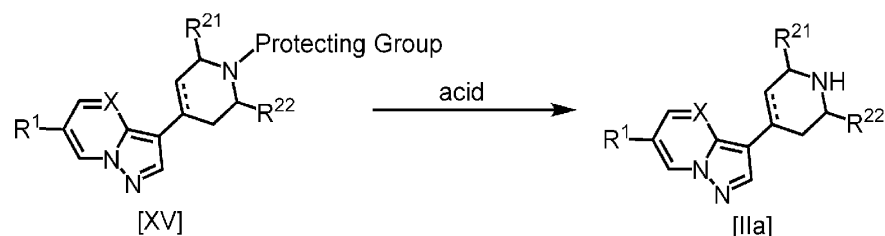
[0097] Intermediate [XVb] may be manufactured by the reaction indicated by the above synthetic scheme. Specifically, intermediate [XVb] may be manufactured by addition of hydrogen to compound [XVa] in an inert solvent in presence of a catalyst.

Any catalysts that are described above may be used in this reaction, and the catalyst preferably used herein includes palladium on carbon (Pd/C), platinum on carbon (Pt/C), platinum oxide (PtO₂).

Any solvents that are described above may be used in this reaction, and the solvent preferably used herein includes ethers (e.g. dioxane and tetrahydrofuran), alcohols (e.g. methanol, ethanol and 2-propanol) and esters (e.g. ethyl acetate).

[0098] General synthesis 11

[Chem.13]



In the above scheme, the protecting group includes alkyl (alkenyl) carbonyl groups, arylcarbonyl groups and alkoxycarbonyl groups and each symbol are as defined above.

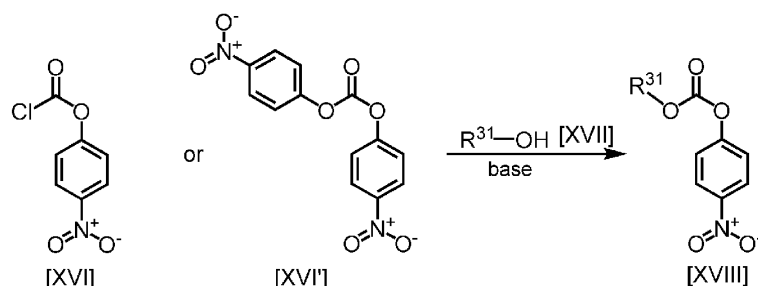
[0099] Intermediate [IIa] may be manufactured by the reaction indicated by the above synthetic scheme. Specifically, intermediate [IIa] may be manufactured by deprotection of the compound [XV] in an inert solvent in presence of an acid.

Any acids that are described above may be used in this reaction, and the acid preferably used herein includes inorganic acids (e.g. hydrochloric acid, sulfuric acid and hydrobromic acid) and organic acids (acetic acid, trifluoroacetic acid and p-toluenesulfonic acid).

Any solvents that are described above may be used in this reaction, and the solvent preferably used herein includes as halogenated hydrocarbons (e.g. chloroform and dichloromethane), ethers (e.g. dioxane and tetrahydrofuran), and alcohols (e.g. methanol, ethanol and 2-propanol).

[0100] General synthesis 12

[Chem.14]



In the above scheme, R³¹ is as defined for Compound [I] above.

[0101] Intermediate [XVIII] may be manufactured according to any of the reactions indicated by the above synthetic scheme. For example, intermediate [XVIII] may be manufactured by reacting compound [XVI] or [XVI'] with compound [XVII] in an inert solvent in the presence of an amine.

Any bases that are listed above as the organic base may be used in this reaction, and the amine preferably used herein includes as an organic base (e.g. trimethylamine, and N,N-diisopropylethylamine (DIPEA)).

Any solvents that are described above may be used in this reaction, and the solvent preferably used herein includes halohydrocarbons (e.g. chloroform, and dichloromethane), ethers (e.g. dioxane and tetrahydrofuran), and nitriles (e.g. acetonitrile).

[0102] In each of the reactions in the above synthetic schemes, the reaction product may be used in the next reaction either as is in the form dissolved in the reaction solution or as a crude product, but it may also be isolated from the reaction mixture by ordinary methods and easily purified by ordinary separation techniques. Examples of ordinary separation techniques include recrystallization, distillation, and chromatography.

[0103] Any starting compounds, intermediate compounds, and product compounds in each of the above steps and Compound [I] include geometric isomers, stereoisomers, optical isomers, and tautomers thereof. Respective isomers may be separated by ordinary optical resolution methods. They may also be manufactured from raw material compounds having suitable optical activity.

[0104] Compound [I] may be manufactured according to any of the above synthetic schemes, or analogous methods thereof.

[0105] Unless otherwise specified, any starting compounds used in the manufacture of Compound [I] are commercially available, or may be produced by known methods or analogous methods thereof.

[0106] Any starting compounds and product compounds in each step above may be used in the form of appropriate salts thereof. Examples of such salts include salts similar to

those listed for salts of Compound [I] below.

- [0107] When any compounds obtained in each step or commercially available compounds used herein are in the free form, they may be converted to corresponding salts by known methods. When any compounds obtained in each step or commercially available compounds used herein are in the salt form, they may be converted to corresponding free forms or into other salts by known methods.
- [0108] Compound [I] may also exist as any pharmaceutically acceptable salts thereof, and in some embodiments, Compound [I] may form an acid addition salt or a salt with a base depending on substituent(s) that are present in Compound [I]. Examples of the "acid" herein include inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, and phosphoric acid; and organic acids such as methanesulfonic acid, p-toluenesulfonic acid, acetic acid, trifluoroacetic acid, citric acid, tartaric acid, maleic acid, fumaric acid, malic acid, lactic acid, and the like. Examples of the "base" herein include inorganic bases such as sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, and potassium bicarbonate; organic bases such as methylamine, diethylamine, trimethylamine, triethylamine, ethanolamine, diethanolamine, triethanolamine, ethylenediamine, tris(hydroxymethyl)methylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, guanidine, pyridine, picoline, and choline; and ammonium salts, and the like. Compound [I] may also form a salt with an amino acid such as lysine, arginine, aspartic acid, glutamic acid, and the like.
- [0109] The present invention also encompasses various hydrates, solvates, and crystal polymorphs of Compound [I] and salts thereof.
- [0110] Compound [I] also includes compounds in which one or more isotope atoms have been substituted for any one or more atoms in any proportions. Examples of isotope atoms include deuterium (^2H or D), tritium (^3H), ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{32}P , ^{35}S , ^{36}Cl , ^{37}Cl , ^{18}F , ^{123}I , ^{125}I , and the like.
- [0111] One embodiment of the present invention includes pharmaceutically acceptable prodrugs of Compound [I]. Compound [I] may be modified on any group(s) including any reactive functional groups of Compound [I] such as -OH, -COOH, amino, and the like, so as to provide prodrugs of Compound [I]. These functional groups may be modified with any group(s) selected appropriately from the protecting groups of hydroxy, carboxy, and amino.
- [0112] Compound [I], or a salt thereof, may be in the form of a pharmaceutically acceptable co-crystal. The co-crystal herein means a crystalline substance composed of two or more independent substances each having different physical properties at room temperature, such as structures, melting points, heat of fusion, and the like. Co-crystals and co-crystal salts may be manufactured appropriately by well-known co-crystallization

methods.

[0113] Compound [I], or a salt thereof, may show CSF1R inhibitory activity in mammals, which leads to reduction of macrophage, microglia, and osteoclast. Compound [I], or a salt thereof, may preferably show highly selective CSF1R inhibitory activity compared to at least any one of other kinases adjacent to CSF1R such as FLT3, cKit, PDGFR including PDGFR α and PDGFR β , and Trk including TrkC, so as to reduce any risks of undesired actions or side effects, including those caused by unexpected inhibition of tyrosine kinases in addition to CSF1R, upon administration of Compound [I], or a salt thereof. In certain embodiments, Compound [I], or a salt thereof, may prevent or reduce activation or proliferation of microglia (i.e., microgliosis) by inhibiting CSF1R particularly expressed in microglia, so that central immunomodulatory function can be reinforced. Compound [I], or a salt thereof, may be beneficial to treat cancers, autoimmune diseases such as rheumatoid arthritis, muscular dystrophy, and asthma. Compound [I], or a salt thereof, may also be beneficial to treat neurological diseases such as Alzheimer's disease (AD), tauopathies, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), HIV-associated neurocognitive disorders (HAND), prion disease, traumatic brain injury (TBI), Parkinson's disease, pain, spinal cord injury, Crohn's disease, radiation-induced lung fibrosis, glaucoma, infections (such as viral, bacterial, and parasitic), cardiovascular diseases such as inflammation post myocardial infarction, and bone diseases.

[0114] Compound [I], or a salt thereof, may also be effective in the treatment, prevention, and/or diagnosis of any two or more diseases described above.

Moreover, Compound [I], or a salt thereof, may be useful as active ingredients in pharmaceuticals, and for example may show few side effects, desirable tolerability, desirable stability (storage stability, metabolic stability, etc.), and the like. Compound [I], or a salt thereof, may also be useful for preventative and/or therapeutic agents for various diseases described herein by inhibiting CSF1R.

In one embodiment, Compound [I], or a salt thereof, may be useful as a Positron Emission Topography (PET) tracer, preferably a PET imaging agent, that may be useful for in vitro, exo vivo, in vivo, or clinical trial tests and diagnostic imaging in humans and/or non-humans. Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O , and ^{13}N , can be useful in PET studies for examining target occupancy. For example, compounds labeled with ^{11}C or ^{18}F may be used for a PET tracer.

[0115] In one embodiment, a medical preparation (herein also referred to as a "pharmaceutical composition") comprising Compound [I] or a salt thereof as an active ingredient is provided.

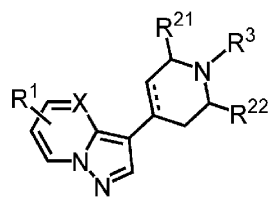
[0116] A medical preparation herein may be selected from various forms depending on therapeutic objectives, and examples of the medical preparation include tablets, pills,

powders, liquids, suspensions, emulsions, granules, capsules, suppositories, injections (liquids, suspensions, etc.), and the like. Tablets include coated tablets such as sugar-coated tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, double tablets, and multilayered tablets.

- [0117] Compound [I], or a salt thereof, may be combined with a pharmaceutically acceptable carrier to be formulated into any forms of a medical preparation. Examples of the carrier include commonly used substances for a component of a medical preparation, including excipients such as lactose; binders such as polyvinylpyrrolidone; disintegrants such as starch; absorption aids such as sodium lauryl sulfate; humectants such as glycerin and starch; adsorbents such as colloidal silicic acid; and lubricants such as magnesium stearate and polyethylene glycol; diluents; fillers; bulking agents; surfactants; and the like.
- [0118] Pharmaceutically acceptable carriers to be used in formulating into a tablet specifically include excipients such as lactose; binders such as polyvinylpyrrolidone; disintegrants such as starch; absorption aids such as sodium lauryl sulfate; humectants such as glycerin and starch; adsorbents such as colloidal silicic acid; and lubricants such as magnesium stearate and polyethylene glycol.
- [0119] Pharmaceutically acceptable carriers to be used in formulating into a pill specifically include excipients such as glucose; binders such as gum arabic powder; and disintegrants such as laminaran.
- [0120] Pharmaceutically acceptable diluents to be used in formulating into a liquid, emulsion, or suspension specifically include water. Any ordinary solubilizing agents and/or buffers as well as colorants, preservatives, aromatics, flavorings, and sweeteners may also be comprised in the preparation, and other drugs may also be comprised as necessary.
- [0121] Pharmaceutically acceptable carriers to be used in formulating into a suppository specifically include cocoa butter and the like.
- [0122] An injection may be formulated into the form of a liquid, emulsion, or suspension. In one embodiment, the injection is preferably sterilized, and is also preferably isotonic with blood. The isotonic injection may comprise a sufficient amount of sodium chloride and soothing agents, and may also optionally comprise other drugs.
- [0123] The amount (herein also referred to as "effective amount") of Compound [I], or a salt thereof, comprised in a medical preparation may be, but is not limited thereto, any amounts conventionally used in the art, and preferably includes any amounts of 1% to 70% of the medical preparation.
- [0124] Any administration routes of a medical preparation may be chosen depending on dosage forms, the age and sex of a patient to be administered, disease status, and other conditions. For example, a medical preparation may be administered orally if it is in

the form of a tablet, pill, liquid, suspension, emulsion, granule, or capsule. A medical preparation may be administered intravenously either alone or in a mixture with an ordinary replacement fluid such as glucose and amino acids if it is in the form of an injection. A medical preparation may be administered intramuscularly, intradermally, subcutaneously, or intraperitoneally as necessary. A medical preparation may be administered rectally if it is in the form of a suppository.

- [0125] The dose of Compound [I], or a salt thereof, to be administered may be any doses selected depending on administration routes, the age and sex of a patient to be administered, the severity of diseases, and other conditions, and includes 0.01 to 100 mg, preferably 0.1 to 50 mg, per 1 kg of body weight per day. The dose may be administered once or separately in several times.
- [0126] Compound [I], or a salt thereof, may be used in combination with at least one therapeutic or preventive drug or standard-of-care agent, which may be referred to as a combined drug herein, useful for one of the above-mentioned diseases. When Compound [I], or a salt thereof, is used in combination with a combined drug, Compound [I], or a salt thereof, and the drug may be administered simultaneously or at the same time, separately or sequentially at about the same time, or separately or sequentially at different times with a suitable interval in between. Compound [I], or a salt thereof, and the combined drug may be formulated into separate preparations or mixed and formulated into a single preparation.
- [0127] Disclosures of all literature cited in the present description are incorporated by reference in the present description in their entireties.
- [0128] The present invention is further illustrated by reference to the following items:
Item 1-1. A compound represented by Formula [I], or a salt thereof:
[Chem.15]



[I]

wherein

R¹ is hydrogen, halogen, -CN, -L¹¹-R¹¹ optionally substituted with one or more R¹², or -R¹¹ optionally substituted with one or more R¹²;

L¹¹ is -C₁₋₃ alkylene-, -C₁₋₃ alkylene-C(=O)-, -O-, -O-C₁₋₃ alkylene-, -O-C₁₋₃ alkylene-O-, -OCH₂C(=O)O-, -C(=O)-, -C(=O)NH-, or -NH-C(=O)-;

R¹¹ is

- a) C₁₋₆ alkyl,
- b) C₁₋₆ haloalkyl,
- c) C₃₋₈ cycloalkyl, or
- d) a saturated or unsaturated 4- to 10-membered monocyclic, bicyclic, or spiro heterocyclyl;

R¹² is each independently halogen, -OH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl-O-C₁₋₆ alkyl, C₃₋₈ cycloalkyl, a saturated or unsaturated 4- to 10-membered monocyclic, bicyclic, or spiro heterocyclyl optionally substituted with one or more C₁₋₆ alkyl;

R²¹ and R²² are hydrogen, or R²¹ and R²² together with the adjacent heterocyclic form a bridged bicyclic ring;

R³ is -L³¹-R³¹ optionally substituted with one or more R³², or R³¹ optionally substituted with one or more R³²;

L³¹ is -C(=O)-, -C(=O)O-, -C(=O)O-C₁₋₃ alkylene-, -C(=O)-C₁₋₃ alkylene-O-, -C(=O)-C₁₋₃ alkylene-O-C₁₋₃ alkylene-, or -C(=O)NH-C₁₋₃ alkylene-;

R³¹ is

- a) C₁₋₆ alkyl,
- b) C₁₋₆ haloalkyl,
- c) C₃₋₈ cycloalkyl,
- d) phenyl, or
- e) a saturated or unsaturated 4- to 10-membered monocyclic, bicyclic, or spiro heterocyclyl;

R³² is each independently halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₃₋₈ cycloalkyl;

X is CR¹ or N; and a bond:

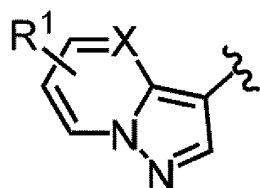
[Chem.16]

is single or double bond;

provided that when R¹ is not hydrogen, then only one R¹ other than hydrogen is present.

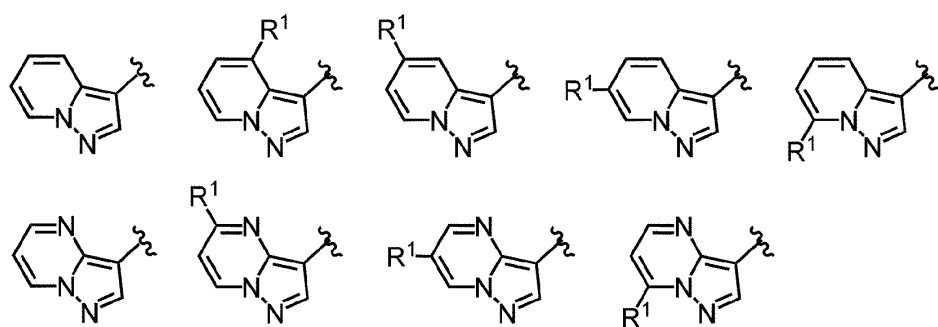
[0129] Item 1-2. The compound according to Item 1-1, or a salt thereof, wherein a moiety represented by the formula:

[Chem.17]



is any one of the following structures:

[Chem.18]



provided that R¹ is halogen, -CN, -L¹¹-R¹¹ optionally substituted with one or more R¹², or -R¹¹ optionally substituted with one or more R¹².

[0130] Item 1-3. The compound according to Item 1-1 or 1-2, or a salt thereof, wherein R³ is not -C(=O)O-tert-butyl.

[0131] Item 1-4. The compound according to any one of Items 1-1 to 1-3, or a salt thereof, wherein R¹¹ is

- a) C₁₋₆ alkyl,
- b) C₁₋₆ haloalkyl,
- c) C₃₋₈ cycloalkyl,
- d1) a saturated or unsaturated 4- to 6-membered monocyclic heterocyclyl containing 1 to 2 nitrogen atoms as ring-constituting heteroatom,
- d2) a saturated 4- to 6-membered monocyclic heterocyclyl containing 1 oxygen atom as ring-constituting heteroatom,
- d3) a saturated or unsaturated 5- to 6-membered monocyclic heterocyclyl containing 1 to 2 nitrogen atoms and 1 oxygen atom as ring-constituting heteroatom,
- d4) an unsaturated 5-membered monocyclic heterocyclyl containing 1 to 2 nitrogen atoms and 1 sulfur atom as ring-constituting heteroatom,

- d5) a saturated or unsaturated 7- to 9-membered bicyclic heterocyclyl containing 2 to 3 nitrogen atoms as ring-constituting heteroatom,
- d6) a saturated or unsaturated 7- to 9-membered bicyclic heterocyclyl containing 1 to 2 nitrogen atoms and 1 oxygen atom as ring-constituting heteroatom,
- d7) a saturated or unsaturated 9-membered bicyclic heterocyclyl containing 1 nitrogen atom, 1 oxygen atom and 1 sulfur atom as ring-constituting heteroatom,
- d8) a saturated or unsaturated 6- to 10-membered bicyclic heterocyclyl containing 1 oxygen atom as ring-constituting heteroatom,
- d9) a saturated 7-membered spiro heterocyclyl containing 1 to 2 nitrogen atoms as ring-constituting heteroatom, or
- d10) a saturated 7- to 8-membered spiro heterocyclyl containing 1 nitrogen atom and 1 oxygen atom as ring-constituting heteroatom.

[0132] Item 1-5. The compound according to any one of Items 1-1 to 1-3, or a salt thereof, wherein R¹¹ is:

- a) C₁₋₆ alkyl,
- b) C₁₋₆ haloalkyl,
- c) C₃₋₈ cycloalkyl, or
- d) a saturated 4- to 10-membered monocyclic, bicyclic, or spiro heterocyclyl.

[0133] Item 1-6. The compound according to any one of Items 1-1 to 1-3, or a salt thereof, wherein R¹¹ is:

- a) C₁₋₆ alkyl,
- b) C₁₋₆ haloalkyl, or
- c) C₃₋₈ cycloalkyl.

[0134] Item 1-7. The compound according to any one of Items 1-1 to 1-6, or a salt thereof, wherein R¹² is each independently halogen, -OH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl-O-C₁₋₆ alkyl, C₃₋₈ cycloalkyl, a saturated 4- to 6-membered monocyclic heterocyclyl containing 1 oxygen atom as ring-constituting heteroatom, or a saturated 6- to 10-membered spiro heterocyclyl containing 2 nitrogen atoms as ring-constituting heteroatom optionally substituted with C₁₋₆ alkyl.

[0135] Item 1-8. The compound according to any one of Items 1-1 to 1-7, or a salt thereof, wherein

L¹¹ is methylene, ethylene, methylene-C(=O)-, -O-, -O-methylene, -O-ethylene, -O-ethylene-O-, -OCH₂C(=O)O-, -C(=O)-, -C(=O)NH-, or -NH-C(=O)-,

R¹¹ is methyl, methyl-d₃, ethyl, propyl, isopropyl, isobutyl, difluoromethyl, trifluoromethyl, difluoroethyl, difluoropropyl, trifluoropropyl, cyclopropyl, cyclobutyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidiny, piperidiny, morpholino, pyrazolyl, thiazolyl, thiadiazolyl, tetrahydroimidazo[1,2-a]pyridiny, dihydroimidazo[2,1-c][1,4]oxaziny, dihydropyrazolo[5,1-c][1,4]oxaziny, dihy-

dropyrano[4,3-d]thiazolyl, hexahydropyrrolo[3,4-c]pyrrolyl, tetrahydrofuro[3,4-c]pyrrolyl, 2-oxabicyclo[2.1.1]hexanyl, 2-azaspiro[3.3]heptanyl, or 2-oxa-6-azaspiro[3.3]heptanyl, and

R¹² is each independently fluoro, methyl, methyl-d₃, difluoromethyl, trifluoromethyl, methoxyethyl, cyclopropyl, -OH, oxetanyl, or 2,6-diazaspiro[3.3]heptanyl optionally substituted with methyl.

- [0136] Item 1-9. The compound according to any one of Items 1-1 to 1-8, or a salt thereof, wherein R¹ is hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ alkyl-O- optionally substituted with one or more deuteriums, OH or C₁₋₆ alkyl-O-, C₁₋₆ alkyl-OC(=O)CH₂O-, C₁₋₆ haloalkyl-O-, C₁₋₆ haloalkyl-O-C₁₋₆ alkylene-, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-O-, C₃₋₈ cycloalkyl-C₁₋₆ alkylene-O- optionally substituted with halogen, C₁₋₆ alkyl or C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl-C(=O)-, C₃₋₈ cycloalkyl-NH-C(=O)-, azetidiny optionally substituted with halogen, azetidiny-C₁₋₆ alkylene-O- optionally substituted with oxetanyl, azetidiny-O- optionally substituted with oxetanyl, piperidiny optionally substituted with oxetanyl, morpholino, morpholino-C₁₋₆ alkylene, morpholino-C₁₋₆ alkylene-O-, morpholino-C(=O)-C₁₋₆ alkylene, pyrazolyl optionally substituted with C₁₋₆ alkyl, C₁₋₆ alkyl substituted with one or more deuteriums, C₁₋₆ alkyl-O-C₁₋₆ alkylene, thiazolyl optionally substituted with C₁₋₆ haloalkyl or diazaspiroheptyl optionally substituted with C₁₋₆ alkyl, thiadiazolyl optionally substituted with C₁₋₆ alkyl, oxetanyl-C₁₋₆ alkylene-O- optionally substituted with halogen or C₁₋₆ alkyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydroimidazo[1,2-a]pyrazinyl, dihydroimidazo[2,1-c][1,4]oxazinyl, dihydropyrano[4,3-d]thiazolyl, dihydropyrazolo[5,1-c][1,4]oxazinyl, hexahydropyrrolo[3,4-c]pyrrolyl, tetrahydrofuro[3,4-c]pyrrolyl, 2-oxabicyclo[2.1.1]hexanyl-C₁₋₆ alkylene-O-, 2-azaspiro[3.3]heptanyl optionally substituted with halogen, 2-oxa-6-azaspiro[3.3]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl-C(=O)-, or 2-azaspiro[3.3]heptanyl-C₁₋₆ alkylene-O- optionally substituted with halogen.

- [0137] Item 1-10. The compound according to any one of Items 1-1 to 1-9, or a salt thereof, wherein R¹ is hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ alkyl-O- optionally substituted with one or more deuteriums, OH or C₁₋₆ alkyl-O-, C₁₋₆ alkyl-OC(=O)CH₂O-, C₁₋₆ haloalkyl-O-, C₁₋₆ haloalkyl-O-C₁₋₆ alkylene-, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-O-, C₃₋₈ cycloalkyl-C₁₋₆ alkylene-O- optionally substituted with halogen, C₁₋₆ alkyl or C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl-C(=O)-, C₃₋₈ cycloalkyl-NH-C(=O)-, azetidiny optionally substituted with halogen, azetidiny-C₁₋₆ alkylene-O- optionally substituted with oxetanyl, azetidiny-O- optionally substituted with oxetanyl, morpholino-C₁₋₆ alkylene, morpholino-C₁₋₆ alkylene-O-, morpholino-C(=O)-C₁₋₆ alkylene, C₁₋₆ alkyl substituted with one or more deuteriums, C₁₋₆ alkyl-O-C₁₋₆ alkylene, oxetanyl-C₁₋₆ alkylene-O- optionally substituted with halogen or C₁₋₆ alkyl, 2-oxabicyclo[2.1.1]hexanyl-C₁₋₆

alkylene-O-, 2-oxa-6-azaspiro[3.3]heptanyl-C(=O)-, or 2-azaspiro[3.3]heptanyl-C₁₋₆ alkylene-O- optionally substituted with halogen.

[0138] Item 1-11. The compound according to any one of Items 1-1 to 1-10, or a salt thereof, wherein R¹ is hydrogen, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ alkyl-O- optionally substituted with one or more deuteriums, OH or C₁₋₆ alkyl-O-, C₁₋₆ alkyl-OC(=O)CH₂ O-, C₁₋₆ haloalkyl-O-, C₁₋₆ haloalkyl-O-C₁₋₆ alkylene-, C₃₋₈ cycloalkyl-O-, C₃₋₈ cycloalkyl-C₁₋₆ alkylene-O- optionally substituted with halogen, C₁₋₆ alkyl or C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl-C(=O)-, C₃₋₈ cycloalkyl-NH-C(=O)-, azetidynyl optionally substituted with halogen, azetidynyl-C₁₋₆ alkylene-O- optionally substituted with oxetanyl, azetidynyl-O- optionally substituted with oxetanyl, morpholino-C₁₋₆ alkylene, morpholino-C₁₋₆ alkylene-O-, morpholino-C(=O)-C₁₋₆ alkylene, C₁₋₆ alkyl substituted with one or more deuteriums, C₁₋₆ alkyl-O-C₁₋₆ alkylene, oxetanyl-C₁₋₆ alkylene-O- optionally substituted with halogen or C₁₋₆ alkyl, 2-oxabicyclo[2.1.1]hexanyl-C₁₋₆ alkylene-O-, 2-oxa-6-azaspiro[3.3]heptanyl-C(=O)-, or 2-azaspiro[3.3]heptanyl-C₁₋₆ alkylene-O- optionally substituted with halogen.

[0139] Item 1-12. The compound according to any one of Items 1-1 to 1-11, or a salt thereof, wherein R¹ is hydrogen, fluoro, chloro, cyano, isopropyl, methoxy, methoxy-d₃, difluoromethoxy, ethoxy, 2-methoxyethoxy, 2-methoxy-2-oxoethoxy, 2,2-difluoroethoxy, 2-(difluoromethoxy)ethoxy, 2-(trifluoromethoxy)ethoxy, 2-hydroxy-2-methylpropoxy, 2-methoxy-2-methylpropoxy, 2,2-difluoropropoxy, 3,3-difluoropropoxy, 3,3,3-trifluoropropoxy, cyclopropyl, cyclopropoxy, cyclopropylmethoxy, cyclopropanecarbonyl, cyclopropylcarbonyl, (1-fluorocyclopropyl)methoxy, (2,2-difluorocyclopropyl)methoxy, 2-(3,3-difluorocyclobutyl)ethoxy, (2,2-difluoro-1-methylcyclopropyl)methoxy, (1-(difluoromethyl)cyclopropyl)methoxy, (1-(trifluoromethyl)cyclopropyl)methoxy, azetidin-1-yl, 3,3-difluoroazetidin-1-yl, (1-(oxetan-3-yl)azetidin-3-yl)oxy, (1-(oxetan-3-yl)azetidin-3-yl)methoxy, 1-methyl-1H-pyrazol-4-yl, 1-(methyl-d₃)-1H-pyrazol-4-yl, 1-(2-methoxyethyl)-1H-pyrazol-4-yl, 1,3,5-trimethyl-1H-pyrazol-4-yl, 1-cyclopropyl-1H-pyrazol-4-yl, 1-cyclopropyl-3,5-dimethyl-1H-pyrazol-4-yl, 3,5-dimethyl-1-(methyl-d₃)-1H-pyrazol-4-yl, 1-(oxetan-3-yl)piperidin-4-yl, (1-methylpiperidin-4-yl)oxy, (oxetan-3-yl)methoxy, (3-fluorooxetan-3-yl)methoxy, (3-methyloxetan-3-yl)methoxy, morpholino, morpholinomethyl, 2-morpholino-2-oxoethyl, 2-morpholinoethoxy, 2-morpholinoethyl, thiazol-4-yl, thiazol-5-yl, (trifluoromethyl)thiazol-4-yl, 1,2,4-thiadiazol-5-yl, 3-methyl-1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-2-yl, tetrahydro-2H-pyran-4-yl, tetrahydrofuran-3-yl, 7-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-2-yl, 5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl,

6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-3-yl,
5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-2-yl,
6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-yl,
((1s,4s)-2-oxabicyclo[2.1.1]hexan-1-yl)methoxy, tetrahydro-
1H-furo[3,4-c]pyrrol-5(3H)-yl, 2-oxa-6-azaspiro[3.3]heptan-6-yl,
2-oxa-6-azaspiro[3.3]heptane-6-carbonyl, 6,6-difluoro-2-azaspiro[3.3]heptan-2-yl,
2-(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)ethoxy, or
2-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)thiazol-5-yl.

[0140] Item 1-13. The compound according to any one of Items 1-1 to 1-12, or a salt thereof, wherein R¹ is hydrogen, fluoro, chloro, cyano, isopropyl, methoxy, methoxy-d₃, difluoromethoxy, ethoxy, 2-methoxyethoxy, 2-methoxy-2-oxoethoxy, 2,2-difluoroethoxy, 2-(difluoromethoxy)ethoxy, 2-(trifluoromethoxy)ethoxy, 2-hydroxy-2-methylpropoxy, 2-methoxy-2-methylpropoxy, 2,2-difluoropropoxy, 3,3-difluoropropoxy, 3,3,3-trifluoropropoxy, cyclopropyl, cyclopropoxy, cyclopropylmethoxy, cyclopropanecarbonyl, cyclopropylcarbonyl, (1-fluorocyclopropyl)methoxy, (2,2-difluorocyclopropyl)methoxy, 2-(3,3-difluorocyclobutyl)ethoxy, (2,2-difluoro-1-methylcyclopropyl)methoxy, (1-(difluoromethyl)cyclopropyl)methoxy, (1-(trifluoromethyl)cyclopropyl)methoxy, (1-(oxetan-3-yl)azetidin-3-yl)oxy, (1-(oxetan-3-yl)azetidin-3-yl)methoxy, (1-methylpiperidin-4-yl)oxy, (oxetan-3-yl)methoxy, (3-fluorooxetan-3-yl)methoxy, (3-methyloxetan-3-yl)methoxy, morpholinomethyl, 2-morpholino-2-oxoethyl, 2-morpholinoethoxy, 2-morpholinoethyl, ((1s,4s)-2-oxabicyclo[2.1.1]hexan-1-yl)methoxy, 2-oxa-6-azaspiro[3.3]heptane-6-carbonyl, or 2-(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)ethoxy.

[0141] Item 1-14. The compound according to any one of Items 1-1 to 1-13, or a salt thereof, wherein R¹ is hydrogen, fluoro, chloro, cyano, isopropyl, methoxy, methoxy-d₃, difluoromethoxy, ethoxy, 2-methoxyethoxy, 2-methoxy-2-oxoethoxy, 2,2-difluoroethoxy, 2-(difluoromethoxy)ethoxy, 2-(trifluoromethoxy)ethoxy, 2-hydroxy-2-methylpropoxy, 2-methoxy-2-methylpropoxy, 2,2-difluoropropoxy, 3,3-difluoropropoxy, 3,3,3-trifluoropropoxy, cyclopropoxy, cyclopropylmethoxy, cyclopropanecarbonyl, cyclopropylcarbonyl, (1-fluorocyclopropyl)methoxy, (2,2-difluorocyclopropyl)methoxy, 2-(3,3-difluorocyclobutyl)ethoxy, (2,2-difluoro-1-methylcyclopropyl)methoxy, (1-(difluoromethyl)cyclopropyl)methoxy, (1-(trifluoromethyl)cyclopropyl)methoxy, (1-(oxetan-3-yl)azetidin-3-yl)oxy, (1-(oxetan-3-yl)azetidin-3-yl)methoxy, (1-methylpiperidin-4-yl)oxy, (oxetan-3-yl)methoxy, (3-fluorooxetan-3-yl)methoxy, (3-methyloxetan-3-yl)methoxy, morpholinomethyl, 2-morpholino-2-oxoethyl, 2-morpholinoethoxy,

2-morpholinoethyl, ((1s,4s)-2-oxabicyclo[2.1.1]hexan-1-yl)methoxy,
2-oxa-6-azaspiro[3.3]heptane-6-carbonyl, or
2-(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)ethoxy.

- [0142] Item 1-15. The compound according to any one of Items 1-1 to 1-14, or a salt thereof, wherein R¹ is hydrogen, halogen, -CN, or -L¹¹-R¹¹ optionally substituted with one or more R¹².
- [0143] Item 1-16. The compound according to any one of Items 1-1 to 1-15, or a salt thereof, wherein L¹¹ is -O-, -O-ethylene, -O-ethylene-O-, -C(=O)NH-, or -NH-C(=O)-; R¹¹ is methyl, cyclopropyl, difluoroethyl, pyrazolyl, tetrahydrofuranyl, thiazolyl, piperidinyl, tetrahydropyranyl, morpholino, tetrahydrofuropyrrolyl, hexahydropyrrolopyrrolyl, azaspiroheptanyl, or oxaazaspiroheptanyl; and R¹² is each independently fluoro, methyl, methyl-d₃, or cyclopropyl.
- [0144] Item 1-17. The compound according to any one of Items 1-1 to 1-16, or a salt thereof, provided that when R¹ is -R¹¹ optionally substituted with one or more R¹², then R¹¹ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₃₋₈ cycloalkyl.
- [0145] Item 1-18. The compound according to any one of Items 1-1 to 1-17, or a salt thereof, provided that when R¹ is -R¹¹ optionally substituted with one or more R¹², then R¹¹ is C₁₋₆ alkyl or C₁₋₆ haloalkyl.
- [0146] Item 1-19. The compound according to any one of Items 1-1 to 1-18, or a salt thereof, wherein R²¹ and R²² are hydrogen.
- [0147] Item 1-20. The compound according to any one of Items 1-1 to 1-19, or a salt thereof, wherein R³¹ is
- a) C₁₋₆ alkyl,
 - b) C₁₋₆ haloalkyl,
 - c) C₃₋₈ cycloalkyl,
 - d) phenyl,
 - e1) a saturated or unsaturated 4- to 6-membered monocyclic heterocyclyl containing 1 to 2 nitrogen atoms as ring-constituting heteroatom,
 - e2) a saturated 4- to 6-membered monocyclic heterocyclyl containing 1 oxygen atom as ring-constituting heteroatom,
 - e3) a saturated or unsaturated 5- to 6-membered monocyclic heterocyclyl containing 1 to 2 nitrogen atoms and 1 oxygen atom as ring-constituting heteroatom,
 - e4) an unsaturated 5-membered monocyclic heterocyclyl containing 1 to 2 nitrogen atoms and 1 sulfur atom as ring-constituting heteroatom,
 - e5) a saturated or unsaturated 7- to 9-membered bicyclic heterocyclyl containing 1 to 2 nitrogen atoms and 1 oxygen atom as ring-constituting heteroatom, or
 - e6) a saturated 7- to 8-membered spiro heterocyclyl containing 1 nitrogen atom and 1 oxygen atom as ring-constituting heteroatom.

- [0148] Item 1-21. The compound according to any one of Items 1-1 to 1-19, or a salt thereof, wherein R^{31} is:
- a) C_{1-6} alkyl,
 - b) C_{1-6} haloalkyl,
 - c) C_{3-8} cycloalkyl,
 - d) phenyl, or
 - e) a saturated 4- to 10-membered monocyclic, bicyclic, or spiro heterocycl.
- [0149] Item 1-22. The compound according to any one of Items 1-1 to 1-21, or a salt thereof, wherein R^{31} is:
- a) C_{1-6} alkyl,
 - b) C_{1-6} haloalkyl,
 - c) C_{3-8} cycloalkyl, or
 - d) phenyl.
- [0150] Item 1-23. The compound according to any one of Items 1-1 to 1-22, or a salt thereof, wherein R^{31} is:
- a) C_{1-6} alkyl,
 - b) C_{1-6} haloalkyl, or
 - c) C_{3-8} cycloalkyl.
- [0151] Item 1-24. The compound according to any one of Items 1-1 to 1-23, or a salt thereof, wherein
- L^{31} is $-C(=O)-$, $-C(=O)O-$, $-C(=O)O$ -methylene-, $-C(=O)O$ -ethylene-, $-C(=O)$ -ethylene- $O-$, $-C(=O)$ -methylene- O -methylene-, or $-C(=O)NH$ -ethylene-,
- R^{31} is methyl, tert-butyl, cyclopropyl, cyclobutyl, cyclohexyl, phenyl, oxazolyl, thiazolyl, oxadiazolyl, pyrimidinyl, tetrahydrofuranyl, azetidynyl, or 6-oxa-1-azaspiro[3.4]octanyl, and
- R^{32} is each independently fluoro, methyl, ethyl, cyclopropyl, difluoromethyl, or trifluoromethyl.
- [0152] Item 1-25. The compound according to any one of Items 1-1 to 1-24, or a salt thereof, wherein
- L^{31} is $-C(=O)-$, $-C(=O)O-$, or $-C(=O)O$ -methylene-,
- R^{31} is methyl, tert-butyl, cyclopropyl, oxazolyl, thiazolyl, or azetidynyl; preferably, cyclopropyl, oxazolyl, thiazolyl, or azetidynyl,
- R^{32} is each independently fluoro, and
- X is CH or N.
- [0153] Item 1-26. The compound according to any one of Items 1-1 to 1-25, or a salt thereof, wherein R^3 is C_{1-6} haloalkyl- O - $C(=O)-$, C_{3-8} cycloalkyl- O - $C(=O)-$ optionally substituted with halogen or C_{1-6} haloalkyl, C_{3-8} cycloalkyl- C_{1-6} alkylene- O - $C(=O)-$ optionally substituted with C_{1-6} alkyl, phenyl- CH_2OCH_2 - $C(=O)-$ optionally substituted

with C₁₋₆ alkyl, phenoxy-C₁₋₆ alkylene-C(=O)- optionally substituted with C₁₋₆ alkyl, phenyl-C₁₋₃ alkylene-NH-C(=O)-, azetidiny-C(=O)- optionally substituted with halogen or C₁₋₆ haloalkyl, oxazolyl-C₁₋₆ alkylene-O-C(=O)- optionally substituted with C₁₋₆ alkyl, oxadiazolyl optionally substituted with C₁₋₆ alkyl or C₃₋₈ cycloalkyl, thiazolyl-C₁₋₆ alkylene-O-C(=O)- optionally substituted with C₁₋₆ haloalkyl, pyrimidinyl optionally substituted with C₁₋₆ alkyl, tetrahydrofuranyl-C₁₋₆ alkylene-O-C(=O)-, 3-oxa-6-azabicyclo[3.1.1]heptanyl-C(=O)-, or 6-oxa-1-azaspiro[3.4]octanyl-C(=O)-.

[0154] Item 1-27. The compound according to any one of Items 1-1 to 1-26, or a salt thereof, wherein R³ is C₁₋₆ haloalkyl-O-C(=O)-, C₃₋₈ cycloalkyl-O-C(=O)- optionally substituted with halogen or C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl-C₁₋₆ alkylene-O-C(=O)- optionally substituted with C₁₋₆ alkyl, phenyl-CH₂OCH₂-C(=O)- optionally substituted with C₁₋₆ alkyl, phenoxy-C₁₋₆ alkylene-C(=O)- optionally substituted with C₁₋₆ alkyl, phenyl-C₁₋₃ alkylene-NH-C(=O)-, azetidiny-C(=O)- optionally substituted with halogen or C₁₋₆ haloalkyl, oxazolyl-C₁₋₆ alkylene-O-C(=O)- optionally substituted with C₁₋₆ alkyl, thiazolyl-C₁₋₆ alkylene-O-C(=O)- optionally substituted with C₁₋₆ haloalkyl, tetrahydrofuranyl-C₁₋₆ alkylene-O-C(=O)-, 3-oxa-6-azabicyclo[3.1.1]heptanyl-C(=O)-, or 6-oxa-1-azaspiro[3.4]octanyl-C(=O)-.

[0155] Item 1-28. The compound according to any one of Items 1-1 to 1-27, or a salt thereof, wherein R³ is 5-ethylpyrimidin-2-yl, 5-methyl-1,2,4-oxadiazol-3-yl, 3-cyclopropyl-1,2,4-oxadiazol-5-yl, (2-(difluoromethyl)azetidin-1-yl)carbonyl, (3,3-difluoroazetidin-1-yl)carbonyl, (3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)carbonyl, 6-oxa-1-azaspiro[3.4]octan-1-ylcarbonyl, azetidin-1-ylcarbonyl, 2-(p-tolyloxy)ethylcarbonyl, 2-phenoxyethylcarbonyl, ((2-methylbenzyl)oxy)methylcarbonyl, phenylethylcarbonyl, 1,1,1-trifluoro-2-methylpropan-2-yloxy carbonyl, 1-fluoro-2-methylpropan-2-yloxy carbonyl, cyclopropoxycarbonyl, cyclopropylmethoxycarbonyl, (1-methylcyclopropyl)methoxycarbonyl, 3,3-difluorocyclobutoxycarbonyl, (1R,3R)-3-(trifluoromethyl)cyclobutoxycarbonyl, (1S,3S)-3-(trifluoromethyl)cyclobutoxycarbonyl, 4,4-difluorocyclohexyloxy carbonyl, benzyloxy carbonyl, oxazol-4-ylmethoxycarbonyl, 1-(oxazol-4-yl)ethoxycarbonyl, (2-methyloxazol-4-yl)methoxycarbonyl, 2-(thiazol-4-yl)ethoxycarbonyl, thiazol-4-ylmethoxycarbonyl, (2-(trifluoromethyl)thiazol-4-yl)methoxycarbonyl, or (tetrahydrofuran-2-yl)methoxycarbonyl.

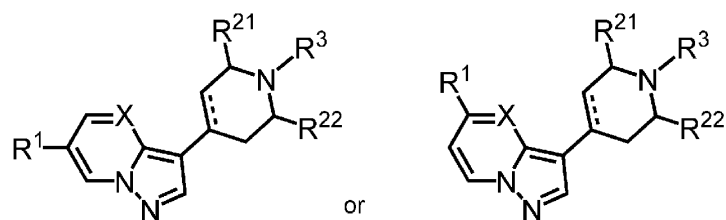
[0156] Item 1-29. The compound according to any one of Items 1-1 to 1-28, or a salt thereof, wherein R³ is (2-(difluoromethyl)azetidin-1-yl)carbonyl, (3,3-difluoroazetidin-1-yl)carbonyl, (3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)carbonyl, 6-oxa-1-azaspiro[3.4]octan-1-ylcarbonyl, azetidin-1-ylcarbonyl,

2-(p-tolyloxy)ethylcarbonyl, 2-phenoxyethylcarbonyl,
 ((2-methylbenzyl)oxy)methylcarbonyl, phenylethylcarbonyl,
 1,1,1-trifluoro-2-methylpropan-2-yloxyethylcarbonyl,
 1-fluoro-2-methylpropan-2-yloxyethylcarbonyl, cyclopropoxycarbonyl, cyclopropyl-
 methoxycarbonyl, (1-methylcyclopropyl)methoxycarbonyl,
 3,3-difluorocyclobutoxycarbonyl, (1R,3R)-3-(trifluoromethyl)cyclobutoxycarbonyl,
 (1S,3S)-3-(trifluoromethyl)cyclobutoxycarbonyl, 4,4-difluorocyclohexyloxyethylcarbonyl,
 benzyloxyethylcarbonyl, oxazol-4-ylmethoxycarbonyl, 1-(oxazol-4-yl)ethoxycarbonyl,
 (2-methyloxazol-4-yl)methoxycarbonyl, 2-(thiazol-4-yl)ethoxycarbonyl, thiazol-
 4-ylmethoxycarbonyl, (2-(trifluoromethyl)thiazol-4-yl)methoxycarbonyl, or
 (tetrahydrofuran-2-yl)methoxycarbonyl.

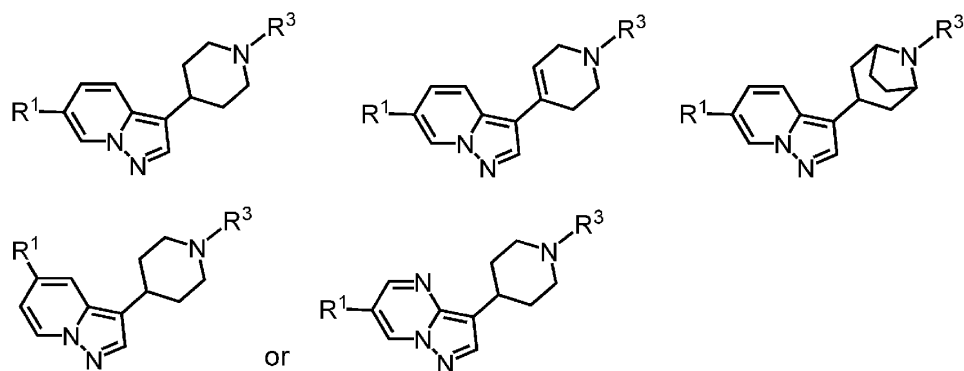
[0157] Item 1-30. The compound according to any one of Items 1-1 to 1-29, or a salt thereof, provided that when R³ is R³¹ optionally substituted with one or more R³², then R³¹ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, or C₃₋₈ cycloalkyl.

[0158] Item 1-31. The compound according to any one of Items 1-1 to 1-30, or a salt thereof, wherein R³ is -L³¹-R³¹ optionally substituted with one or more R³².

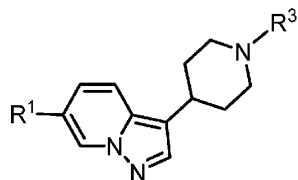
[0159] Item 1-32. The compound according to any one of Items 1-1 to 1-31, or a salt thereof, wherein the compound of Formula [I] is
 [Chem.19]



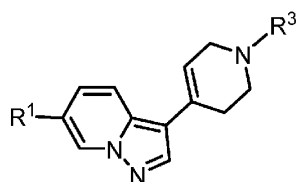
[0160] Item 1-33. The compound according to any one of Items 1-1 to 1-32, or a salt thereof, wherein the compound of Formula [I] is
 [Chem.20]



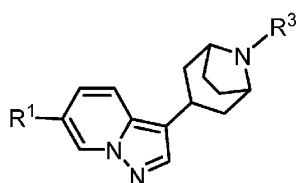
- [0161] Item 1-34. The compound according to any one of Items 1-1 to 1-33, or a salt thereof, wherein the compound of Formula [I] is
[Chem.21]



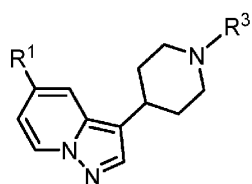
- [0162] Item 1-35. The compound according to any one of Items 1-1 to 1-33, or a salt thereof, wherein the compound of Formula [I] is
[Chem.22]



- [0163] Item 1-36. The compound according to any one of Items 1-1 to 1-33, or a salt thereof, wherein the compound of Formula [I] is
[Chem.23]

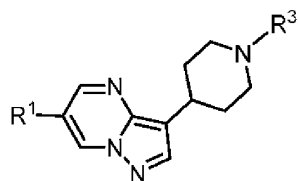


- [0164] Item 1-37. The compound according to any one of Items 1-1 to 1-33, or a salt thereof, wherein the compound of Formula [I] is
[Chem.24]



- [0165] Item 1-38. The compound according to any one of Items 1-1 to 1-33, or a salt thereof, wherein the compound of Formula [I] is

[Chem.25]



[0166] Item 1-39. The compound according to any one of Items 1-1 to 1-32, or a salt thereof, wherein X is CH.

[0167] Item 1-40. The compound according to any one of Items 1-1 to 1-32, or a salt thereof, wherein X is N.

[0168] Item 1-41. The compound according to any one of Items 1-1 to 1-32, or a salt thereof, wherein the bond:

[Chem.26]



is single bond.

[0169] Item 1-42. The compound according to any one of Items 1-1 to 1-32, or a salt thereof, wherein the bond:

[Chem.27]



is double bond.

[0170] Item 1-43. The compound according to any one of Items 1-1 to 1-42, or a salt thereof, wherein R¹ is -L¹¹-R¹¹ optionally substituted with one or more R¹²; L¹¹ is -O- or -O-ethylene-O-; R¹¹ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, or a saturated 4- to 6-membered monocyclic heterocyclyl; and R¹² is halogen, C₁₋₆ alkyl optionally substituted with one or more deuteriums, or C₁₋₆ haloalkyl.

[0171] Item 1-44. The compound according to any one of Items 1-1 to 1-43, or a salt thereof, wherein R¹ is 2-methoxyethoxy, cyclopropoxy, (1-methylpiperidin-4-yl)oxy, 2,2-difluoroethoxy, 1-cyclopropyl-3,5-dimethyl-1H-pyrazol-4-yl, 1-cyclopropyl-1H-pyrazol-4-yl, tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl, 6,6-difluoro-2-azaspiro[3.3]heptan-2-yl, 2-oxa-6-azaspiro[3.3]heptan-6-yl, thiazol-5-yl, or 1-methyl-1H-pyrazol-4-yl.

[0172] Item 1-45. The compound according to any one of Items 1-1 to 1-44, or a salt thereof, wherein R¹ is 2-methoxyethoxy, cyclopropoxy, (1-methylpiperidin-4-yl)oxy, or 2,2-difluoroethoxy.

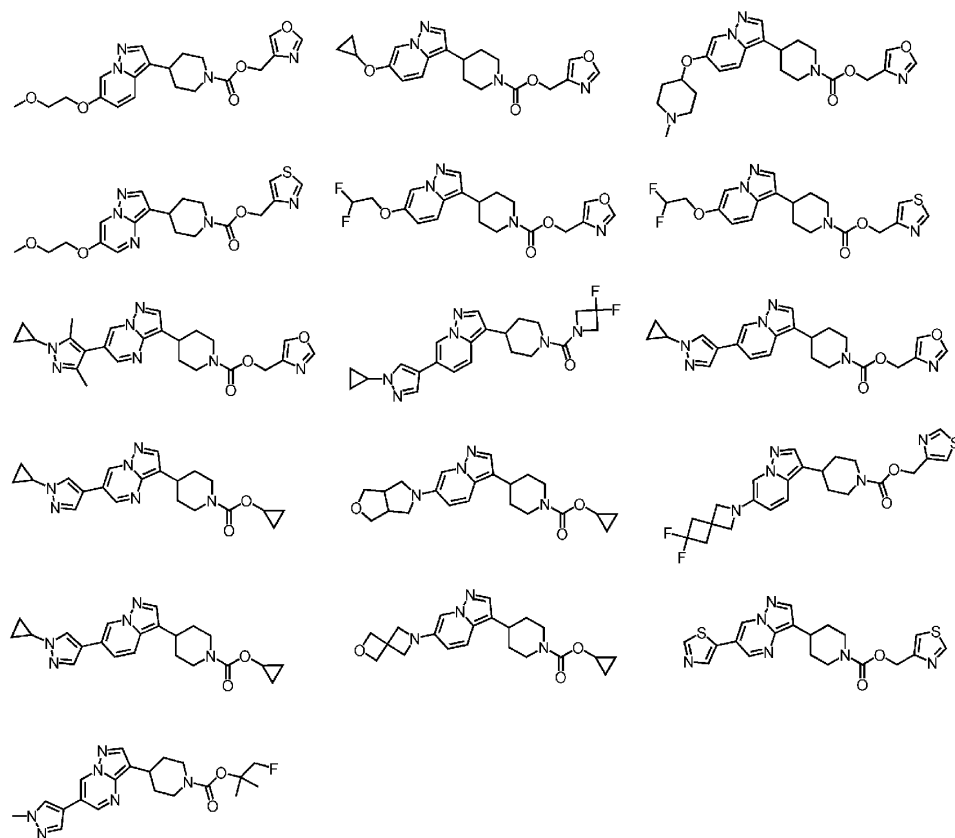
[0173] Item 1-46. The compound according to any one of Items 1-1 to 1-45, or a salt

thereof, wherein R¹ is hydrogen, halogen, -CN, or -L¹¹-R¹¹ optionally substituted with one or more R¹².

[0174] Item 1-47. The compound according to any one of Items 1-1 to 1-46, or a salt thereof, wherein R³ is cyclopropoxycarbonyl, (1-fluoromethyl-2-methylpropan-2-yl)oxycarbonyl, oxazol-4-ylmethoxycarbonyl, thiazol-4-ylmethoxycarbonyl, or 3,3-difluoroazetidin-1-ylcarbonyl.

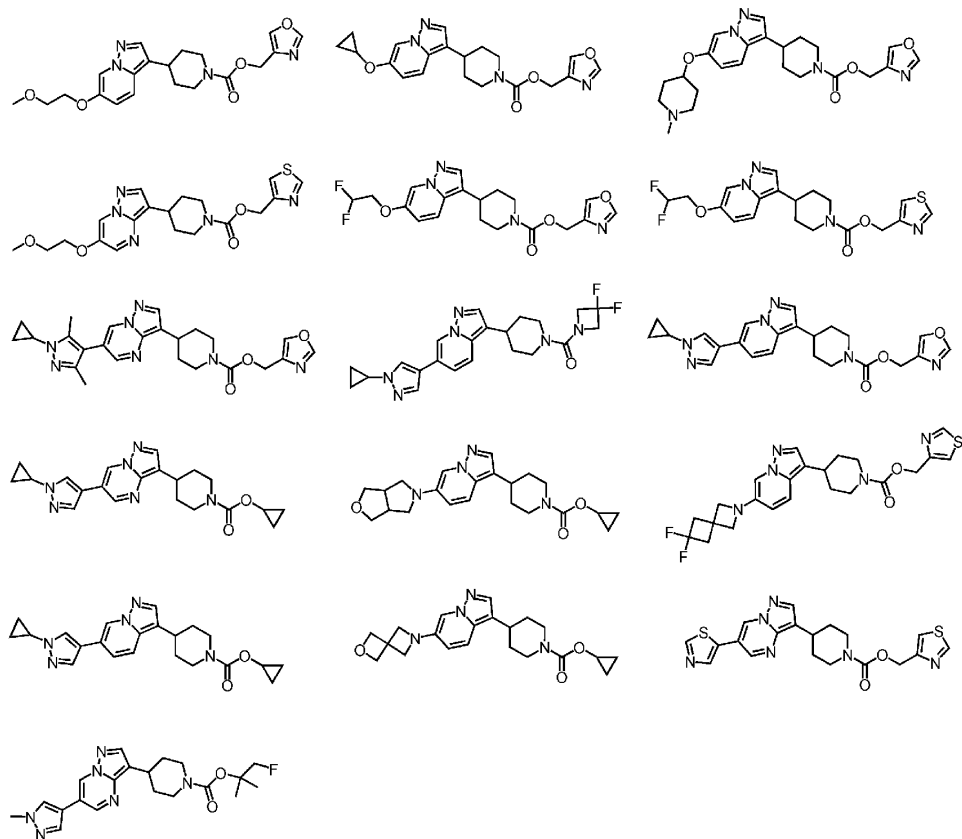
[0175] Item 1-48. The compound according to Item 1-1, or a salt thereof, wherein the compound is selected from the group consisting of the following compounds.

[Chem.28]



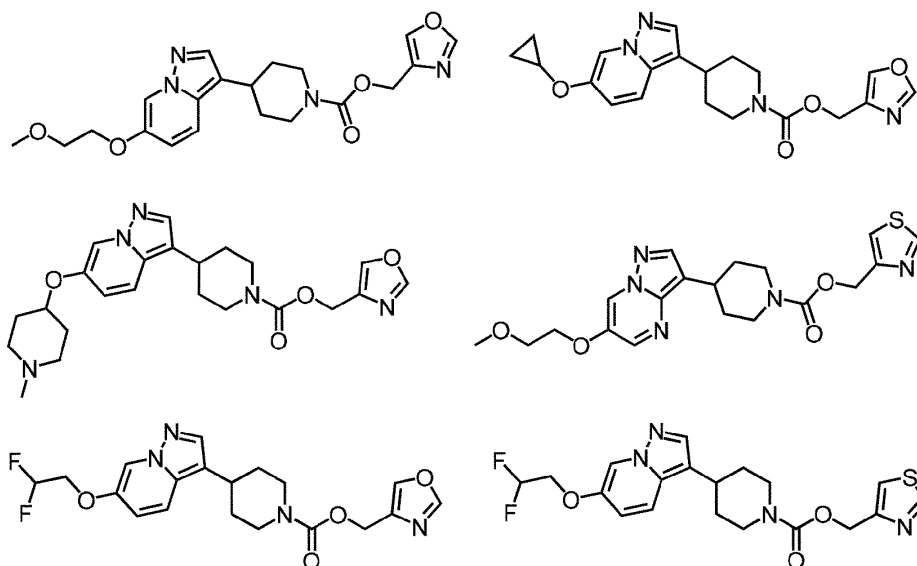
[0176] Item 1-49. The compound according to Item 1-1, wherein the compound is selected from the group consisting of the following compounds.

[Chem.29]



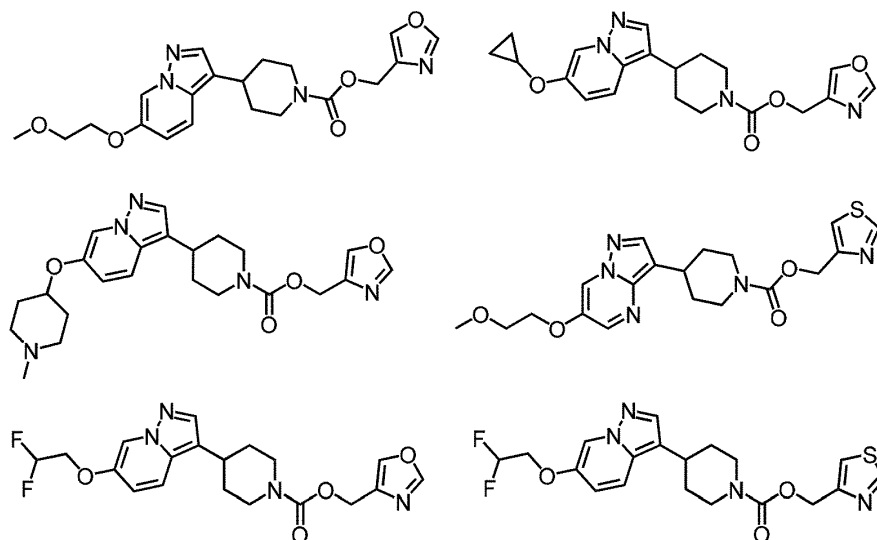
[0177] Item 1-50. The compound according to Item 1-1, or a salt thereof, wherein the compound is selected from the group consisting of the following compounds.

[Chem.30]



[0178] Item 1-51. The compound according to Item 1-1, wherein the compound is selected from the group consisting of the following compounds.

[Chem.31]



[0179] Item 1-52. The compound according to Item 1-1, wherein the compound is selected from the compounds of Examples 1 to 152 as shown in Table 3.

[0180] Item 2. A pharmaceutical composition comprising a compound according to any one

of Items 1-1 to 1-52, or a salt thereof, as an active ingredient and a pharmaceutically acceptable carrier or excipient.

- [0181] Item 3-1. A therapeutic, preventative, and/or diagnostic agent for a disease caused by CSF1R comprising a compound according to any one of Items 1-1 to 1-52, or a salt thereof, as an active ingredient.
- [0182] Item 3-2. The agent according to Item 3-1, wherein the disease caused by CSF1R is selected from Alzheimer's disease (AD), tauopathies, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), HIV-associated neurocognitive disorders (HAND), prion disease, trauma brain injury (TBI), Parkinson's disease, pain, spinal cord injury, Crohn's disease, radiation-induced lung fibrosis, glaucoma, infections (such as viral, bacterial, and parasitic), cardiovascular diseases such as inflammation post myocardial infarction, bone diseases, muscular dystrophy, or asthma.
- [0183] Item 3-3. The agent according to Item 3-1 or 3-2, for use in simultaneous, separate, or sequential combination with at least one therapeutic or preventive drug for a disease selected from the group consisting of Alzheimer's disease (AD), tauopathies, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), HIV-associated neurocognitive disorders (HAND), prion disease, trauma brain injury (TBI), Parkinson's disease, pain, spinal cord injury, Crohn's disease, radiation-induced lung fibrosis, glaucoma, infections (such as viral, bacterial, and parasitic), cardiovascular diseases such as inflammation post myocardial infarction, bone diseases, muscular dystrophy, or asthma.
- [0184] Item 4-1. A method for treating, preventing, and/or diagnosing a disease caused by CSF1R, which comprises administering to a human in need thereof an effective amount of a compound according to any one of Items 1-1 to 1-52, or a salt thereof.
- [0185] Item 4-2. The method according to Item 4-1, wherein the disease caused by CSF1R is selected from Alzheimer's disease (AD), tauopathies, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), HIV-associated neurocognitive disorders (HAND), prion disease, trauma brain injury (TBI), Parkinson's disease, pain, spinal cord injury, Crohn's disease, radiation-induced lung fibrosis, glaucoma, infections (such as viral, bacterial, and parasitic), cardiovascular diseases such as inflammation post myocardial infarction, bone diseases, muscular dystrophy, or asthma.
- [0186] Item 4-3. The method according to Item 4-1 or 4-2, the method further comprising: administering at least one therapeutic or preventive drug for a disease selected from the group consisting of Alzheimer's disease (AD), tauopathies, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), HIV-associated neurocognitive disorders (HAND), prion disease, trauma brain injury (TBI), Parkinson's disease, pain, spinal cord injury, Crohn's disease, radiation-induced lung fibrosis, glaucoma, infections (such as viral, bacterial, and parasitic), cardiovascular diseases such as inflammation

post myocardial infarction, bone diseases, muscular dystrophy, or asthma.

[0187] Item 5-1. A compound according to any one of Items 1-1 to 1-52, or a salt thereof, for use in the treatment, prevention, and/or diagnosis of a disease caused by CSF1R.

[0188] Item 5-2. The compound, or a salt thereof, for use according to Item 5-1, wherein the disease caused by CSF1R is selected from Alzheimer's disease (AD), tauopathies, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), HIV-associated neurocognitive disorders (HAND), prion disease, trauma brain injury (TBI), Parkinson's disease, pain, spinal cord injury, Crohn's disease, radiation-induced lung fibrosis, glaucoma, infections (such as viral, bacterial, and parasitic), cardiovascular diseases such as inflammation post myocardial infarction, bone diseases, muscular dystrophy, or asthma.

[0189] Item 5-3. The compound, or a salt thereof, for use according to Item 5-1 or 5-2, wherein the compound, or a salt thereof, is administered in simultaneous, separate, or sequential combination with at least one therapeutic or preventive drug for a disease selected from the group consisting of Alzheimer's disease (AD), tauopathies, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), HIV-associated neurocognitive disorders (HAND), prion disease, trauma brain injury (TBI), Parkinson's disease, pain, spinal cord injury, Crohn's disease, radiation-induced lung fibrosis, glaucoma, infections (such as viral, bacterial, and parasitic), cardiovascular diseases such as inflammation post myocardial infarction, bone diseases, muscular dystrophy, or asthma.

[0190] Item 6-1. Use of a compound according to any one of Items 1-1 to 1-52, or a salt thereof, in the manufacture of a medicament for treating, preventing, and/or diagnosing a disease caused by CSF1R.

[0191] Item 6-2. The use according to Item 6-1, wherein the disease caused by CSF1R is selected from Alzheimer's disease (AD), tauopathies, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), HIV-associated neurocognitive disorders (HAND), prion disease, trauma brain injury (TBI), Parkinson's disease, pain, spinal cord injury, Crohn's disease, radiation-induced lung fibrosis, glaucoma, infections (such as viral, bacterial, and parasitic), cardiovascular diseases such as inflammation post myocardial infarction, bone diseases, muscular dystrophy, or asthma.

[0192] Item 6-3. The use according to Item 6-1 or 6-2, wherein the medicament is administered in simultaneous, separate, or sequential combination with at least one therapeutic or preventive drug for a disease selected from the group consisting of Alzheimer's disease (AD), tauopathies, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), HIV-associated neurocognitive disorders (HAND), prion disease, trauma brain injury (TBI), Parkinson's disease, pain, spinal cord injury, Crohn's disease, radiation-induced lung fibrosis, glaucoma, infections (such as viral, bacterial,

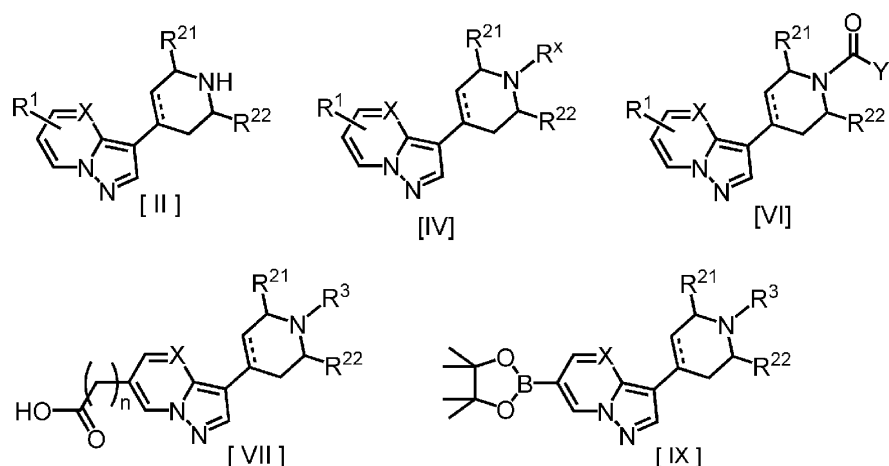
and parasitic), cardiovascular diseases such as inflammation post myocardial infarction, bone diseases, muscular dystrophy, or asthma.

[0193] Item 7. A process for preparing a compound of Formula [I], or a salt thereof, as described herein.

[0194] Item 8-1. An intermediate compound in the process for preparing a compound of Formula [I], or a salt thereof, as described herein.

[0195] Item 8-2. The compound according to Item 8-1, or a salt thereof, represented by any one of the compounds of Formulae [II], [IV], [VI], [VII], and [IX]:

[Chem.32]



wherein R^x is a protecting group selected from alkyl (alkenyl) carbonyl groups, aryl-carbonyl groups, and alkoxycarbonyl groups, Y² is a leaving group selected from phenyloxy groups including 4-nitrophenyloxy, n is 0 or 1, and the other symbols are as defined in Item 1-1.

[0196] Item 8-3. The compound according to Item 8-1, or a salt thereof, wherein the compound is selected from the compounds of Reference Examples 1 to 244 as shown in Table 2.

Examples

[0197] The present invention is explained in more detail with reference to Test Examples, Reference Examples, and Examples as below, which are not to be construed as limitative, and the examples may be modified without departing from the scope of the invention.

Herein, the following abbreviations may be used.

[0198]

[Table 1-1]

Abbreviations	Words
REX	Reference Example number
EX	Example number
STR	Structural formula
RProp	Manufacturing method (numbers indicate that the compound was manufactured using the corresponding raw materials in the same way as the reference example compound having that number as a reference example number)
Prop	Manufacturing method (numbers indicate that the compound was manufactured using the corresponding raw materials in the same way as the example compound having that number as an example number)
Data	Physical property data (NMR1: δ (ppm) in $^1\text{H-NMR}$ in DMSO-d_6 ; NMR2: δ (ppm) in $^1\text{H-NMR}$ in CDCl_3 ; NMR3: δ (ppm) in $^1\text{H-NMR}$ in CD_3OD ; MS: Mass spectrum)
AcOEt	Ethyl acetate
AcOH	Acetic acid
AcOK	potassium acetate
AcONa	Sodium acetate
ATP	Adenosine triphosphate
AUC	Area under curve
BBr_3	Boron tribromide
BINAP	($\pm$)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
n-BuLi	n-Butyllithium
$\text{tBu}_3\text{P} \cdot \text{HBF}_4$	tri-tert-Butylphosphonium tetraphenylborate
$(\text{BPin})_2$	Bis(pinacolato)diboron
BrettPhos	2-Dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl
cataCXium	Butyl-di-1-adamantylphosphine
CDI	1,1'-Carbonyldiimidazole
C_{max}	The maximum plasma concentration that a drug achieved
COMU	(1-Cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylaminomorpholinocarbenium hexafluorophosphate
m-CPBA	m-Chloroperoxybenzoic acid
CPME	Cyclopentyl methyl ether
Cs_2CO_3	Cesium carbonate
DavePhos	2-(Dicyclohexylphosphino)-2'-(dimethylamino)biphenyl
DBU	1,8-Diazabicyclo[5.4.0]-7-undecene
DCC	Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEAD	Diethylazodicarboxylate
Dess-Martin	1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one
DHP	3,4-Dihydro-2H-pyran
DIBAL	Diisobutylaluminum hydride
DIBOC	Di-t-butyl dicarbonate
DIPEA	Diisopropylethylamine
DMA	N,N-Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine

[Table 1-2]

DME	Dimethoxyethane
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
EGTA	Ethylene glycol-bis(2-aminoethylether)-N,N,N',N'-tetraacetic acid
EPPS	3-[4-(2-Hydroxyethyl)-1-piperazinyl]propanesulfonic acid
Et ₂ O	Diethyl ether
EtOH	Ethanol
HATU	o-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HCl	Hydrochloric acid
Hexane	n-Hexane
HOBt	1-Hydroxybenzotriazole
IBX	2-Iodoxybenzoic acid
IPA	2-Propanol
IPE	Diisopropyl ether
K ₂ CO ₃	Potassium carbonate
K ₃ PO ₄	Tripotassium phosphate
KHCO ₃	Potassium hydrogen carbonate
KOH	Potassium hydroxide
KOtBu	Potassium tert-butoxide
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazide
LiOH	Lithium hydroxide
Me ₄ tBuXPhos Pd G ₃	Methanesulfonato (2-di-tert-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl) palladium (II)
MeCN	Acetonitrile
MEK	2-Butanone
MeOH	Methanol
MsCl	Methanesulfonyl Chloride
Me ₄ tBuXphos	2-Di-tert-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl
MgSO ₄	Magnesium sulfate
NaBH ₄	Sodium borohydride
Na ₂ CO ₃	Sodium carbonate
NaH	Sodium hydride
NaHCO ₃	Sodium hydrogen carbonate
NaOH	Sodium hydroxide
NaOtBu	Sodium t-butoxide
Na ₂ SO ₄	Sodium sulfate
NBS	N-Bromosuccinimide
NCS	N-Chlorosuccinimide
NHS	N-Hydroxysuccinimide
NMP	N-Methylpyrrolidone

[Table 1-3]

Pd/C	Palladium-carrying carbon
Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium (0)
Pd(tBu ₃ P) ₂	Bis(tri- <i>t</i> -butylphosphine)palladium
PdCl ₂ (dppf) · DCM	[1,1'-Bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane adduct
PdCl ₂ (PPh ₃) ₂	Bis(triphenylphosphine)palladium (II) chloride
Pd(OAc) ₂	Palladium (II) acetate
Pd(PPh ₃) ₄	Tetrakis(triphenylphosphine)palladium (0)
Pt/C	Platinum-carrying carbon
PEG	Polyethylene glycol
PPTS	Pyridinium <i>p</i> -toluenesulfonate
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TCDI	1,1'-Thiocarbonyldiimidazole
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
t _{max}	The time at which the C _{max} was observed
TMB	Tetramethylbenzidine
TosMIC	Tosylmethyl isocyanide
TPP	Triphenylphosphine
TsCl	<i>p</i> -Toluenesulfonyl chloride
<i>p</i> -TsOH · H ₂ O	<i>p</i> -Toluenesulfonic acid monohydrate
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XantPhos Pd G ₃	[(4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2'-amino-1,1'-biphenyl)]palladium (II) methanesulfonate
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
WSC	3-Ethyl-1-(3-dimethylaminopropyl)carbodiimide
ZCl	Benzyl chloroformate
Zn(CN) ₂	Zinc cyanide

- [0199] In the following Examples, “room temperature (RT)” 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.
- [0200] ¹H-NMR (proton nuclear magnetic resonance spectrum) was measured by Fourier-transform type NMR (either of Bruker AVANCE III 400 (400 MHz), Bruker AVANCE III HD (400 MHz) or Bruker AVANCE III HD (500 MHz)).
- [0201] Mass spectrum (MS) was measured by LC/MS (either of ACQUITY UPLC H-Class, Agilent 1290 Infinity II/6130 or Shimadzu Nexera/LCMS-2020). As an ionization method, ESI method was used. The data indicate actual measured values (found). Generally, molecular ion peaks ([M+H]⁺, [M-H]⁻, etc.) were observed. In the case of a salt, a molecular ion peak or fragment ion peak of free form was generally observed.
- [0202] Supercritical fluid chromatography (SFC) was used for chiral separation.
- [0203] In silica gel column chromatography, when denoted as basic, aminopropylsilane-bound silica gel was used.
- [0204] The absolute configuration of a compound was determined by known X-ray crystal

structure analysis (e.g., "Basic Course for Chemists 12, X-ray Crystal Structure Analysis" written by Shigeru Ohba and Shigenobu Yano, 1st edition, 1999) or estimated from the empirical rule of Shi asymmetric epoxidation (Waldemar Adam, Rainer T. Fell, Chantu R. Saha-Moller and Cong-Gui Zhao: Tetrahedron: Asymmetry 1998, 9, 397-401; Yuanming Zhu, Yong Tu, Hongwu Yu, Yian Shi: Tetrahedron Lett. 1988, 29, 2437-2440).

[0205] Reference Examples

Reference Example 1. Synthesis of 4-nitrophenyl (oxazol-4-ylmethyl) carbonate

To a solution of 4-(hydroxymethyl)-1,3-oxazole (10 g) in DCM (200 mL) under nitrogen, bis(4-nitrophenyl) carbonate (29.45 g) and TEA (21 mL) were added at 0°C. After stirred at 0°C for 5 min, the mixture was stirred at room temperature under nitrogen for 3 hours, and then the mixture was concentrated. AcOEt and 10% K₂CO₃ aq. were added to the residue. The mixture was stirred at room temperature 5-10 min. The organic layer was separated and then concentrated. The residue was triturated in IPE (150 mL) at room temperature overnight. The solid was collected by filtration, washed with IPE to obtain the object compound (22.19 g).

[0206] Reference Example 2. Synthesis of tert-butyl

(1R,5S)-3-(6-(2,2-difluoroethoxy)pyrazolo[1,5-a]pyridin-3-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate

To a mixture of tert-butyl (1S,5R)-3-(6-(benzyloxy)pyrazolo[1,5-a]pyridin-3-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (336 mg) and Pd/C (200 mg) in EtOAc/EtOH (6 mL) (1/1) was stirred at 40°C under hydrogen for 2 h. The mixture was stored under nitrogen overnight. The mixture was stirred at 40°C under hydrogen for 1 h. The reaction mixture was filtered through Celite. The filtrate was concentrated to obtain the intermediate compound (289 mg).

To a solution of the intermediate compound (289 mg) in DMF (4 mL) were added 2,2-difluoroethyl trifluoromethanesulfonate (200 mg) and K₂CO₃ (161 mg) at room temperature. The mixture was stirred for 3 h. The reaction mixture was diluted with water and extracted with AcOEt. The organic layer was concentrated. The residue was purified by basic-silica gel column chromatography (Hexane/AcOEt) to obtain the object compound (231 mg) as diastereomer mixtures (d.r. 7 : 3).

[0207] Reference Example 4. Synthesis of tert-butyl

(1R,5S)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate

To a solution of tert-butyl (1R,5S)-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (2 g) in THF (25 mL) at -78°C was added LDA (6.66 mL) slowly and the reaction mixture was stirred for 10 min. A solution of N-phenyltrifluoromethanesulfonimide

(3.49 g) in THF (15 mL) was added. The reaction mixture was stirred at -78°C for 30 min warmed to room temperature for 5 h. Sat. NH₄Cl aq. was added and extracted with AcOEt. The organic layer was washed with brine and concentrated. The residue was purified by column chromatography (Si, Hexane/AcOEt=95/5-80/20) to give the desired as yellow oil. The mixture of the triflate, bis(pinacolato)diboron (2.71 g), PdCl₂(dppf) · DCM (0.725 g), dppf (0.492 g) and AcOK (2.61 g) in dioxane (50 mL) was stirred under nitrogen at 80°C for 2 h. The mixture was diluted with AcOEt and H₂O, extracted with AcOEt. The organic layer was concentrated. The residue was purified by silica gel column chromatography twice (Hexane/AcOEt and Hexane/DCM/AcOEt) to obtain the object compound (1136 mg).

[0208] Reference Example 5. Synthesis of

3-(piperidin-4-yl)-5-(tetrahydro-2H-pyran-4-yl)pyrazolo[1,5-a]pyridine

To a mixture of tert-butyl

4-(5-(tetrahydro-2H-pyran-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (66.9 mg) in DCM (2 mL), TFA (267 µL) was added at 0°C. The mixture was stirred at room temperature for 3 h, and then H₂O was added. 2N NaOH aq. was added to the mixture at 0°C for the basification. The mixture was extracted with DCM, the organic layer was concentrated to obtain the object compound (47.8 mg).

[0209] Reference Example 6. Synthesis of tert-butyl

4-(5-(tetrahydro-2H-pyran-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a mixture of tert-butyl

4-(5-(3,6-dihydro-2H-pyran-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (138.5 mg) in EtOH/AcOEt (1/1) (5 mL) under nitrogen, 10% Pd/C (wet, NX type) (116 mg) was added. Nitrogen was replaced with hydrogen. The mixture was stirred at 40°C for 1h. The mixture was stirred at 50°C for 0.5 h. The mixture was stirred under nitrogen at room temperature overnight. The mixture was stirred at 50°C for more 1.5 h (total time was 2 h) under hydrogen. The mixture was filtered through Celite, and the filtrate was concentrated. The residue was purified by amino silica gel column chromatography (Hexane/AcOEt) to obtain the object compound (66.9 mg).

[0210] Reference Example 7. Synthesis of tert-butyl

4-(5-(3,6-dihydro-2H-pyran-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate

To a mixture of tert-butyl

4-(5-bromopyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (232.6 mg) in DME/H₂O (10/1) (5 mL), PdCl₂(dppf) · DCM (50.2 mg), 3,6-Dihydro-2H-pyran-4-boronic acid pinacol ester (258 mg) and K₃PO₄ (392 mg) were added at room temperature. The mixture was stirred at 80°C under nitrogen for

overnight. H₂O was added to the mixture, and then the mixture was extracted with AcOEt. The organic layer was concentrated. The residue was purified by amino silica gel column chromatography (Hexane/AcOEt) to obtain the object compound (138.5 mg).

[0211] Reference Example 8. Synthesis of tert-butyl

4-(5-bromopyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate

To a mixture of 5-bromo-3-iodopyrazolo[1,5-a]pyridine (796.1 mg) and Pd(Ph₃P)₄ (142 mg) in DME/H₂O (10/1) (20 mL), 3,6-dihydro-2H-pyridine-1-tert-butoxycarbonyl-4-boronic acid, pinacol ester (915 mg) and K₃PO₄ (1570 mg) were added. The mixture was stirred at 80°C overnight under nitrogen. H₂O was added to the reaction mixture at 0°C, and then the mixture was extracted with AcOEt. The organic layer was concentrated and the residue was purified by silica gel column chromatography (Hexane/AcOEt) to obtain the object compound (442 mg).

[0212] Reference Example 10. Synthesis of tert-butyl

4-(5-methoxypyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a mixture of tert-butyl 4-(5-hydroxypyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (61.1 mg) in DMF (1 mL), K₂CO₃ (53.2 mg) and iodomethane (17.98 µL) were added to the mixture at 0°C. The mixture was stirred at room temperature for 8 h. H₂O was added to the mixture at 0°C, and the mixture was extracted with AcOEt. The organic layer was concentrated. The residue was purified by amino silica gel column chromatography (Hexane/AcOEt) to obtain the object compound (46.4 mg).

[0213] Reference Example 13. Synthesis of 5-(benzyloxy)-3-bromopyrazolo[1,5-a]pyridine

To a solution of 5-(phenylmethoxy)pyrazolo[1,5-a]pyridine (252.6 mg) in DMF (8 mL) was added NBS (241 mg) at 0°C. The mixture was stirred at room temperature for 2 h. H₂O (200 mL) was added to the mixture at 0°C to form a precipitate. The mixture was filtered and the precipitate was collected. The precipitate was washed with H₂O to obtain the object compound (285 mg).

[0214] Reference Example 15. Synthesis of tert-butyl

4-(6-hydroxypyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a mixture of tert-butyl 4-(6-(benzyloxy)pyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (24.67 g) in AcOEt/EtOH (800 mL) (1/1) under nitrogen, 10% Pd-C (12.82 g) (wetted with water) was added at room temperature. Nitrogen was replaced with hydrogen. The mixture was stirred at 30°C for 2.5 h.

The mixture was filtered through Celite and the Celite was washed with AcOEt and DCM to obtain the filtrate. The filtrate was concentrated and dried. The residue was

trituated at room temperature in hexane/AcOEt (1/1) (200 mL). The solid was collected, washed with hexane and dried to obtain the object compound (16.60 g).

[0215] Reference Example 16. Synthesis of tert-butyl

4-(6-(benzyloxy)pyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate

To a suspension of 6-(benzyloxy)-3-bromopyrazolo[1,5-a]pyridine (20 g) and 3,6-dihydro-2H-pyridine-1-tert-butoxycarbonyl-4-boronic acid, pinacol ester (24.98 g) in DME/H₂O (330 ml) (10/1) under nitrogen, K₃PO₄ (35.04 g) and PdCl₂(dppf) · DCM (2.69 g) were added. After degassed, the mixture was refluxed under nitrogen overnight. AcOEt and H₂O were added. The mixture was stirred at room temperature and passed through Celite, and the Celite was washed with AcOEt and dioxane. The organic layer was washed with brine and concentrated. The residue was purified by basic-silica gel chromatography (DCM/AcOEt) to obtain the object compound (24.67 g).

[0216] Reference Example 17. Synthesis of 6-(benzyloxy)-3-bromopyrazolo[1,5-a]pyridine

To a mixture of 6-(phenylmethoxy)pyrazolo[1,5-a]pyridine (15.30 g) in DMF (220 ml) under nitrogen, NBS (12.14 g) was added at 0°C. The mixture was stirred at 0°C under nitrogen for 2.5 h. H₂O (-700 ml) was added. Then, the mixture was stirred at room temperature. The solid was collected, washed with H₂O and dried to obtain the object compound (20.02 g).

[0217] Reference Example 19. Synthesis of

6-(2-methoxyethoxy)-3-(piperidin-4-yl)pyrazolo[1,5-a]pyridine

To a mixture of tert-butyl 4-(6-(2-methoxyethoxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (1650.9 mg) in DCM (65 mL) was added TFA (6775 µL) at 0°C. The mixture was stirred at room temperature under nitrogen for 2 h. H₂O was added to the mixture at 0°C, then 2N NaOH was added. The mixture was extracted with DCM. The organic layer was concentrated. The residue was suspended in IPE, and the solid was collected and dried to obtain the object compound (1.008 g).

[0218] Reference Example 20. Synthesis of tert-butyl

4-(6-(2-methoxyethoxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a mixture of 2-Bromoethyl methyl ether (1.184 ml) and tert-butyl 4-(6-hydroxypyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (2 g) in MeCN (30 mL) were added Cs₂CO₃ (6.16 g) and sodium iodide (0.472 g) at 0°C. The mixture was stirred at 50°C for 3 h under nitrogen. H₂O was added to the mixture at 0°C. The mixture was extracted with DCM. The organic layer was collected and concentrated to obtain the crude material. The crude was purified by basic-silica gel chromatography (hexane/AcOEt). The material was suspended in IPE at refluxing temperature. The solid was collected and dried to obtain the object compound (1.65 g).

[0219] Reference Example 21. Synthesis of6-(2,2-difluoroethoxy)-3-(piperidin-4-yl)pyrazolo[1,5-a]pyridine

To a solution of tert-butyl 4-(6-(2,2-difluoroethoxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (16.85 g) in DCM (200 mL) was added TFA (35 mL) at 0°C. The mixture was stirred at room temperature and concentrated. The residue was dissolved in DCM. 5N NaOH aq. (60 mL) was added at 0°C. The mixture was extracted with DCM. The organic layer was concentrated. The crude was purified by NH-silica gel chromatography (AcOEt/MeOH) to obtain the object compound (10.91 g).

[0220] Reference Example 22. Synthesis of tert-butyl4-(6-(2,2-difluoroethoxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a solution of tert-butyl 4-(6-hydroxypyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (7.47 g) in DMF (70 mL) under nitrogen, K₂CO₃ (4.88 g) and a solution of 2,2-difluoroethyl trifluoromethanesulfonate (6.31 g) in DMF (5 mL) were added. The mixture was stirred at room temperature for 8 h. K₂CO₃ (665.8 mg) was added. 2,2-Difluoroethyl trifluoromethanesulfonate (690.8 mg) was added. The mixture was stirred at room temperature under nitrogen overnight. 2,2-Difluoroethyl trifluoromethanesulfonate (385.3 mg) was added. The mixture was stirred at room temperature under nitrogen for 1 h. H₂O (160 mL) was added. The solid was collected and dried, then was triturated in IPE and dried to obtain the object compound (7.22 g).

[0221] Reference Example 27. Synthesis of tert-butyl4-(6-(2-hydroxy-2-methylpropoxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a solution of tert-butyl 4-(6-(2-methoxy-2-oxoethoxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (102.7 mg) in THF (10 mL) under nitrogen, methylmagnesium bromide (0.3 mL) was added at 0°C. The mixture was stirred at 0°C under nitrogen for 30 min. Sat. NH₄Cl aq. and AcOEt were added. The mixture was extracted with AcOEt. The organic layer was concentrated to obtain the object compound (102.2 mg).

[0222] Reference Example 31. Synthesis of tert-butyl4-(6-cyanopyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a mixture of tert-butyl 4-[6-(trifluoromethylsulfonyloxy)pyrazolo[1,5-a]pyridin-3-yl]piperidine-1-carboxylate (400 mg) in DMF (3 mL) was added Zn(CN)₂ (157 mg) and Pd(PPh₃)₄ (103 mg) and the mixture was stirred at 80°C for 3 h. The reaction mixture was quenched by sat. NaHCO₃ aq. and filtered. The solid was purified by silica gel column chromatography (hexane/AcOEt) to obtain the object compound (33 mg).

[0223] Reference Example 34. Synthesis of (S)-(2,2-difluoro-1-methylcyclopropyl)methyl methanesulfonate

To a mixture of (1S)-2,2-difluoro-1-methylcyclopropane-1-carboxylic acid (200 mg) in ether (5 mL) was added LAH (167 mg) under nitrogen at 0°C. It was stirred at room temperature for 18 h. The mixture was quenched with H₂O (0.167 mL), 15% NaOH aq. (0.167 mL), and H₂O (0.501 mL). The mixture was stirred at room temperature for 30 min. To the mixture was added MgSO₄ and filtered. The filtrate was concentrated under reduced pressure. To the mixture of the crude in DCM (5 mL) was added MsCl (298 µL) and TEA (614 µL) at 0°C. The mixture was stirred at room temperature for 3 h. The mixture was quenched by H₂O, extracted with DCM and the organic layer was concentrated to obtain the object compound (294 mg)(containing DCM). The crude was used without any further purifications.

[0224] Reference Example 39. Synthesis of tert-butyl 4-(6-chloropyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To the mixture of tert-butyl 4-(6-chloropyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (400 mg) and platinum (IV) oxide (54.4 mg) was added EtOH (10 mL) at room temperature. The mixture was stirred at 40°C under hydrogen for 10 h. The crude was filtered through Celite and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt) to obtain the object compound (93 mg).

[0225] Reference Example 45. Synthesis of tert-butyl 4-(6-(2,2-difluoropropoxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a solution of tert-butyl 4-(6-(2-oxopropoxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (177 mg) in DCM (5 mL) was added bis(2-methoxyethyl)aminosulfur trifluoride (262 µL) at 0°C under nitrogen. The mixture was warmed to room temperature and stirred for 7 h. The reaction mixture was diluted with sat. NaHCO₃ aq. and extracted with DCM. The organic layer was concentrated. The residue was purified by basic-silica gel column chromatography (hexane/AcOEt) to obtain the object compound (165 mg).

[0226] Reference Example 55. Synthesis of benzyl 3-((tosyloxy)methyl)azetidine-1-carboxylate

To a solution of 1-Cbz-azetidine-3-yl methanol (1000 mg) in pyridine (4 mL) was added TsCl (1292 mg) at 0°C and this was stirred at room temperature for 24 h. It was diluted by AcOEt and 1M HCl. The organic layer was washed by 1M HCl and concentrated. The residue was purified by silica gel column (hexane/AcOEt) to obtain the object compound (1.3 g).

[0227] Reference Example 58. Synthesis of tert-butyl 4-(6-(2-(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)ethoxy)pyrazolo[1,5-a]pyridin-3-yl)pi

piperidine-1-carboxylate

To a solution of tert-butyl

4-(6-(2-hydroxyethoxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (202.5 mg) in DCM (20 mL) under nitrogen, Dess-Martin (748.3 mg) was added at room temperature. The mixture was stirred at room temperature under nitrogen for 55 min. Dess-Martin (108.4 mg) was added at room temperature. The mixture was stirred at room temperature under nitrogen for 55 min. DCM and sat. $\text{Na}_2\text{S}_2\text{O}_3$ aq. was added at 0°C. The water layer was extracted with DCM and AcOEt. The combined organic layer was concentrated to obtain the intermediate compound. To a solution of the intermediate compound in DCE (20 mL), 6,6-difluoro-2-azaspiro[3.3]heptane hydrochloride (131.8 mg) and sodium triacetoxymethylborohydride (253.2 mg) were added at room temperature. The mixture was stirred at room temperature overnight. H_2O , sat. NaHCO_3 aq. and DCM were added at room temperature. The organic layer was separated and then concentrated. The residue was purified by basic-silica gel chromatography (hexane/AcOEt) to obtain the object compound (71.4 mg).

[0228] Reference Example 59. Synthesis of tert-butyl

4-(6-(2-hydroxyethoxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a solution of tert-butyl

4-(6-(2-methoxy-2-oxoethoxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (258.7 mg) in THF (15 mL) under nitrogen, LAH (30.9 mg) was added at 0°C. The mixture was stirred at 0°C for 10 min. Hexane and $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$ were added at 0°C. The mixture was stirred at 0°C under nitrogen for 10 min. $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$ was added at 0°C. Then, the mixture was stirred at room temperature under nitrogen. The mixture was filtrated with Celite and then concentrated. The residue was purified by silica gel chromatography (hexane/AcOEt) to obtain the object compound (202.5 mg).

[0229] Reference Example 71. Synthesis of tert-butyl

4-(6-(3,6-dihydro-2H-pyran-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate

A mixture of 6-bromo-3-chloropyrazolo[1,5-a]pyridine (780 mg), 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester (920 mg), $\text{PdCl}_2(\text{dppf}) \cdot \text{DCM}$ (138 mg) and K_3PO_4 (2145 mg) in DME/ H_2O (15 mL) was stirred at 80°C under nitrogen for 2 h. The mixture was diluted with H_2O , AcOEt and filtered through Celite. The filtrate was extracted with AcOEt. The organic layer was concentrated to obtain the intermediate compound. To the mixture of the intermediate compound, tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate (1.6 g), palladium (II) acetate (80 mg), SPhos (280 mg) and K_3PO_4 (1.4 g) in DME/ H_2O (30 mL) was stirred at 80°C under nitrogen for 8 h. To the mixture were added tert-butyl

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate (0.8 g), palladium (II) acetate (40 mg), S-Phos (140 mg) and K_3PO_4 (0.7 g) at room temperature. The mixture was stirred at 80°C under nitrogen for 16 h. The mixture was diluted with H_2O and AcOEt, filtered through Celite and washed with AcOEt. The organic layer was concentrated. The residue was purified by basic-silica gel column chromatography (hexane/AcOEt) to obtain the object compound (1142 mg).

[0230] Reference Example 72. Synthesis of 6-bromo-3-chloropyrazolo[1,5-a]pyridine

To a solution of 6-bromopyrazolo[1,5-a]pyridine (5400 mg) in MeCN (80 mL) was added NCS (3660 mg) at room temperature. The mixture was stirred at room temperature overnight. The mixture was warmed to 50°C and stirred for 8 h. The mixture was diluted with H_2O (300 mL) and stirred for 1 h. The resulting precipitate was collected by filtration to obtain the object compound (6067 mg).

[0231] Reference Example 77. Synthesis of tert-butyl

4-(6-cyclopropoxypyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a mixture of tert-butyl 4-(6-hydroxypyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (100 mg) in NMP (1 mL) were added Cs_2CO_3 (205 mg) and cyclopropyl bromide (126 μ L) at room temperature. The mixture was stirred at 150°C for 2 h under microwave irradiation. The mixture was diluted with H_2O and extracted with AcOEt. The organic layers were concentrated. The residue was purified by basic-silica gel chromatography (hexane/AcOEt) to obtain the object compound (40 mg).

[0232] Reference Example 78. Synthesis of tert-butyl

4-(6-((1-methylpiperidin-4-yl)oxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a solution of tert-butyl 4-(6-(piperidin-4-yloxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (227.2 mg) in DCE (10 mL) under nitrogen, formaldehyde solution (47 μ L) and sodium triacetoxyborohydride (227.4 mg) were added at 0°C. The mixture was stirred at room temperature under nitrogen for 3.5 h. AcOEt and sat. $NaHCO_3$ aq. were added at room temperature. The organic layer was separated and then concentrated. The residue was purified by basic-silica gel chromatography (hexane/AcOEt) to obtain the object compound (197.5 mg).

[0233] Reference Example 79. Synthesis of tert-butyl

4-(6-(piperidin-4-yloxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a solution of benzyl 4-((3-(1-(tert-butoxycarbonyl)piperidin-4-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)piperidine-1-carboxylate (342.1 mg) in AcOEt (50 mL), Pd/C (244.5 mg) (10%, NX-type, wetted with water) was added at room temperature. The mixture was stirred at room

temperature under hydrogen for 22 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated. The residue was purified by basic-silica gel chromatography (AcOEt/MeOH) to obtain the object compound (227.2 mg).

[0234] Reference Example 80. Synthesis of benzyl

4-((3-(1-(tert-butoxycarbonyl)piperidin-4-yl)pyrazolo[1,5-a]pyridin-6-yl)oxy)piperidine-1-carboxylate

To a suspension of tert-butyl 4-(6-hydroxypyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (247.8 mg) in MeCN (10 ml) under nitrogen, Cs₂CO₃ (454.8 mg) and a solution of benzyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (625.4 mg) in MeCN (10 ml) were added at room temperature. The mixture was refluxed under nitrogen for 4 h 10 min. AcOEt and H₂O were added. The water layer was extracted with AcOEt. The combined organic layers were concentrated. The residue was purified by basic-silica gel chromatography (Hexane/AcOEt) to obtain the mixture of the object compound and benzyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (496.9 mg). To a solution of the mixture (496.9 mg) in MeCN (20 ml) under nitrogen were added tert-butyl 4-(6-hydroxypyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (279.1 mg) and Cs₂CO₃ (664 mg) at room temperature. The mixture was refluxed under nitrogen overnight. AcOEt was added at room temperature. The mixture was filtered through Celite. The filtrate was concentrated. The residue was purified by basic-silica gel chromatography (Hexane/AcOEt) to obtain the object product (342.1 mg).

[0235] Reference Example 84. Synthesis of tert-butyl

4-(6-bromopyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate

To a solution of 6-bromo-3-iodopyrazolo[1,5-a]pyridine (102.3 mg) and 3,6-dihydro-2H-pyridine-1-tert-butoxycarbonyl-4-boronic acid, pinacol ester (120 mg) in dioxane / H₂O (10/1) (22 mL) under nitrogen, PdCl₂(dppf) · DCM (22.2 mg) and K₃PO₄ (245.9 mg) were added at room temperature. The mixture was refluxed overnight. H₂O, AcOEt and brine were added at room temperature. The organic layers were concentrated. The residue was purified by basic-silica gel chromatography (hexane/AcOEt) to obtain the object compound (69.7 mg).

[0236] Reference Example 85. Synthesis of benzyl

4-(6-(2-morpholinoethyl)pyrazolo[1,5-a]pyrimidin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate

The mixture of benzyl 4-(6-bromopyrazolo[1,5-a]pyrimidin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (952 mg), (E)-2-Ethoxyvinylboronic acid pinacol ester (0.586 mL), PdCl₂(dppf) · DCM (188 mg) and K₃PO₄ (1467 mg) in DME/H₂O (10 mL) was stirred at 80°C under nitrogen for 4 h. The mixture was diluted with H₂O and extracted with

AcOEt. The organic layer was concentrated. The residue was purified by column chromatography (Si, hexane/AcOEt) to give the intermediate compound (761 mg). To a solution of the intermediate compound in THF (15 mL) was added HCl (1.5 mL) at room temperature. The mixture was stirred at 60°C for 5 h. The mixture was diluted with H₂O and extracted with AcOEt. The organic layer was concentrated to obtain the intermediate compound. To a solution of the intermediate compound in DCM (20 mL) were added morpholine (0.401 mL), AcOH (0.264 mL) and sodium triacetoxyborohydride (976 mg) at room temperature. The mixture was stirred overnight. The mixture was diluted with sat. NaHCO₃ aq. and extracted with DCM. The organic layer was concentrated. The residue was purified by basic-silica gel column chromatography (hexane/AcOEt) to obtain the object compound (195 mg).

[0237] Reference Example 87. Synthesis of

2-chloro-1-(4-(6-methoxypyrazolo[1,5-a]pyridin-3-yl)piperidin-1-yl)ethan-1-one

To a mixture of 6-methoxy-3-(piperidin-4-yl)pyrazolo[1,5-a]pyridine (50 mg) in THF (1 mL), TEA (60.3 µL) was added at 0°C and Chloroacetic chloride (22.38 µL)/THF (1 mL) was added dropwise at 0°C. The mixture was stirred at room temperature under nitrogen for 2 h. sat. NH₄Cl aq was added to the mixture. The mixture was extracted with AcOEt. The organic layer was collected and concentrated to obtain the object compound (quantitative yield).

[0238] Reference Example 89. Synthesis of thiazol-4-ylmethyl

4-(6-(2-methoxy-2-oxoethyl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

A mixture of benzyl 4-(6-(2-methoxy-2-oxoethyl)pyrazolo[1,5-a]pyrimidin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (410 mg) and 10% Pd/C (220 mg) in AcOEt/EtOH (1/1) (10 mL) was stirred at 50°C under hydrogen for 4h. The reaction mixture was filtered through Celite, and the filtrate was concentrated. The residue was used for next step without further purification. To a solution of the residue in DCM (8 mL) were added TEA (281 µL) and 4-nitrophenyl(thiazol-4-ylmethyl)carbonate (257 mg) at room temperature. The mixture was stirred overnight. The mixture was concentrated and purified by basic-silica gel column chromatography (hexane/AcOEt) to obtain the object compound (128 mg).

[0239] Reference Example 90. Synthesis of benzyl

4-(6-(2-methoxy-2-oxoethyl)pyrazolo[1,5-a]pyrimidin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate

A mixture of benzyl 4-(6-bromopyrazolo[1,5-a]pyrimidin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (871 mg), 1-(tert-butyldimethylsilyloxy)-1-methoxyethene (2300 µL), zinc fluoride (654 mg), Pd₂(dba)₃ (193 mg) and tri-tert-butylphosphine tetrafluoroborate (306 mg) in

DMF (18 mL) was stirred under nitrogen at 90°C for 16 h. To the mixture were added 1-(tert-butyldimethylsilyloxy)-1-methoxyethene (1.4 mL), zinc fluoride (218 mg), Pd₂(dba)₃ (96 mg) and tri-tert-butylphosphine tetrafluoroborate (122 mg) at room temperature. The mixture was stirred at 90°C for 5 h. The mixture was diluted with H₂O, AcOEt and filtered through Celite. The filtrate was extracted with AcOEt. The organic layer was concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt) to obtain the object compound (410 mg).

[0240] Reference Example 91. Synthesis of

6-(2-methoxyethoxy)-3-(piperidin-4-yl)pyrazolo[1,5-a]pyrimidine

To a solution of tert-butyl 4-(6-(2-methoxyethoxy)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate (193 mg) in DCM (10 ml), TFA (1 ml) was added at room temperature. The mixture was stirred at room temperature for 2.5h. The mixture was concentrated and azeotroped with toluene in vacuo. To the crude (TFA salt) were added DCM and 1N NaOH aq. The water layer was extracted with DCM. The combined organic layers were concentrated. The residue was purified by basic-silica gel chromatography (AcOEt/MeOH) to obtain the object compound (128.7 mg).

[0241] Reference Example 92. Synthesis of tert-butyl

4-(6-(2-methoxyethoxy)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

To a solution of tert-butyl 4-(6-hydroxypyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate (207.3 mg) in DMF (10 mL) under nitrogen were added 2-bromoethyl methyl ether (124 µL) and Cs₂CO₃ (286 mg) at room temperature. The mixture was stirred at 60°C overnight. AcOEt and H₂O were added to the mixture at room temperature. The water layer was extracted with AcOEt. The combined organic layers were concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt then AcOEt/MeOH) to obtain the object compound (193 mg).

[0242] Reference Example 93. Synthesis of tert-butyl

4-(6-hydroxypyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

To a suspension of tert-butyl 4-(6-(benzyloxy)pyrazolo[1,5-a]pyrimidin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (2.72 g) in EtOH (50 mL), a suspension of 10% Pd/C (523 mg) in EtOH (20 mL) was added at room temperature. The mixture was stirred at 50°C under hydrogen for 7 h. The reaction mixture was filtered through Celite. The filtrate was concentrated to obtain the crude product (2.18 g). The same reaction was repeated to obtain the object product (2.13 g).

[0243] Reference Example 94. Synthesis of tert-butyl

4-(6-(benzyloxy)pyrazolo[1,5-a]pyrimidin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate

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To a solution of 6-(benzyloxy)-3-bromopyrazolo[1,5-a]pyrimidine (4.09 g), 3,6-Dihydro-2H-pyridine-1-tert-butoxycarbonyl-4-boronic acid, pinacol ester (6.24 g) and K_3PO_4 (8.56 g) in DME/H₂O (10:1) (60 mL) under argon, $Pd(OAc)_2$ (0.302 g) and SPhos (0.828 g) were added at room temperature. The mixture was stirred at 80°C overnight. To the reaction mixture was added AcOEt and H₂O at room temperature. The mixture was filtered through Celite. The organic layer was concentrated. The residue was purified by silica gel chromatography (heptan/AcOEt) to obtain the object compound (3.24g).

[0244] Reference Example 95. Synthesis of tert-butyl

4-(6-(2,2-difluoroethoxy)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

To a solution of tert-butyl 4-(6-hydroxypyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate (250 mg) in DMF (4 mL) were added Cs_2CO_3 (512 mg) and 1,1-Difluoro-2-iodoethane (138 μ L) at room temperature. The mixture was stirred at 60°C for 3 h. The mixture was diluted with H₂O and the resulting precipitate was collected by filtration and dried to obtain the object product (238 mg).

[0245] Reference Example 101. Synthesis of tert-butyl

4-(6-hydroxypyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate

To a mixture of tert-butyl 4-(6-bromopyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (209 mg), KOH (146 mg), $Pd_2(dba)_3$ (25.3 mg) and $Me_4tButylXphos$ (26.6 mg) in dioxane / H₂O (1:1) (6 mL) was stirred at 100°C under argon overnight. 1N HCl (3 mL) was added at 0°C. The mixture was extracted with AcOEt, and the organic layer was concentrated. The residue was purified by basic-silica gel chromatography (heptan/AcOEt/MeOH) to obtain the object compound (96 mg).

[0246] Reference Example 104. Synthesis of tert-butyl

4-(6-(6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-yl)pyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate

To a mixture of 2-(3-chloropyrazolo[1,5-a]pyridin-6-yl)-6,7-dihydro-4H-pyrano[4,3-d]thiazole (56.3 mg), SPhos (15.84 mg) and $Pd(OAc)_2$ (4.33 mg) in DME/H₂O (10/1) (2 mL), 3,6-dihydro-2H-pyridine-1-tert-butoxycarbonyl-4-boronic acid, pinacol ester (119 mg) and K_3PO_4 (123 mg) was added. The mixture was stirred at 90°C under nitrogen overnight. H₂O was added to the mixture at 0°C, and the mixture was extracted with DCM. The organic layer was concentrated, and then the residue was purified by silica gel column chromatography (Hexane/AcOEt) to obtain the object compound (29.7 mg).

[0247] Reference Example 105. Synthesis of2-(3-chloropyrazolo[1,5-a]pyridin-6-yl)-6,7-dihydro-4H-pyrano[4,3-d]thiazole

To a mixture of 3-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (251 mg) in 1,4-dioxane:H₂O (10:1) (6 mL), Xantphos (59.2 mg), Pd(OAc)₂ (22.95 mg), 2-bromo-6,7-dihydro-4H-pyrano[4,3-d]thiazole (150 mg) and K₂CO₃ (283 mg) were added. The mixture was stirred at 80°C under nitrogen overnight. H₂O was added to the mixture at 0°C, and the mixture was extracted with DCM. The organic layer was concentrated, and then the residue was purified by silica gel column chromatography (Hexane/AcOEt) to obtain the object compound (56.3 mg).

[0248] Reference Example 106. Synthesis of3-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine

To a mixture of PdCl₂(dppf) · DCM (0.037 g) in 1,4-dioxane (5 mL), 6-bromo-3-chloropyrazolo[1,5-a]pyridine (0.208 g) and bis(pinacolato)diboron (0.274 g) and AcOK (0.221 g) were added at room temperature. The mixture was refluxed overnight under nitrogen. H₂O was added to the mixture and the mixture was extracted with DCM. The organic layer was concentrated and then the residue was diluted with IPE and filtered through Celite. The filtrate was concentrated to obtain the object compound.

[0249] Reference Example 108. Synthesis of tert-butyl4-(6-(cyclopropylcarbamoyl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a solution of 3-(1-(tert-butoxycarbonyl)piperidin-4-yl)pyrazolo[1,5-a]pyridine-6-carboxylic acid (121 mg) in THF (2 mL), DIPEA (73 µL), HATU (160 mg) and cyclopropylamine (36 µL) were added. The mixture was stirred at room temperature for 3 h. Sat. NaHCO₃ aq. and AcOEt were added to the mixture. The organic layer was separated by phase separator (Whatman, filter paper 1PS), and the solvent was removed. The residue was purified by basic-silica gel column chromatography (heptane/AcOEt) to obtain the object compound (85 mg).

[0250] Reference Example 109. Synthesis of3-(1-(tert-butoxycarbonyl)piperidin-4-yl)pyrazolo[1,5-a]pyridine-6-carboxylic acid

To a solution of methyl 3-(1-(tert-butoxycarbonyl)piperidin-4-yl)pyrazolo[1,5-a]pyridine-6-carboxylate (436 mg) in MeOH/THF (1/1) (10 mL) was added 5M NaOH aq. (0.5 mL), and the mixture was stirred at 50°C for 1 h. After cooling the reaction mixture at 0°C, and the reaction mixture was diluted with water, and the mixture was acidified with 6M HCl. The mixture was extracted with AcOEt. The organic layer was concentrated to obtain the object compound (451 mg).

[0251] Reference Example 111. Synthesis of methyl

3-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)pyrazolo[1,5-a]pyridine-6-carboxylate

A mixture of tert-butyl 4-(6-bromopyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (2.88 g), TEA (3.18 mL) and XantPhos Pd G3 (181 mg) in DMF/MeOH (4/1) (50 mL) was stirred under a carbon monoxide atmosphere. The reaction mixture was stirred at 70°C for overnight. The reaction mixture was concentrated, water was added to the residue, and then the mixture was extracted with AcOEt. The organic layer was concentrated, and then the residue was purified by basic-silica gel column chromatography (heptane/AcOEt) to obtain the object compound (2.29 g).

[0252] Reference Example 114. Synthesis of tert-butyl

4-(6-formylpyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a solution of tert-butyl 4-(6-(hydroxymethyl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (225 mg) in DMSO (4 mL), IBX (285 mg) was added at room temperature. The mixture was stirred at room temperature for 1 h. sat. NaHCO₃ aq. was added at room temperature. The mixture was extracted with AcOEt. The organic layer was concentrated and then the residue was purified by silica gel chromatography (heptane/AcOEt) to obtain the object compound (170 mg).

[0253] Reference Example 115. Synthesis of tert-butyl

4-(6-(hydroxymethyl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a solution of methyl 3-(1-(tert-butoxycarbonyl)piperidin-4-yl)pyrazolo[1,5-a]pyridine-6-carboxylate (0.359 g) in THF (5 mL), DIBAL (1M in toluene) (3.00 mL) was slowly added at 0°C. The mixture was stirred at 0°C for 30 min under Argon. Then, 1N HCl was added at 0°C. The mixture was extracted with AcOEt. The organic layer was concentrated. The residue was purified by silica gel column chromatography (heptane/AcOEt/MeOH) to obtain the object compound (225 mg).

[0254] Reference Example 127. Synthesis of

6-(1-cyclopropyl-3,5-dimethyl-1H-pyrazol-4-yl)-3-(piperidin-4-yl)pyrazolo[1,5-a]pyrimidine

To a solution of tert-butyl 4-(6-(1-cyclopropyl-3,5-dimethyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate (471 mg) in DCM (10 mL) was added TFA (1.5mL) at room temperature. The mixture was stirred for 2 h. The mixture was concentrated. The residue was purified by basic-silica gel column chromatography (AcOEt/MeOH) to obtain the object compound (237 mg).

[0255] Reference Example 128. Synthesis of tert-butyl

4-(6-(1-cyclopropyl-3,5-dimethyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

A mixture of tert-butyl

4-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate (828 mg), 4-bromo-1-cyclopropyl-3,5-dimethyl-1H-pyrazole (416 mg), Pd(OAc)₂ (43.4 mg), Xantphos (224 mg) and K₂CO₃ (535 mg) in dioxane/H₂O (10/1) (12 mL) was stirred at 100°C under nitrogen overnight. The mixture was diluted with H₂O and extracted with AcOEt. The organic layer was concentrated. The residue was purified by column chromatography (hexane/AcOEt) to obtain the object product.

[0256] Reference Example 129. Synthesis of tert-butyl

4-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

A mixture of tert-butyl

4-(6-(((trifluoromethyl)sulfonyl)oxy)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate (542.2 mg), PdCl₂(dppf) · DCM (49.2 mg), AcOK (236 mg) and Bis(pinacolato)diboron (397 mg) in 1,4-dioxane (6 mL) was stirred at 80°C under nitrogen for 2 h. The reaction mixture was concentrated and diluted with AcOEt. The mixture was filtered through Celite and concentrated to obtain the object product.

[0257] Reference Example 130. Synthesis of tert-butyl

4-(6-(((trifluoromethyl)sulfonyl)oxy)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

To a solution of tert-butyl

4-(6-hydroxypyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate (117 mg) in THF (3 mL), DIPEA (77 µL) and N-phenyltrifluoromethanesulfonimide (144 mg) were added at 0°C. After stirred at 0°C for 30 min, sat. NH₄Cl aq. was added at 0°C. The mixture was extracted with AcOEt. The organic layer was concentrated. The residue was purified by silica gel column chromatography (heptane/AcOEt) to obtain the object compound (75 mg).

[0258] Reference Example 136. Synthesis of

6-(1-methyl-1H-pyrazol-4-yl)-3-(piperidin-4-yl)pyrazolo[1,5-a]pyrimidine

To a solution of tert-butyl

4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate (776 mg) in DCM (20 mL) was added TFA (2 mL) at room temperature. The mixture was stirred at room temperature for 2 h 25 min. The reaction mixture was concentrated. To the residue were added DCM and 1 mol/L NaOH aq.. The organic layer was concentrated to obtain the object compound (628.4 mg).

[0259] Reference Example 137. Synthesis of tert-butyl

4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

To a suspension of tert-butyl

4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3,6-dihydropyridine-1 (2H)-carboxylate (992 mg) in EtOH (100 mL) was added Pd/C (144.9 mg) (10%, type NX wetted with water). The mixture was stirred at 50°C under hydrogen for 6 h. The reaction mixture was filtered through Celite and concentrated. The reaction was repeated. To a suspension of the residue in EtOH (100 mL), Pd/C (647.9 mg) was added. The mixture was stirred at 50°C under hydrogen for 2 h. The reaction mixture was filtered through Celite and concentrated. The crude was purified by NH-silica gel chromatography (hexane/AcOEt) to obtain the object compound (776.0 mg).

[0260] Reference Example 138. Synthesis of tert-butyl

4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3,6-dihydropyridine-1 (2H)-carboxylate

To a solution of 3-chloro-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine (713.7 mg) in dioxane/H₂O (33 mL) (10/1) under nitrogen, 3,6-dihydro-2H-pyridine-1-tert-butoxycarbonyl-4-boronic acid, pinacol ester (1.67 g), K₃PO₄ (1.91 g), Pd(OAc)₂ (64.7 mg) and SPhos (275.9 mg) were added at room temperature. The mixture was refluxed under nitrogen overnight. To the reaction mixture were added H₂O, AcOEt. The organic layer was concentrated. The residue was purified by basic-silica gel chromatography (hexane/AcOEt) to obtain the object compound (992 mg).

[0261] Reference Example 139. Synthesis of

3-chloro-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine

To a solution of 6-bromo-3-chloropyrazolo[1,5-a]pyrimidine (773.1 mg) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (889 mg) in dioxane/H₂O (33 mL) (10/1) under nitrogen, K₃PO₄ (2.05 g) and PdCl₂(dppf) · DCM (186.3 mg) were added at room temperature. The mixture was refluxed under nitrogen overnight. To the reaction mixture were added H₂O and AcOEt. The organic layer was concentrated. The residue was triturated in IPE. The solid was collected to obtain the object compound (713.7 mg).

[0262] Reference Example 142. Synthesis of

6-(1-cyclopropyl-1H-pyrazol-4-yl)-3-(piperidin-4-yl)pyrazolo[1,5-a]pyridine

To a solution of tert-butyl

4-(6-(1-cyclopropyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (472 mg) in DCM (10 mL) was added TFA (1 mL) at room temperature. The mixture was stirred for 5 h and concentrated (azeotroped with toluene). The residue was purified by basic-silica gel column chromatography AcOEt/MeOH to obtain the

object compound (322 mg).

[0263] Reference Example 143. Synthesis of tert-butyl

4-(6-(1-cyclopropyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

A mixture of tert-butyl 4-(6-(1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (770 mg), cyclopropyl bromide (1.3 ml) and Cs_2CO_3 (3414 mg) in DMF (15 mL) was stirred at 180 °C in a microwave oven for 3 h. The mixture was diluted with H_2O , combined and extracted with AcOEt. The water layer was extracted with DCM. The organic layer was concentrated. The residue was purified by basic-silica gel column chromatography (hexane/AcOEt/MeOH) to obtain the object compound (472mg).

[0264] Reference Example 144. Synthesis of tert-butyl

4-(6-(1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a suspension of tert-butyl 4-(6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (697 mg, 1.544 mmol) in MeOH (20 mL) was added p-TsOH · H_2O (587 mg, 3.09 mmol) at room temperature. The mixture was stirred for 3 h. The mixture was diluted with sat. NaHCO_3 aq. and extracted with DCM. The organic layer was concentrated. The residue was purified by basic-silica gel column chromatography (AcOEt/MeOH) to obtain the object compound (507 mg).

[0265] Reference Example 145. Synthesis of rac-tert-butyl

4-(6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

A mixture of rac-tert-butyl 4-(6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (2.329 g) and 10% Pd/C (wet) (2g) in EtOH (100 mL) was stirred at 50°C under hydrogen for 12 h. The mixture was diluted with AcOEt, filtered through Celite and washed with AcOEt and DCM. The filtrate was concentrated. The residue was purified by basic-silica gel column chromatography (hexane/AcOEt) to obtain the object compound (2.08 g).

[0266] Reference Example 146. Synthesis of rac-tert-butyl

4-(6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate

A mixture of rac-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1500 mg), 3-chloro-6-bromo-pyrazolo[1,5-a]pyridine (1 g), $\text{PdCl}_2(\text{dppf}) \cdot \text{DCM}$ (353 mg) and K_3PO_4 (2751 mg, 12.96 mmol) in 1,4-dioxane/ H_2O (9/1) (30 ml) was stirred at 80°C under nitrogen for 2 h. To the mixture were added AcOE and Si-silica

gel. The mixture was stirred for 2 h and filtered through Celite. The filtrate was concentrated to obtain the intermediate (2.5 g). A mixture of the intermediate, 3,6-dihydro-2H-pyridine-1-tert-butoxycarbonyl-4-boronic acid, pinacol ester (2 g), Pd(OAc)₂ (145 mg), SPhos (355 mg) and K₃PO₄ (2.8 g) in DME/H₂O (9/1) (50 mL) was stirred at 80°C under nitrogen overnight. To the mixture were added 3,6-dihydro-2H-pyridine-1-tert-butoxycarbonyl-4-boronic acid, pinacol ester (1 g), Pd(OAc)₂ (145 mg), SPhos (355 mg) and K₃PO₄ (1.8 g) at room temperature. The mixture was stirred at 80°C under nitrogen for 4 h. The reaction mixture was diluted with H₂O and AcOEt, and filtered through Celite. The organic layer was concentrated. Celite was washed with DCM. The filtrate was concentrated. The residues were combined and purified by silica gel column chromatography (hexane/AcOEt) to obtain the object compound (1.86 g).

[0267] Reference Example 167. Synthesis of

6-(3-(piperidin-4-yl)pyrazolo[1,5-a]pyridin-6-yl)-2-oxa-6-azaspiro[3.3]heptane

To a solution of tert-butyl 4-(6-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (334 mg) in DCM (4 mL) was added TFA (1.0 mL), and then the mixture was stirred at room temperature for 1 h. 1 mol/L NaOH aq. was added to the mixture at 0°C for the basification. The mixture was extracted with DCM. The organic layer was concentrated to obtain the object compound (243 mg).

[0268] Reference Example 168. Synthesis of tert-butyl

4-(6-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

A mixture of tert-butyl 4-(6-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (792 mg) and Pd/C (5% w/w, wet, type NX, 231 mg) in EtOH (50 mL) was stirred at 40°C under hydrogen for 7.5 h. The mixture was filtered through Celite, and the filtrate was concentrated. The residue was purified by basic-silica gel column chromatography (heptane/AcOEt) to obtain the object compound (378 mg).

[0269] Reference Example 169. Synthesis of tert-butyl

4-(6-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate

To a mixture of 6-(3-chloropyrazolo[1,5-a]pyridin-6-yl)-2-oxa-6-azaspiro[3.3]heptane (2.81 g) in DME/H₂O (10:1) (55 mL) were added 3,6-dihydro-2H-pyridine-1-tert-butoxycarbonyl-4-boronic acid, pinacol ester (6.96 g), Pd(OAc)₂ (126 mg), SPhos (462 mg) and K₃PO₄ (7.17 g). The mixture was stirred at 90

°C for overnight under an argon atmosphere. The reaction mixture was cooled to room temperature, and AcOEt and H₂O were added thereto. The mixture was filtered through Celite. The organic layer was washed with brine and concentrated to obtain the object compound (3.36 g).

[0270] Reference Example 170. Synthesis of

6-(3-chloropyrazolo[1,5-a]pyridin-6-yl)-2-oxa-6-azaspiro[3.3]heptane

A mixture of 2-oxa-6-azaspiro[3.3]heptane (4.0 g), 6-bromo-3-chloropyrazolo[1,5-a]pyridine (4.26 g), Pd(OAc)₂ (0.413 g), BINAP (1.719 g) and Cs₂CO₃ (17.99 g) in toluene (180 mL) was stirred under nitrogen at 100°C for overnight. The mixture was diluted with H₂O, AcOEt and filtered through Celite. The filtrate was extracted with AcOEt. The organic layer was concentrated. The residue was dissolved with DCM and stirred with NH-silica for 1h. The mixture was filtered through Celite. The filtrate was concentrated. The residue was triturated with AcOEt/IPE (=1/1, 30 mL) to obtain the object compound (3.48 g).

[0271] Reference Example 171. Synthesis of

6-(1-cyclopropyl-1H-pyrazol-4-yl)-3-(piperidin-4-yl)pyrazolo[1,5-a]pyrimidine

To a solution of tert-butyl 4-(6-(1-cyclopropyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate (619 mg) in DCM (15 mL) was added TFA (1.5 mL) at room temperature. The mixture was stirred for 2 h. The reaction mixture was concentrated and co-evaporated with toluene. The residue was purified by basic-silica gel column chromatography (AcOEt/MeOH) to obtain the object compound (435 mg).

[0272] Reference Example 172. Synthesis of tert-butyl

4-(6-(1-cyclopropyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

A mixture of cyclopropyl bromide (1.2 ml), tert-butyl 4-(6-(1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate (734 mg) and Cs₂CO₃ (1947 mg) in DMF (10 mL) was stirred at 180°C in microwave oven for 1 h. The reaction mixture was diluted with H₂O and extracted with AcOEt. The organic layer was dried concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt) to obtain the object compound (440 mg).

[0273] Reference Example 173. Synthesis of tert-butyl

4-(6-(1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

To a suspension of tert-butyl 4-(6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate (1253 mg) in MeOH (50 mL) was added p-toluenesulfonic acid monohydrate (1053 mg) at room temperature. The mixture was stirred for 3 h. The reaction mixture was diluted with sat.NaHCO₃ aq. and extracted with DCM. The

organic layer was concentrated. The residue was triturated with IPE (10mL) to obtain the object compound (889 mg).

- [0274] Reference Example 174. Synthesis of rac-tert-butyl 4-(6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

A mixture of rac-tert-butyl 4-(6-(((trifluoromethyl)sulfonyl)oxy)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate (1.5 g), 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.667 g), PdCl₂(dppf) · DCM (0.136 g) and K₃PO₄ (2.121 g) in DME/H₂O (9/1) (40 mL) was stirred at 80°C under nitrogen for 4 h. The mixture was diluted with H₂O and extracted with AcOEt. The organic layer was concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt) to obtain the object compound (1.383 g).

- [0275] Reference Example 175. Synthesis of (3aR,6aS)-5-(3-(piperidin-4-yl)pyrazolo[1,5-a]pyridin-6-yl)hexahydro-1H-furo[3,4-c]pyrrole

To a solution of tert-butyl 4-(6-((3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (310 mg) in DCM (10 mL), TFA (1 mL) was added at 0°C. The mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated. The residue was purified by basic-silica gel chromatography (MeOH/DCM) to obtain the object compound (230 mg).

- [0276] Reference Example 176. Synthesis of tert-butyl 4-(6-((3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a solution of tert-butyl 4-(6-((3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)pyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (518 mg) in EtOH (20 mL), 5% Pd/C, wet (type NX) (232 mg) was added at room temperature. The mixture was stirred at 60°C under hydrogen for 3.5 h. The reaction mixture was allowed to cool to room temperature and filtered through Celite and concentrated. The residue was purified by silica gel chromatography (heptane/AcOE) to obtain the object compound (310 mg).

- [0277] Reference Example 177. Synthesis of tert-butyl 4-(6-((3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)pyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate

A mixture of (3aR,6aS)-5-(3-chloropyrazolo[1,5-a]pyridin-6-yl)hexahydro-1H-furo[3,4-c]pyrrole

(389 mg), 6-dihydro-2H-pyridine-1-tert-butoxycarbonyl-4-boronic acid, pinacol ester (912 mg), Pd(OAc)₂ (33.1 mg), SPhos (121 mg) and K₃PO₄ (939 mg) in DME/H₂O (10:1) (22 mL) was stirred at 90°C under argon overnight. After cooling to room temperature, H₂O and AcOEt were added to the reaction mixture. The mixture was filtered through Celite. The organic layer was washed with brine and concentrated. The residue was purified by silica gel chromatography (heptane/AcOEt) to obtain the object compound (518 mg).

[0278] Reference Example 178. Synthesis of

(3aR,6aS)-5-(3-chloropyrazolo[1,5-a]pyridin-6-yl)hexahydro-1H-furo[3,4-c]pyrrole

A mixture of cis-hexahydro-1H-furo[3,4-c]pyrrole (528 mg), 3-chloro-6-bromo-pyrazolo[1,5-a]pyridine (900 mg), Pd(OAc)₂ (52.4 mg), BINAP (218 mg) and Cs₂CO₃ (6.334 g) in toluene (20 mL) was stirred at 100°C under Ar for 7 h. After cooling to room temperature, H₂O and AcOEt were added to the reaction mixture. The organic layer was washed with brine and concentrated. The residue was purified by basic-silica gel chromatography (heptane/AcOEt) to obtain the object compound (389 mg).

[0279] Reference Example 180. Synthesis of cyclopropyl

4-(6-(((trifluoromethyl)sulfonyl)oxy)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

To a solution of tert-butyl 4-(6-(((trifluoromethyl)sulfonyl)oxy)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate (400 mg) in DCM (12 mL) was added TFA (0.8 mL) at 0°C. The mixture was stirred at room temperature for 5 h. The mixture was concentrated, co-evaporated with toluene to obtain the intermediate (TFA salt). To a solution of the intermediate in DCM (12 mL) were added TEA (0.743 mL) and cyclopropyl(4-nitrophenyl)carbonate (238 mg) at room temperature. The mixture was stirred for 3 h. The mixture was concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt) to obtain the object compound (364 mg).

[0280] Reference Example 183. Synthesis of

6-(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)-3-(piperidin-4-yl)pyrazolo[1,5-a]pyridine

To a solution of tert-butyl 4-(6-(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (517 mg) in DCM (10 mL), TFA (2 mL) was added at 0°C. The mixture was stirred at room temperature for 2 h. After cooled to 0°C, 5mol/L NaOH aq. was added. The water layer was extracted with DCM. The organic layer was concentrated to obtain the object compound (414 mg).

[0281] Reference Example 184. Synthesis of tert-butyl

4-(6-(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1

-carboxylate

To a solution of tert-butyl

4-(6-(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)pyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydro pyridine-1(2H)-carboxylate (704 mg) in EtOH/DCM (1:1) (30 mL), 5% Pd/C (304 mg) was added at room temperature. The mixture was stirred at 40°C for 1.5 h. After cooled, the reaction mixture was filtered through Celite. The filtrate was concentrated. The residue was purified by basic-silica gel chromatography (heptane/AcOEt) to obtain the object compound (517 mg).

[0282] Reference Example 185. Synthesis of tert-butyl

4-(6-(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)pyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydro pyridine-1(2H)-carboxylate

A mixture of

3-chloro-6-(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)pyrazolo[1,5-a]pyridine (509 mg), 3,6-dihydro-2H-pyridine-1-tert-butoxycarbonyl-4-boronic acid, pinacol ester (1110 mg), Pd(OAc)₂ (20.14 mg), SPhos (73.7 mg) and K₃PO₄ (1142 mg) in DME/H₂O (10:1) (20 mL) was stirred at 90°C under Argon overnight. After cooled to room temperature, H₂O and AcOEt were added. The mixture was filtered through Celite. The organic layer was washed with brine and concentrated. The residue was purified by silica gel chromatography twice (1st: basic-silica, heptane/AcOEt, 2nd: diol-silica, heptane/AcOEt) to obtain the object compound (704 mg).

[0283] Reference Example 186. Synthesis of

3-chloro-6-(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)pyrazolo[1,5-a]pyridine

A mixture of 6,6-difluoro-2-aza-spiro[3.3]heptane trifluoroacetate (0.927 g), 3-chloro-6-bromo-pyrazolo[1,5-a]pyridine (0.579 g), Pd(OAc)₂ (0.034 g), BINAP (0.140 g) and Cs₂CO₃ (3.67 g) in toluene (10 mL) was stirred at 100°C for 24 h under argon. After cooled, H₂O and AcOEt were added at room temperature. The mixture was filtered through Celite. The organic layer was washed with brine and concentrated. The residue was purified by silica gel chromatography (heptane/AcOEt) to obtain the object compound (509 mg).

[0284] Reference Example 194. Synthesis of tert-butyl

6-(5-bromothiazol-2-yl)-2,6-diazaspiro[3.3]heptane-2-carboxylate

To a solution of 2,5-dibromothiazole (1.0684 g) in DMSO (15 mL) under nitrogen, DIPEA (1.5 mL) and 1,1-dimethylethyl 2,6-diazaspiro[3.3]heptane-2-carboxylate (978.7 mg) were added at room temperature. The mixture was stirred at 70°C under nitrogen overnight. AcOEt and H₂O were added at room temperature. The mixture was extracted with AcOEt. The organic layer was concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt) to obtain the object compound (1.2328 g).

[0285] Reference Example 213. Synthesis of5-(pyrazolo[1,5-a]pyridin-6-yl)-1,2,4-thiadiazole

The mixture of 6-bromopyrazolo[1,5-a]pyridine (500 mg), bis(pinacolato)diboron (967 mg), potassium acetate (747 mg) and PdCl₂(dppf) · DCM (104 mg) in 1,4-Dioxane (10 ml) was stirred at 100°C under N₂ for 2 h. The mixture was diluted with AcOEt and filtered. Filtrate was concentrated to give the intermediate boronic acid ester. The mixture of the intermediate boronic acid ester, Pd(OAc)₂ (57.0 mg), xantphos (147 mg), K₂CO₃ (701 mg) and 5-bromo-1,2,4-thiadiazole (279 µl) in 1,4-Dioxane/H₂O (10 ml)(9/1) was stirred at 100°C under nitrogen for 2 h. To the mixture were added AcOEt and Na₂SO₄. The mixture was filtered through a pad of celite. The filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt) to obtain the object compound (352 mg).

[0286] Reference Example 216. Synthesis of5-(3-(piperidin-4-yl)pyrazolo[1,5-a]pyrimidin-6-yl)thiazole

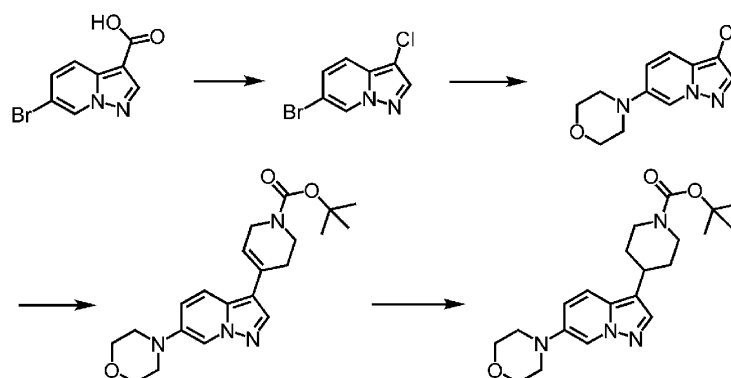
To a solution of tert-butyl 4-(6-(thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate (411 mg) in DCM (12 mL) was added TFA (1.5 ml) at 0°C. The mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated and co-evaporated with DCM. The residue was cooled to 0°C, basified by addition of 1 mol/L NaOH aq. and extracted with DCM. The organic layer was concentrated and purified by basic-silica gel column chromatography (AcOEt/MeOH) to obtain the object compound (180 mg).

[0287] Reference Example 217. Synthesis of tert-butyl4-(6-(thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

The mixture of tert-butyl 4-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate (0.475 g), 5-bromo-1,3-thiazole (0.119 mL), Pd(OAc)₂ (0.012 g), Xantphos (0.032 g) and K₂CO₃ (0.460 g) in dioxane/H₂O (6/1) (10 ml) was stirred at 100°C under nitrogen for 2 h. The reaction mixture was diluted with AcOEt. To the mixture was added Na₂SO₄. The mixture was filtered through a pad of celite and washed with AcOEt. The filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt) to obtain the object compound (411 mg).

[0288] Reference Example 222. Synthesis of tert-butyl4-[6-(morpholin-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperidine-1-carboxylate

[Chem.33]



Step 1: synthesis of 6-bromo-3-chloropyrazolo[1,5-a]pyridine.

A suspension of 6-bromopyrazolo[1,5-a]pyridine-3-carboxylic acid (5.0 g), N-chlorosuccinimide (4.2 g) and NaHCO_3 (7.0 g) in DMF (70 mL) was stirred at 50°C for 4 hours. The reaction was partitioned between AcOEt and brine. The organic layer was concentrated in vacuo to give the desired product (4.9 g) which was used in the next step without further purification.

^1H NMR (400 MHz, DMSO-d_6): 9.15 (dd, $J = 1.6, 0.9$ Hz, 1H), 8.20 (s, 1H), 7.64 (dd, $J = 9.4, 0.9$ Hz, 1H), 7.48 (dd, $J = 9.4, 1.6$ Hz, 1H).

[0289] Step 2: synthesis of 4-{3-chloropyrazolo[1,5-a]pyridin-6-yl}morpholine.

A suspension of 6-bromo-3-chloropyrazolo[1,5-a]pyridine (1.0 g), morpholine (0.38 mL), Pd_2dba_3 (210 mg), sodium tert-butoxide (630 mg), DavePhos (130 mg) in toluene (20 mL) was stirred at 90°C for 4 hours. Further morpholine (0.1 mL) and Pd_2dba_3 (100 mg) were added and stirring was maintained at the same temperature overnight. The reaction mixture was filtered through Celite and the residue was partitioned between AcOEt and water. The organic layer was concentrated in vacuo and the residue was recrystallised from acetone to give the desired product (522 mg).

LCMS: $[\text{M}+\text{H}]^+ = 238$

[0290] Step 3: synthesis of tert-butyl

4-[6-(morpholin-4-yl)pyrazolo[1,5-a]pyridin-3-yl]-1,2,3,6-tetrahydropyridine-1-carboxylate.

A suspension of 4-{3-chloropyrazolo[1,5-a]pyridin-6-yl}morpholine (42 mg), {1-[(tert-butoxy)carbonyl]-1,2,3,6-tetrahydropyridin-4-yl}boronic acid (60 mg), $\text{Pd}(\text{OAc})_2$ (2 mg), SPhos (7 mg), K_3PO_4 (75 mg) in dioxane (5 mL) and water (0.25 mL) was stirred at reflux for 4 hours. The reaction mixture was filtered through Celite. The filtrate was partitioned between AcOEt and water. The organic phase was concentrated in vacuo and the residues was purified by column chromatography (SiO_2 , AcOEt:MeOH) to give 40 mg of the desired product.

LCMS: $[M+H]^+ = 385$

[0291] Step 4: synthesis of tert-butyl

4-[6-(morpholin-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperidine-1-carboxylate.

As suspension of tert-butyl

4-[6-(morpholin-4-yl)pyrazolo[1,5-a]pyridin-3-yl]-1,2,3,6-tetrahydropyridine-1-carboxylate (40 mg) and Pd/C (10%, 20 mg) in THF (1 mL) and MeOH (1 mL) was stirred under H_2 at room temperature for 6 hours. The reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (SiO_2 , AcOEt) to give 5 mg of the desired product.

LCMS: $[M+H]^+ = 387$.

[0292] Reference Example 224. Synthesis of

4-(3-chloropyrazolo[1,5-a]pyridin-6-yl)morpholine

To a solution of 6-bromo-3-chloropyrazolo[1,5-a]pyridine (562.2 mg) in toluene (20 mL) under nitrogen, $Pd_2(dba)_3$ (115.9 mg), BrettPhos (199.2 mg), NaOtBu (377.3 mg) and morpholine (253 μ L) were added at room temperature. The mixture was refluxed for 3 h 35 min. H_2O and AcOEt were added at room temperature. The organic layer was concentrated. The residue was purified by basic-silica gel column chromatography (hexane/AcOEt) to obtain the object compound (317.8 mg).

[0293] Reference Example 235. Synthesis of tert-butyl

4-(6-cyclopropylpyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

To a solution of tert-butyl

4-(6-(((trifluoromethyl)sulfonyl)oxy)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate (75 mg), potassium cyclopropyltrifluoroborate (49.3 mg) and Cs_2CO_3 (163 mg) in toluene/ H_2O (10:1) (5 mL) under argon, $Pd(OAc)_2$ (7.48 mg) and cataCXium(R) (23.88 mg) were added at room temperature. The mixture was stirred at 130°C under argon for 2 h. H_2O was added at room temperature. The mixture was extracted with AcOEt. The organic layer was concentrated. The residue was purified by silica gel column chromatography (heptane/AcOEt) to obtain the object compound (43 mg).

[0294] Reference Example 242. Synthesis of

6-(1-methyl-1H-pyrazol-4-yl)-3-(piperidin-4-yl)pyrazolo[1,5-a]pyridine

To a suspension of 3-chloro-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (635.7 mg) and

1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (2.7 g) in dioxane/ H_2O (33 mL) (10/1) under nitrogen, $Pd(OAc)_2$ (123.9 mg), SPhos (490.2 mg) and K_3PO_4 (3.9 g) were added at room temperature. The mixture was refluxed under nitrogen overnight. H_2O and AcOEt were added at room temperature. The mixture was extracted with AcOEt. The organic layer was concentrated. The residue was purified by basic-silica gel column chromatography

(Hexane/AcOEt) to obtain the intermediate compound (1.2291 g). To a solution of the intermediate compound in EtOH (100 mL), Pd/C (1.27 g) (10%, type NX wetted with water) was added at room temperature. The mixture was stirred at 50°C for 2.5 h under hydrogen. The mixture was filtered through Celite and the filtrate was concentrated to obtain the intermediate compound. To a solution of intermediate compound in DCM (20 mL), TFA (4 mL) was added at room temperature. The mixture was stirred at room temperature for 8 h 20 min. The mixture was concentrated. The residue was treated with 1N NaOH aq. The mixture was extracted with AcOEt and DCM. The organic layer was concentrated. The residue was purified by basic-silica gel column chromatography (AcOEt/MeOH) to obtain the object compound (295.6 mg).

[0295] Reference Example 244. Synthesis of tert-butyl

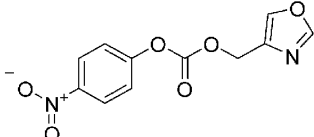
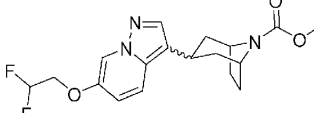
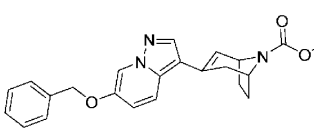
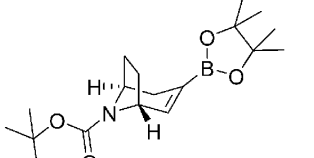
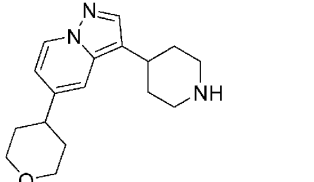
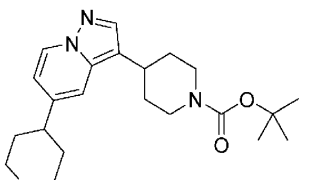
4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate

To a solution of 6-bromo-3-iodopyrazolo[1,5-a]pyridine (1.2042 g) and N-Boc-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester (1.1960 g) in dioxane/H₂O (22 mL) (10/1) under nitrogen, K₃PO₄ (1.24 g) and Pd(PPh₃)₄ (216 mg) were added at room temperature. The mixture was stirred at 50 to 100°C for 5 h 20 min. H₂O and AcOEt were added at room temperature. The mixture was extracted with AcOEt. The organic layer was concentrated. The residue was purified by silica gel and basic-silica gel column chromatography (Hexane/AcOEt) to obtain the intermediate compound (243.2 mg). To a solution of the intermediate (243.2 mg) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (400.5 mg) in dioxane/H₂O (11 mL) (10/1) under nitrogen, K₃PO₄ (798.6 mg) and PdCl₂(dppf) · DCM (45 mg) were added at room temperature. The mixture was refluxed for 4 h. H₂O and AcOEt were added at room temperature. The mixture was extracted with AcOEt. The organic layer was concentrated. The residue was purified by silica gel column chromatography (Hexane/AcOEt) and basic-silica gel chromatography (Hexane/AcOEt) to obtain the object compound (113.3 mg).

[0296] The compounds of Reference Examples were manufactured in the same manner as in any of the above Reference Examples. Structural formulae and physicochemical data of the compounds of Reference Examples 1 to 244 are shown in the following table.

[0297]

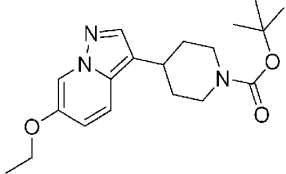
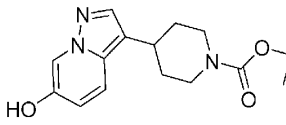
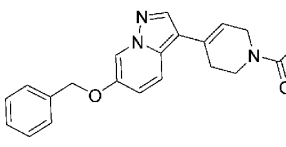
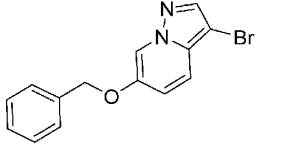
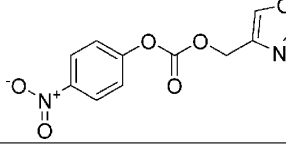
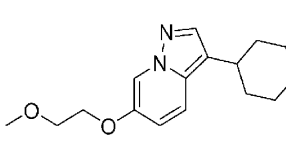
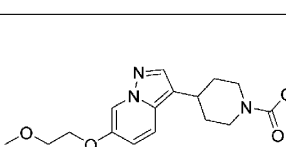
[Table 2-1]

REX	STR	RProp	Physicochemical Data
1		1	NMR2: 5.27 (2H, s), 7.36–7.43 (2H, m), 7.82 (1H, d, J=0.9 Hz), 7.94 (1H, d, J=0.9 Hz), 8.25–8.32 (2H, m). M+H: 265.1
2		2	M+H:405
3		7	NMR2: 1.45 (9H, s), 1.76 (1H, s), 1.95–2.07 (2H, m), 2.26 (2H, d, J=16.7 Hz), 3.00–3.30 (1H, brm), 4.50 (2H, s), 5.05 (2H, s), 6.28 (1H, s), 7.02 (1H, dd, J=9.7, 2.2 Hz), 7.30–7.47 (5H, m), 7.60 (1H, d, J=9.7 Hz), 7.78 (1H, s), 8.08 (1H, d, J=2.2 Hz).
4		4	NMR2: 1.24 (12H, s), 1.44 (9H, s), 1.57–1.66 (1H, m), 1.87–1.96 (3H, m), 2.12 (1H, brs), 2.77 (1H, brs), 4.35 (2H, brs), 6.75 (1H, brs).
5		5	NMR2: 1.66–1.98 (8H, m), 2.80 (3H, qd, J=11.6, 3.8 Hz), 2.89 (1H, tt, J=12.0, 3.8 Hz), 3.22 (2H, dt, J=12.4, 3.2 Hz), 3.49–3.61 (2H, m), 4.11 (2H, dt, J=11.5, 3.4 Hz), 6.59 (1H, dd, J=7.3, 2.0 Hz), 7.27 (1H, s), 7.78 (1H, s), 8.35 (1H, d, J=7.3 Hz). M+H: 286.3
6		6	NMR2: 1.50 (9H, s), 1.62 - 1.64(1H, m), 1.66 - 1.76 (2H, m), 1.83 (3H, td, J=9.5, 3.6 Hz), 1.84–2.00 (2H, m), 2.75–2.94 (4H, m), 3.50–3.61 (2H, m), 4.11 (2H, dt, J=11.5, 3.4 Hz), 4.25 (2H, s), 6.61 (1H, dd, J=7.2, 1.9 Hz), 7.24 (1H, d, J=1.9 Hz), 7.75 (1H, s), 8.35 (1H, d, J=7.2 Hz). M+H: 386.3

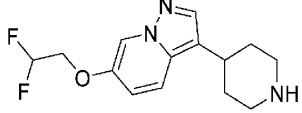
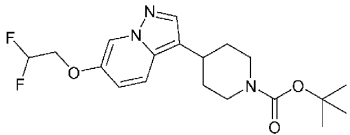
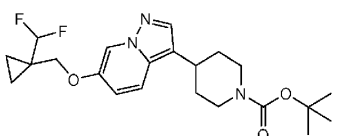
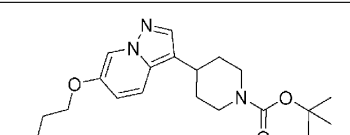
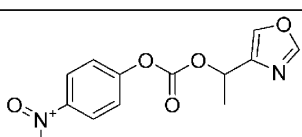
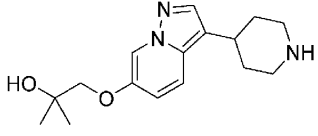
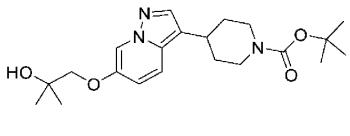
[Table 2-2]

7		7	NMR2: 1.51 (9H, s), 2.52 – 2.60 (4H, m), 3.68 (2H, t, J=5.7 Hz), 3.97 (2H, t, J=5.5 Hz), 4.14 (2H, s), 4.38 (2H, q, J=2.8 Hz), 5.95 (1H, s), 6.30 (1H, tt, J=3.1, 1.6 Hz), 6.88 (1H, dd, J=7.4, 2.0 Hz), 7.53 – 7.59 (1H, m), 7.90 (1H, s), 8.35 (1H, dd, J=7.4, 0.9 Hz). M+H: 382.3
8		8	NMR2: 1.50 (9H, s), 2.56 (2H, s), 3.70 (2H, t, J=6.0 Hz), 4.11 (2H, d, J=3.1 Hz), 5.94 (1H, s), 6.86 (1H, dd, J=7.4, 2.1 Hz), 7.85 (1H, dd, J=2.1, 0.8 Hz), 7.91 (1H, s), 8.29 (1H, dd, J=7.4, 0.8 Hz). M-tBu+2H: 322.1, 324.1, M+H: 378.2, 380.2
9		5	NMR2: 1.64–1.78 (2H, m), 1.87–1.97 (2H, m), 2.72–2.87 (3H, m), 3.21 (2H, dt, J=12.4, 3.4 Hz), 3.86 (3H, s), 6.40 (1H, dd, J=7.6, 2.6 Hz), 6.64 (1H, dd, J=2.7, 0.7 Hz), 7.72 (1H, s), 8.23 (1H, dd, J=7.5, 0.7 Hz). M+H: 232.2
10		10	NMR2: 1.49 (9H, s), 1.56–1.74 (2H, m), 1.91 (2H, d, J=13.1 Hz), 2.79–2.90 (3H, m), 3.87 (3H, s), 4.24 (2H, s), 6.42 (1H, dd, J=7.6, 2.7 Hz), 6.60 (1H, d, J=2.7 Hz), 7.70 (1H, s), 8.23 (1H, d, J=7.6 Hz). M+H: 332.3
11		6	NMR2: 1.50 (9H, s), 1.63 (2H, brs), 1.91 (2H, s), 2.77 (1H, tt, J=12.4, 3.6 Hz), 2.86 (2H, s), 4.22 (2H, s), 6.46 (1H, d, J=7.5 Hz), 6.68 (1H, d, J=2.5 Hz), 7.67 (1H, s), 8.24 (1H, d, J=7.5 Hz). M-tBu+2H: 262.2, M+H: 318.44
12		7	NMR2: 1.51 (9H, s), 2.55 (2H, s), 3.67 (2H, t, J=5.7 Hz), 4.11 (2H, s), 5.11 (2H, s), 5.81 (1H, s), 6.54 (1H, dd, J=7.6, 2.6 Hz), 6.96 (1H, d, J=2.6 Hz), 7.35–7.38 (1H, m), 7.41–7.47 (4H, m), 7.84 (1H, s), 8.27 (1H, d, J=7.6 Hz). M+H: 406.4
13		13	NMR2: 5.11 (2H, d, J=1.9 Hz), 6.55–6.56 (1H, m), 6.77 (1H, d, J=2.6 Hz), 7.31–7.40 (1H, m), 7.37–7.49 (4H, m), 7.83 (1H, s), 8.26 (1H, d, J=7.5 Hz). M+H: 303.1, 305.2

[Table 2-3]

14		10	NMR2: 1.49 (9H, s), 1.60–1.72 (2H, m), 1.87–1.94 (2H, m), 2.87 (3H, tt, J=11.9, 3.1 Hz), 4.22 (2H, s), 6.89 (1H, dd, J=9.5, 1.9 Hz), 7.35 (1H, d, J=9.6 Hz), 7.64 (1H, s), 8.08 (2H, d, J=1.9 Hz). M+H: 346.3
15		6/15	NMR2: 1.49 (9H, s), 1.60–1.72 (2H, m), 1.87–1.94 (2H, m), 2.87 (3H, tt, J=11.9, 3.1 Hz), 4.22 (2H, s), 6.89 (1H, dd, J=9.5, 1.9 Hz), 7.35 (1H, d, J=9.6 Hz), 7.64 (1H, s), 8.08 (2H, d, J=1.9 Hz).
16		7/16	NMR2: 1.50 (9H, s), 2.57 (2H, brs), 3.67 (2H, t, J=5.6 Hz), 4.10 (2H, brs), 5.06 (2H, s), 5.93 (1H, brs), 7.03 (1H, dd, J=9.7, 2.2 Hz), 7.32–7.41 (1H, m), 7.38–7.48 (4H, m), 7.60 (1H, d, J=9.6 Hz), 7.82 (1H, s), 8.09 (1H, d, J=2.2 Hz).
17		13/17	NMR2: 5.06 (2H, s), 7.08 (1H, dd, J=9.6, 2.1 Hz), 7.33–7.47 (6H, m), 7.81 (1H, s), 8.08 (1H, d, J=2.1 Hz).
18		1	NMR2: 2.49 (3H, s), 5.19 (2H, s), 7.35–7.43 (2H, m), 7.66 (1H, s), 8.23–8.32 (2H, m).
19		5/19	NMR2: 1.64–1.76 (2H, m), 1.89–1.96 (2H, m), 2.73–2.90 (3H, m), 3.19 (2H, dt, J=12.4, 3.1 Hz), 3.47 (3H, s), 3.75–3.80 (2H, m), 4.07–4.13 (2H, m), 6.93 (1H, dd, J=9.6, 2.1 Hz), 7.39 (1H, dd, J=9.6, 0.8 Hz), 7.69 (1H, s), 8.04 (1H, d, J=2.1 Hz). M+H: 276.2
20		10/20	NMR2: 1.49 (9H, s), 1.63–1.74 (2H, m), 1.92 (2H, d, J=13.2 Hz), 2.83–2.93 (3H, m), 3.47 (3H, s), 3.75–3.80 (2H, m), 4.07–4.13 (2H, m), 4.23 (2H, brs), 6.94 (1H, dd, J=9.7, 2.2 Hz), 7.37 (1H, d, J=9.7 Hz), 7.67 (1H, s), 8.04 (1H, d, J=2.2 Hz) M+H: 376.4

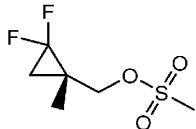
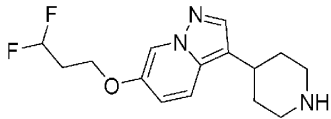
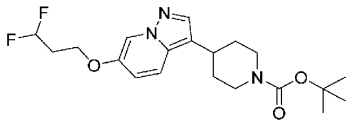
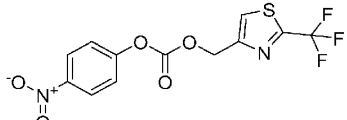
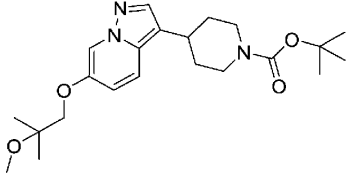
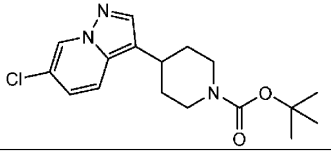
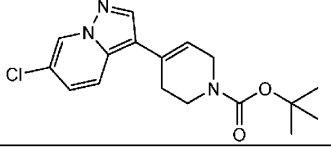
[Table 2-4]

21		5/21	NMR2: 1.65–1.77 (2H, m), 1.89–1.96 (2H, m), 2.73–2.82 (2H, m), 2.82–2.91 (1H, m), 3.20 (2H, dt, J=12.6, 3.4 Hz), 4.17 (2H, td, J=13.0, 4.0 Hz), 6.11 (1H, dd, J=54.9, 4.0 Hz), 6.91 (1H, dd, J=9.6, 2.3 Hz), 7.44 (1H, d, J=9.6 Hz), 7.73 (1H, s), 8.06 (1H, d, J=2.3 Hz).
22		10/22	NMR2: 1.49 (9H, s), 1.63–1.75 (2H, m), 1.92 (2H, d, J=13.2 Hz), 2.85–2.98 (3H, m), 4.13–4.25 (4H, m), 6.11 (1H, dd, J=54.9, 4.0 Hz), 6.93 (1H, dd, J=9.7, 2.2 Hz), 7.42 (1H, d, J=9.6 Hz), 7.71 (1H, s), 8.06 (1H, d, J=2.2 Hz).
23		10	NMR2: 0.74–0.84 (2H, m), 0.99–1.05 (2H, m), 1.49 (9H, s), 1.63 – 1.78 (2H, m), 1.92 (2H, d, J=13.3 Hz), 2.77–2.97 (3H, m), 3.96 (2H, s), 4.09–4.40 (2H, m), 5.98 (1H, t, J=57.7 Hz), 6.90 (1H, dd, J=9.6, 2.1 Hz), 7.38 (1H, d, J=9.7 Hz), 7.68 (1H, s), 7.99 (1H, d, J=2.3 Hz) M+H: 422
24		10	NMR2: 1.49 (9H, s), 1.61–1.75 (2H, m), 1.92 (2H, d, J=13.2 Hz), 2.60–2.72 (2H, m), 2.84–2.94 (3H, m), 4.18 (2H, d, J=6.3 Hz), 4.23 (2H, brs), 6.89 (1H, dd, J=9.6, 2.1 Hz), 7.40 (1H, d, J=9.6 Hz), 7.69 (1H, s), 8.03 (1H, d, J=2.1 Hz). M+H: 414.5
25		1	NMR2: 1.76 (3H, d, J = 6.6 Hz), 5.90 (1H, q, J = 6.6 Hz), 7.35–7.43 (2H, m), 7.71–7.77 (1H, m), 7.91 (1H, s), 8.23–8.32 (2H, m).
26		5	NMR2: 1.37 (6H, s), 1.76–1.88 (2H, m), 1.98 (2H, d, J=13.4 Hz), 2.80–2.94 (3H, m), 3.28 (2H, d, J=12.2 Hz), 3.78 (2H, s), 6.93 (1H, dd, J=9.6, 2.1 Hz), 7.41 (1H, d, J=9.6 Hz), 7.71 (1H, s), 8.04 (1H, d, J=2.1 Hz). M+H: 290.3
27		27	NMR2: 1.37 (6H, s), 1.49 (s, 9H), 1.61–1.76 (2H, m), 1.92 (2H, d, J=13.2 Hz), 2.14 (1H, s), 2.84–2.95 (3H, m), 3.78 (2H, s), 4.23 (2H, s), 6.93 (1H, dd, J=9.6, 2.1 Hz), 7.39 (1H, dd, J=9.7, 0.8 Hz), 7.68 (1H, s), 8.03 (1H, d, J=2.1 Hz). M+H: 390.4

[Table 2-5]

28		10	NMR2: 1.49 (9H, s), 1.62–1.74 (2H, m), 1.91 (2H, d, J=13.1 Hz), 2.84–2.94 (3H, m), 3.83 (3H, s), 4.23 (2H, s), 4.62 (2H, s), 6.98 (1H, dd, J=9.7, 2.2 Hz), 7.41 (1H, d, J=9.7 Hz), 7.69 (1H, s), 8.02 (1H, d, J=2.2 Hz). M+H: 390.4
29		5	NMR2: 1.69–1.81 (2H, m), 1.92–1.96 (2H, m), 1.99–2.03 (2H, m), 2.21–2.31 (2H, m), 2.27–2.41 (1H, m), 2.67–2.92 (5H, m), 3.19–3.26 (2H, m), 3.93 (2H, t, J=6.0 Hz), 6.83 (1H, dd, J=9.6, 2.1 Hz), 7.40 (1H, dd, J=9.6, 0.8 Hz), 7.69 (1H, s), 7.99 (1H, d, J=2.1 Hz). M+H: 336.1
30		10	NMR2: 1.49 (6H, s), 1.63–1.74 (2H, m), 1.90–1.93 (2H, m), 1.98–2.06 (2H, m), 2.21–2.39 (3H, m), 2.68–2.80 (2H, m), 2.83–2.93 (3H, m), 3.93 (2H, t, J=6.0 Hz), 4.23 (2H, s), 6.85 (1H, dd, J=9.6, 2.3 Hz), 7.37 (1H, d, J=9.6 Hz), 7.67 (1H, s), 7.98 (1H, d, J=2.3 Hz). M+H: 436.4
31		31	NMR2: 1.49 (9H, s), 1.64–1.76 (2H, m), 1.88–1.94 (2H, m), 2.78–3.02 (3H, m), 4.17–4.36 (2H, m), 7.13 (1H, dd, J=9.3, 1.5 Hz), 7.54–7.59 (1H, m), 7.98 (1H, s), 8.79–8.83 (1H, m). M-tBu+2H: 271
32		10	NMR2: 0.88–1.00 (2H, m), 1.15–1.24 (2H, m), 1.49 (9H, s), 1.63–1.74 (2H, m), 1.85–2.00 (2H, m), 2.73–2.95 (3H, m), 4.04 (2H, s), 4.11–4.41 (2H, m), 6.91 (1H, dd, J=9.7, 2.1 Hz), 7.38 (1H, d, J=9.6 Hz), 7.68 (1H, s), 7.99 (1H, d, J=2.1 Hz). M+H: 440
33		10	NMR2: 1.18–1.29 (1H, m), 1.32–1.44 (4H, m), 1.49 (9H, s), 1.62–1.74 (2H, m), 1.86–1.99 (2H, m), 2.81–2.93 (3H, m), 3.84–3.90 (1H, m), 3.94–4.01 (1H, m), 4.10–4.37 (2H, m), 6.92 (1H, dd, J=9.6, 2.1 Hz), 7.38 (1H, d, J=9.8 Hz), 7.68 (1H, s), 8.00 (1H, d, J=2.1 Hz). M+H: 422

[Table 2-6]

34		34	NMR2: 1.18–1.28 (1H, m), 1.33–1.37 (3H, m), 1.38–1.46 (1H, m), 3.05 (3H, s), 4.14 (1H, dd, J=10.8, 1.8 Hz), 4.31 (1H, ddd, J=10.8, 2.6, 1.8 Hz).
35		5	NMR2: 1.48-1.63 (1H, m), 1.63-1.79 (2H, m), 1.87-1.99 (2H, m), 2.28-2.44 (2H, m), 2.70-2.95 (3H, m), 3.13-3.27 (2H, m), 4.11 (2H, t, J=6.0 Hz), 6.09 (1H, tt, J=56.5, 4.7 Hz), 6.85 (1H, dd, J=9.6, 2.1 Hz), 7.41 (1H, d, J=9.6 Hz), 7.71 (1H, s), 7.99-8.07 (1H, m).
36		10	NMR2: 1.49 (9H, s), 1.60-1.79 (2H, m), 1.82-2.00 (2H, m), 2.24-2.47 (2H, m), 2.73-2.99 (3H, m), 4.11 (2H, t, J=6.0 Hz), 4.15-4.44 (2H, m), 6.10 (1H, tt, J=56.5, 4.7 Hz), 6.87 (1H, dd, J=9.6, 2.1 Hz), 7.38 (1H, dd, J=9.6, 0.6 Hz), 7.68 (1H, s), 8.03 (1H, d, J=1.5 Hz).
37		1	NMR2: 5.47 (2H, d, J=0.7 Hz), 7.36-7.45 (2H, m), 7.70 (1H, s), 8.26-8.34 (2H, m).
38		10	NMR2: 1.32 (6H, s), 1.49 (9H, s), 1.68 (2H, s), 1.92 (2H, d, J=13.2 Hz), 2.83–2.93 (3H, m), 3.31 (3H, s), 3.80 (2H, s), 4.23 (2H, brs), 6.95 (1H, dd, J=9.7, 2.1 Hz), 7.37 (1H, d, J=9.7 Hz), 7.67 (1H, s), 8.03 (1H, d, J=2.1 Hz). M+H: 404.4
39		39	M+H: 336
40		7	NMR2: 1.50 (9H, s), 2.57 (2H, s), 3.67 (2H, t, J=5.7 Hz), 4.07–4.16 (2H, m), 5.95 (1H, s), 7.11 (1H, dd, J=9.6, 1.8 Hz), 7.64 (1H, d, J=9.4 Hz), 7.92 (1H, s), 8.46–8.50 (1H, m). M+H: 334,336

[Table 2-7]

41		5	NMR2: 0.80-0.89 (2H, m), 1.16-1.30 (2H, m), 1.45-1.62 (1H, m), 1.62-1.79 (2H, m), 1.87-1.98 (2H, m), 2.72-2.92 (3H, m), 3.14-3.24 (2H, m), 4.19 (2H, d, J=20.8 Hz), 6.95 (1H, dd, J=9.6, 2.1 Hz), 7.42 (1H, dd, J=9.6, 0.7 Hz), 7.71 (1H, s), 8.05 (1H, dd, J=2.1, 0.6 Hz).
42		10	NMR2: 0.79-0.91 (2H, m), 1.17-1.29 (2H, m), 1.48 (9H, s), 1.58-1.78 (2H, m), 1.86-1.98 (2H, m), 2.79-2.96 (3H, m), 4.13-4.32 (4H, m), 6.93-7.00 (1H, m), 7.39 (1H, dd, J=9.6, 0.6 Hz), 7.68 (1H, s), 8.05 (1H, dd, J=2.1, 0.7 Hz).
43		5	NMR2: 1.65-1.77 (2H, m), 1.89-1.97 (2H, m), 2.73-2.83 (2H, m), 2.81-2.93 (1H, m), 3.19 (2H, dt, J=12.2, 3.2 Hz), 4.16 (2H, dd, J=5.8, 3.4 Hz), 4.22 (2H, dd, J=5.8, 3.4 Hz), 6.32 (1H, t, J=73.9 Hz), 6.91 (1H, dd, J=9.6, 2.1 Hz), 7.42 (1H, d, J=9.6 Hz), 7.71 (1H, s), 8.04 (1H, d, J=2.1 Hz). M+H: 312.3
44		10	NMR2: 1.49 (9H, s), 1.62-1.75 (2H, m), 1.91-1.95 (2H, m), 2.85-2.94 (3H, m), 4.16 (2H, dd, J=5.7, 3.5 Hz), 4.23 (4H, dd, J=5.7, 3.4 Hz), 6.32 (1H, d, J=73.9 Hz), 6.92 (1H, dd, J=9.6, 2.1 Hz), 7.39 (1H, d, J=9.6 Hz), 7.69 (1H, s), 8.04 (1H, d, J=2.1 Hz). M+H: 412.4
45		45	NMR2: 1.49 (9H, s), 1.63 - 1.74 (2H, m), 1.79 (3H, t, J=18.8 Hz), 1.92 (2H, d, J=13.2 Hz), 2.86 (2H, s), 2.90 (1H, ddt, J=12.0, 8.3, 3.7 Hz), 4.09 (2H, t, J=11.2 Hz), 4.23 (2H, s), 6.94 (1H, dd, J=9.7, 2.2 Hz), 7.41 (1H, d, J=9.7 Hz), 7.70 (1H, s), 8.06 (1H, d, J=2.2 Hz).
46		10	NMR2: 1.49 (9H, s), 1.58-1.75 (2H, m), 1.92 (2H, d, J=13.2 Hz), 2.31 (3H, s), 2.86 (2H, s), 2.89 (1H, ddt, J=12.0, 8.3, 3.7 Hz), 4.23 (2H, s), 4.54 (2H, s), 6.97 (1H, dd, J=9.6, 2.2 Hz), 7.42 (1H, d, J=9.6 Hz), 7.69 (1H, s), 7.97 (1H, d, J=2.2 Hz).
47		5	M+H: 330.4

[Table 2-8]

48		10	NMR2: 1.49 (9H, s), 1.61–1.76 (2H, m), 1.92 (2H, d, J=13.1 Hz), 2.80–2.95 (3H, m), 4.15–4.22 (4H, m), 4.29–4.36 (2H, m), 6.92 (1H, dd, J=9.6, 2.1 Hz), 7.40 (1H, d, J=9.6 Hz), 7.69 (1H, s), 8.04 (1H, d, J=2.1 Hz). M+H: 430.4
49		10	NMR2: 0.34–0.41 (2H, m), 0.63–0.73 (2H, m), 1.23–1.34 (1H, m), 1.49 (9H, s), 1.67–1.74 (2H, m), 1.92 (2H, d, J=13.1 Hz), 2.80–2.92 (3H, brm), 3.78 (2H, d, J=6.9 Hz), 4.23 (2H, s), 6.91 (1H, dd, J=9.7, 2.1 Hz), 7.37 (1H, d, J=9.7 Hz), 7.66 (1H, s), 7.98 (1H, d, J=2.1 Hz).
50		5	NMR2: 1.58–1.81 (3H, m), 1.87–2.00 (2H, m), 2.70–2.94 (3H, m), 3.15–3.26 (2H, m), 4.31 (2H, d, J=19.8 Hz), 4.66–4.79 (2H, m), 4.90 (2H, dd, J=18.9, 8.8 Hz), 6.92 (1H, dd, J=9.6, 2.2 Hz), 7.43 (1H, dd, J=9.6, 0.7 Hz), 7.72 (1H, s), 8.08 (1H, dd, J=2.2, 0.6 Hz).
51		10	NMR2: 1.49 (9H, s), 1.61–1.78 (2H, m), 1.85–1.98 (2H, m), 2.75–2.97 (3H, m), 4.14–4.39 (4H, m), 4.66–4.79 (2H, m), 4.90 (2H, dd, J=18.9, 8.8 Hz), 6.93 (1H, dd, J=9.6, 2.2 Hz), 7.40 (1H, dd, J=9.6, 0.6 Hz), 7.70 (1H, s), 8.09 (1H, dd, J=2.2, 0.6 Hz).
52		78	M+H: 443
53		6	NMR2: 1.49 (9H, s), 1.57–1.76 (3H, m), 1.88–1.95 (2H, m), 2.88 (3H, tt, J=12.0, 3.7 Hz), 3.13–3.25 (1H, m), 3.53–3.60 (2H, m), 3.80 (2H, t, J=8.1 Hz), 4.10 (2H, d, J=6.5 Hz), 4.19 (2H, d, J=42.2 Hz), 6.90 (1H, dd, J=9.6, 2.1 Hz), 7.37 (1H, d, J=9.6 Hz), 8.03 (1H, d, J=2.3 Hz) M+H: 387
54		10	NMR2: 1.49 (9H, s), 1.63–1.79 (2H, m), 1.88–1.95 (2H, m), 2.81–2.95 (3H, m), 2.98–3.14 (1H, m), 3.92 (2H, dd, J=8.9, 5.4 Hz), 4.02–4.12 (2H, m), 4.12–4.38 (4H, m), 5.12 (2H, s), 6.86 (1H, dd, J=9.7, 2.1 Hz), 7.27–7.41 (6H, m), 7.68 (1H, s), 7.99–8.04 (1H, m). M+H: 522

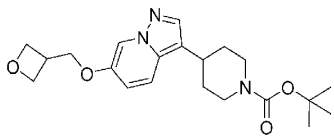
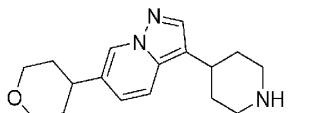
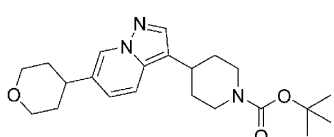
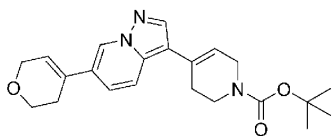
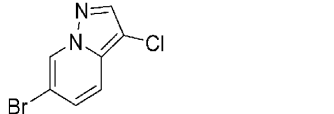
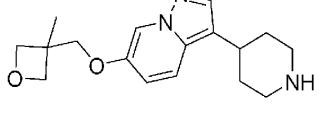
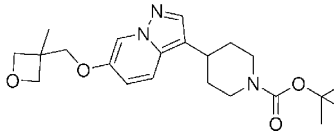
[Table 2-9]

55		55	NMR2: 2.45 (3H, s), 2.84–2.94 (1H, m), 3.63–3.75 (2H, m), 4.05 (2H, t, J=8.7 Hz), 4.14 (2H, d, J=6.8 Hz), 5.07 (2H, s), 7.26–7.42 (7H, m), 7.76–7.83 (2H, m) M+H: 376
56		6	NMR2: 1.49 (9H, s), 1.64–1.76 (2H, m), 1.92 (2H, d, J=13.2 Hz), 2.86 (2H, s), 2.91 (1H, tt, J=12.0, 3.7 Hz), 4.24 (2H, s), 6.99–7.06 (1H, m), 7.42–7.49 (1H, m), 7.77 (1H, s), 8.37 (1H, ddd, J=4.4, 2.2, 0.8 Hz).
57		7	NMR2: 1.50 (9H, s), 2.57 (2H, s), 3.68 (2H, t, J=5.6 Hz), 4.11 (2H, s), 5.95 (1H, s), 7.05–7.13 (1H, m), 7.64–7.71 (1H, m), 7.92 (1H, s), 8.38 (1H, ddd, J=4.3, 2.2, 0.8 Hz).
58		58	NMR2: 1.49 (9H, s), 1.62–1.74 (2H, m), 1.85–1.95 (2H, m), 2.70 (4H, t, J=12.2 Hz), 2.83–2.93 (5H, m), 3.40 (4H, s), 3.94 (2H, t, J=5.3 Hz), 4.21 (2H, brs), 6.89 (1H, dd, J=9.7, 2.1 Hz), 7.37 (1H, d, J=9.7 Hz), 7.67 (1H, s), 7.99 (1H, d, J=2.1 Hz).
59		59	NMR2: 1.49 (9H, s), 1.63–1.75 (2H, m), 1.92 (2H, d, J=13.1 Hz), 2.08 (1H, s), 2.84–2.94 (3H, m), 4.00 (2H, q, J=4.6 Hz), 4.07 (2H, t, J=4.6 Hz), 4.23 (2H, brs), 6.92 (1H, dd, J=9.6, 2.1 Hz), 7.39 (1H, d, J=9.6 Hz), 7.68 (1H, s), 8.05 (1H, d, J=2.1 Hz).
60		5	NMR2: 1.25–1.38 (1H, m), 1.54–1.78 (4H, m), 1.87–1.98 (2H, m), 2.02–2.18 (1H, m), 2.73–2.93 (3H, m), 3.15–3.24 (2H, m), 4.02 (2H, dt, J=7.4, 1.6 Hz), 6.89 (1H, dd, J=9.6, 2.2 Hz), 7.41 (1H, dd, J=9.6, 0.7 Hz), 7.70 (1H, s), 8.01 (1H, dd, J=2.1, 0.7 Hz).

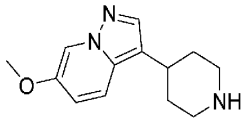
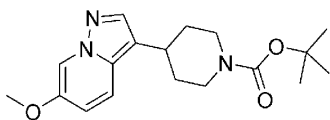
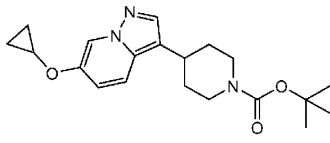
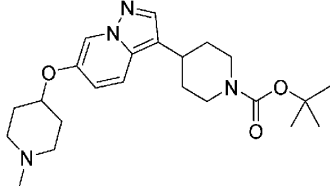
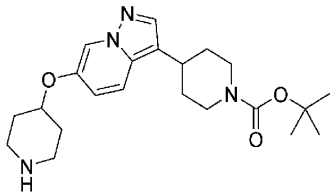
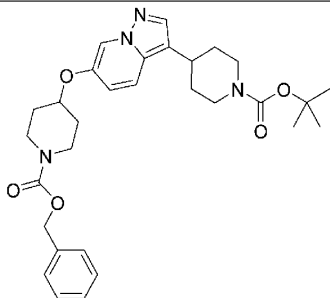
[Table 2-10]

61		10	NMR2: 1.21-1.39 (1H, m), 1.49 (9H, s), 1.57-1.79 (3H, m), 1.85-2.00 (2H, m), 2.01-2.20 (1H, m), 2.75-2.98 (3H, m), 4.02 (2H, d, J=7.3 Hz), 4.10-4.38 (2H, m), 6.90 (1H, dd, J=9.6, 2.2 Hz), 7.39 (1H, d, J=9.0 Hz), 7.68 (1H, s), 8.02 (1H, d, J=1.6 Hz).
62		10	NMR2: 1.49 (9H, s), 1.59-1.74 (4H, m), 1.86-1.95 (4H, m), 2.76-2.93 (3H, m), 3.00 (1H, t, J=3.2 Hz), 3.88 (2H, s), 4.20 (2H, s), 4.23 (2H, s), 6.95 (1H, dd, J=9.6, 2.1 Hz), 7.37 (1H, dd, J=9.6, 0.8 Hz), 7.67 (1H, s), 8.05 (1H, d, J=2.1 Hz).
63		10	NMR2: 1.48 (9H, s), 1.62-1.78 (4H, m), 1.88-1.95 (2H, m), 2.01 (2H, d, J=13.2 Hz), 2.89 (2H, s), 3.02 (1H, t, J=3.2 Hz), 3.05-3.15 (1H, m), 3.88 (2H, s), 4.20 (2H, brs), 4.24 (2H, s), 7.83 (1H, s), 8.27 (1H, d, J=2.7 Hz), 8.37 (1H, d, J=2.7 Hz).
64		78	NMR2: 1.49 (9H, s), 1.59-1.74 (2H, m), 1.91 (2H, d, J=13.2 Hz), 2.80-2.93 (3H, m), 3.30-3.36 (2H, m), 3.82-3.91 (3H, m), 4.23 (2H, s), 4.53-4.59 (2H, m), 4.70-4.76 (2H, m), 4.76-4.84 (1H, m), 6.86 (1H, dd, J=9.6, 2.1 Hz), 7.39 (1H, d, J=9.6 Hz), 7.68 (1H, s), 7.82 (1H, d, J=2.1 Hz).
65		6	NMR2: 1.49 (9H, s), 1.62-1.74 (2H, m), 1.91 (2H, d, J=13.2 Hz), 2.80-2.93 (3H, m), 3.78-3.85 (2H, m), 3.94-4.00 (2H, m), 4.22 (2H, s), 4.90-4.98 (1H, m), 6.86 (1H, dd, J=9.6, 2.1 Hz), 7.39 (1H, d, J=9.6 Hz), 7.67 (1H, s), 7.77 (1H, d, J=2.1 Hz).
66		10	NMR2: 1.49 (9H, s), 1.62-1.74 (2H, m), 1.91 (2H, d, J=13.1 Hz), 2.80-2.93 (3H, m), 4.08-4.16 (2H, m), 4.23 (2H, s), 4.38-4.45 (2H, m), 4.83-4.90 (1H, m), 5.12 (2H, s), 6.85 (1H, dd, J=9.6, 2.0 Hz), 7.30-7.38 (5H, brm), 7.41 (1H, d, J=9.6 Hz), 7.68 (1H, s), 7.75 (1H, d, J=2.0 Hz).
67		5	NMR2: 1.53-1.64 (1H, m), 1.64-1.79 (2H, m), 1.88-1.99 (2H, m), 2.71-2.94 (3H, m), 3.14-3.26 (2H, m), 3.39-3.56 (1H, m), 4.17 (2H, d, J=6.6 Hz), 4.59 (2H, t, J=6.1 Hz), 4.90 (2H, dd, J=7.8, 6.3 Hz), 6.88 (1H, dd, J=9.6, 2.2 Hz), 7.41 (1H, dd, J=9.6, 0.6 Hz), 7.71 (1H, s), 8.04 (1H, dd, J=2.1, 0.6 Hz).

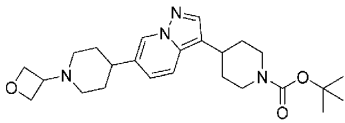
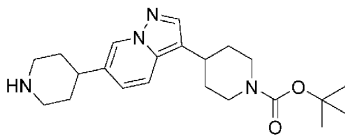
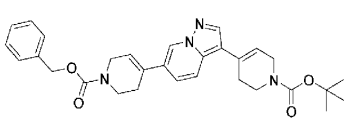
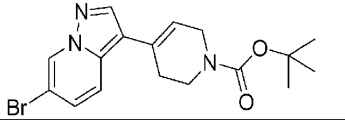
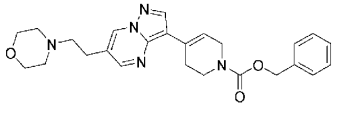
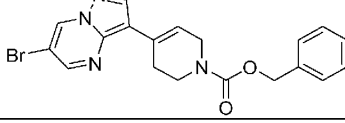
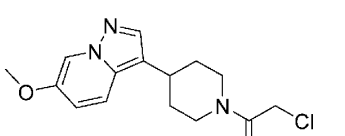
[Table 2-11]

68		10	NMR2: 1.49 (9H, s), 1.61-1.77 (2H, m, J=6.4 Hz), 1.85-1.99 (2H, m), 2.77-2.99 (3H, m), 3.41-3.55 (1H, m), 4.18 (2H, d, J=6.5 Hz), 4.25 (2H, brs), 4.54-4.64 (2H, m), 4.90 (2H, dd, J=7.9, 6.3 Hz), 6.90 (1H, dd, J=9.6, 2.2 Hz), 7.39 (1H, d, J=9.6 Hz), 7.68 (1H, s), 8.05 (1H, d, J=2.1 Hz).
69		5	NMR2: 1.70-2.10 (8H, brm), 2.71-2.81 (1H, m), 2.83-2.98 (3H, m), 3.32 (2H, d, J=12.5 Hz), 3.49-3.59 (2H, m), 4.07-4.14 (2H, m), 6.99 (1H, dd, J=9.2, 1.6 Hz), 7.49 (1H, d, J=9.2 Hz), 7.77 (1H, s), 8.26 (1H, s). M+H:286
70		6	NMR2: 1.49 (9H, s), 1.66-1.74 (2H, m), 1.80-1.84 (4H, m), 1.92 (2H, d, J=13.3 Hz), 2.71-2.81 (1H, m), 2.86-2.96 (3H, m), 3.49-3.60 (2H, m), 4.07-4.14 (2H, m), 4.23 (2H, s), 6.99 (1H, dd, J=9.2, 1.6 Hz), 7.44 (1H, dd, J=9.2, 0.9 Hz), 7.74 (1H, s), 8.26 (1H, dd, J=1.6, 0.9 Hz).
71		71	NMR2: 1.50 (9H, s), 2.52 (2H, s), 2.59 (2H, brs), 3.68 (2H, t, J=5.8 Hz), 3.97 (2H, t, J=5.4 Hz), 4.12 (2H, brs), 4.36 (2H, d, J=2.8 Hz), 5.97 (1H, brs), 6.22 (1H, brs), 7.30 (1H, dd, J=9.5, 1.7 Hz), 7.64 (1H, d, J=9.4 Hz), 7.91 (1H, s), 8.39 (1H, s).
72		72	NMR2: 7.21-7.29 (1H, m), 7.44 (1H, dd, J=9.4, 0.7 Hz), 7.87 (1H, s), 8.55 (1H, dd, J=1.6, 0.9 Hz).
73		5	NMR2: 1.46 (3H, s), 1.54-1.82 (3H, m), 1.88-2.00 (2H, m), 2.72-2.93 (3H, m), 3.14-3.26 (2H, m), 4.00 (2H, s), 4.48 (2H, d, J=6.0 Hz), 4.65 (2H, d, J=6.0 Hz), 6.91 (1H, dd, J=9.6, 2.1 Hz), 7.42 (1H, dd, J=9.6, 0.6 Hz), 7.71 (1H, s), 8.05 (1H, dd, J=2.1, 0.7 Hz).
74		10	NMR2: 1.46 (3H, s), 1.49 (9H, s), 1.61-1.78 (2H, m), 1.85-1.99 (2H, m), 2.77-2.97 (3H, m), 4.00 (2H, s), 4.22 (2H, brs), 4.48 (2H, d, J=6.0 Hz), 4.64 (2H, d, J=6.0 Hz), 6.92 (1H, dd, J=9.6, 2.2 Hz), 7.39 (1H, dd, J=9.6, 0.6 Hz), 7.68 (1H, s), 8.05 (1H, d, J=1.5 Hz).

[Table 2-12]

75		5	NMR2: 1.69–1.79 (2H, m), 1.90–1.98 (2H, m), 2.75–2.81 (2H, m), 2.78–2.84 (1H, m), 2.87 (1H, tt, J=12.0, 3.8 Hz), 3.21 (2H, dt, J=12.7, 3.3 Hz), 3.82 (3H, s), 6.87 (1H, dd, J=9.6, 2.2 Hz), 7.39 (1H, dd, J=9.6, 0.8 Hz), 7.69 (1H, s), 8.01 (1H, dd, J=2.2, 0.8 Hz). M+H: 232.2
76		10	NMR2: 1.49 (9H, s), 1.65–1.75 (2H, m), 1.93 (2H, s), 2.83–2.93 (3H, m), 3.82 (3H, s), 4.23 (2H, brs), 6.88 (1H, dd, J=9.6, 2.1 Hz), 7.36 (1H, d, J=9.6 Hz), 7.67 (1H, s), 8.01 (1H, d, J=2.2 Hz). M+H: 394.5
77		10/77	NMR2: 0.78–0.85 (4H, m), 1.49 (9H, s), 1.64–1.78 (2H, m), 1.84–1.98 (2H, m), 2.78–2.94 (3H, m), 3.70–3.77 (1H, m), 4.08–4.37 (2H, m), 6.85 (1H, dd, J=9.6, 2.1 Hz), 7.36 (1H, d, J=10.0 Hz), 7.68 (1H, s), 8.32 (1H, d, J=2.2 Hz). M+H: 358
78		78	NMR2: 1.49 (9H, s), 1.60–1.75 (2H, m), 1.82–1.95 (4H, brm), 2.01–2.09 (2H, brm), 2.28 (2H, brs), 2.32 (3H, s), 2.72 (2H, brs), 2.82–2.93 (3H, m), 4.17–4.22 (3H, brm), 6.90 (1H, dd, J=9.6, 2.1 Hz), 7.38 (1H, d, J=9.6 Hz), 7.68 (1H, s), 8.07 (1H, d, J=2.1 Hz).
79		6/79	NMR2: 1.49 (9H, s), 1.59–1.75 (4H, m), 1.92 (2H, d, J=13.2 Hz), 2.01–2.09 (2H, m), 2.68–2.77 (2H, m), 2.80–2.90 (3H, m), 3.07–3.19 (2H, m), 4.22–4.25 (3H, m), 6.90 (1H, d, J=9.6 Hz), 7.38 (1H, d, J=9.6 Hz), 7.67 (1H, s), 8.07 (1H, s).
80		10/80	NMR2: 1.49 (9H, s), 1.63–1.75 (2H, m), 1.82 (2H, brs), 1.90–1.92 (4H, brm), 1.97 (3H, s), 2.84–2.93 (3H, m), 3.38–3.47 (2H, m), 3.72–3.82 (2H, m), 4.22 (2H, s), 4.32–4.40 (1H, m), 5.15 (2H, s), 6.89 (1H, dd, J=9.6, 2.1 Hz), 7.29–7.42 (6H, m), 7.68 (1H, s), 8.07 (1H, d, J=2.1 Hz).

[Table 2-13]

81		78	NMR2: 1.49 (9H, s), 1.62-2.02 (10H, m), 2.52 (1H, s), 2.78-2.98 (5H, m), 3.47-3.57 (1H, m), 4.01-4.39 (2H, m), 4.61-4.73 (4H, m), 7.00 (1H, dd, J=9.2, 1.5 Hz), 7.44 (1H, dd, J=9.2, 0.9 Hz), 7.73 (1H, s), 8.26 (1H, d, J=0.7 Hz).
82		6	NMR2: 1.49 (9H, s), 1.54-1.78 (5H, m), 1.82-1.99 (4H, m), 2.55-2.69 (1H, m), 2.69-2.95 (5H, m), 3.18-3.26 (2H, m), 4.13-4.35 (2H, m), 7.00 (1H, dd, J=9.2, 1.5 Hz), 7.40-7.46 (1H, m), 7.73 (1H, s), 8.23-8.27 (1H, m).
83		7	NMR2: 1.51 (9H, s), 2.45-2.69 (4H, m), 3.67 (2H, t, J=5.7 Hz), 3.76 (2H, t, J=5.7 Hz), 4.06-4.17 (2H, m), 4.17-4.26 (2H, m), 5.19 (2H, s), 5.96 (1H, s), 6.03-6.27 (1H, m), 7.22-7.44 (6H, m), 7.64 (1H, d, J=9.0 Hz), 7.91 (1H, s), 8.38 (1H, s).
84		7/84	NMR2: 1.50 (9H, s), 2.57 (2H, br), 3.67 (2H, m), 4.11 (2H, brs), 5.95 (1H, brs), 4.19 (1H, dd, J=9.5, 1.65 Hz), 7.59 (1H, d, J=9.5 Hz), 7.90 (1H, s), 8.58 (1H, d, J=0.8 Hz).
85		85	NMR2: 2.52 (4H, s), 2.62-2.72 (4H, m), 2.83 (2H, t, J=7.1 Hz), 3.70-3.80 (6H, m), 4.23 (2H, q, J=2.6 Hz), 5.18 (2H, s), 6.65 (1H, brd, J=18.3 Hz), 7.29-7.34 (1H, m), 7.34-7.42 (4H, m), 8.05 (1H, s), 8.41 (1H, d, J=2.1 Hz), 8.56 (1H, d, J=2.1 Hz).
86		8	NMR2: 2.68 (2H, brs), 3.77 (2H, brs), 4.23 (2H, q, J=2.9 Hz), 5.18 (2H, s), 6.62 (1H, brd, J=15.7 Hz), 7.32 (1H, t, J=6.7 Hz), 7.32-7.42 (4H, m), 8.07 (1H, s), 8.45 (1H, d, J=2.2 Hz), 8.78 (1H, d, J=2.2 Hz).
87		87	NMR2: 1.78 (2H, m), 1.98-2.09 (2H, m), 2.80 (1H, td, J=13.0, 2.8 Hz), 3.02 (1H, tt, J=11.9, 3.8 Hz), 3.24-3.34 (1H, m), 3.83 (3H, s), 3.99 (1H, ddt, J=13.8, 4.3, 2.3 Hz), 4.11 (1H, d, J=12.0 Hz), 4.15 (1H, d, J=12.0 Hz), 4.70 (1H, d, J=13.4 Hz), 6.90 (1H, dd, J=9.6, 2.2 Hz), 7.36 (1H, d, J=9.6 Hz), 7.67 (1H, s), 8.03 (1H, d, J=2.2 Hz). M+H: 308.3, 310.46

[Table 2-14]

88		109	NMR1: 1.64 – 1.76 (2H, m), 1.90 – 1.97 (2H, m), 3.00 (2H, s), 3.10 (1H, tt, J=11.9, 3.7 Hz), 3.70 (2H, s), 4.11 (2H, d, J=13.1 Hz), 5.20 (2H, s), 7.70 (1H, d, J=2.0 Hz), 8.08 (1H, s), 8.41 (1H, d, J=2.1 Hz), 8.92 (1H, d, J=2.0 Hz), 9.10 (1H, d, J=2.1 Hz). M+H: 402
89		89	NMR2: 1.79 (2H, s), 2.03 (2H, brs), 2.99 (2H, brs), 3.16 (1H, tt, J=12.1, 3.7 Hz), 3.67 (2H, s), 3.76 (3H, s), 4.31 (2H, s), 5.33 (2H, brd, J=6.2 Hz), 7.38 (1H, d, J=2.1 Hz), 7.93 (1H, s), 8.36 (1H, d, J=2.2 Hz), 8.57 (1H, d=2.1 Hz), 8.81 (1H, d, J=2.2 Hz).
90		90	NMR2: 2.70 (2H, s), 3.69 (2H, s), 3.76 (3H, s), 3.75–3.80 (2H, m), 4.23 (2H, q, J=2.8 Hz), 5.18 (2H, s), 6.62 (1H, s), 7.28–7.34 (1H, m), 7.34–7.42 (4H, m), 8.08 (1H, s), 8.42 (1H, d, J=2.3 Hz), 8.59 (1H, d, J=1.0 Hz).
91		5/91	NMR2: 1.67–1.79 (2H, m), 2.01 (2H, d, J=13.0 Hz), 2.76–2.85 (2H, m), 3.03–3.13 (1H, m), 3.18 (2H, dt, J=12.5, 3.2 Hz), 3.47 (3H, s), 3.77–3.82 (2H, m), 4.11–4.16 (2H, m), 7.86 (1H, s), 8.23 (1H, d, J=2.7 Hz), 8.36 (1H, d, J=2.7 Hz).
92		10/92	NMR2: 1.48 (9H, s), 1.60–1.78 (2H, m), 2.01 (2H, d, J=12.4 Hz), 2.80–3.80 (2H, brm), 3.09 (1H, m), 3.47 (3H, s), 3.77–3.82 (2H, m), 4.11–4.17 (2H, m), 4.22 (2H, s), 7.83 (1H, s), 8.23 (1H, d, J=2.6 Hz), 8.37 (1H, d, J=2.6 Hz). M+H: 377
93		6/93	NMR1: 1.41 (9H, s), 1.55–1.69 (2H, m), 1.83–1.95 (2H, m), 2.69–2.94 (2H, m), 2.94–3.08 (1H, m), 3.93–4.14 (2H, m), 7.88 (1H, s), 8.31 (1H, d, J=2.6 Hz), 8.40 (1H, d, J=2.6 Hz), 10.27 (1H, brs).
94		94/104	NMR2: 1.49 (9H, s), 2.57–2.71 (2H, m), 3.62–3.73 (2H, m), 4.10–4.18 (2H, m), 5.10 (2H, s), 6.62 (1H, s), 7.34–7.49 (5H, m), 7.97 (1H, s), 8.23 (1H, d, J=2.8 Hz), 8.43 (1H, d, J=2.7 Hz).

[Table 2-15]

95		10/95	NMR2: 1.48 (9H, s), 1.67–1.79 (2H, m), 2.00 (2H, d, J=13.1 Hz), 2.89 (2H, brs), 3.10 (1H, tt, J=11.9, 3.7 Hz), 4.10–4.30 (4H, brm), 6.14 (1H, dd, J=54.6, 3.9 Hz), 7.88 (1H, s), 8.25 (1H, d, J=2.7 Hz), 8.36 (1H, d, J=2.7 Hz).
96		6	NMR2: 1.48 (9H, s), 1.67–1.75 (2H, m), 1.74–1.91 (4H, m), 2.01–2.04 (2H, m), 2.82–2.92 (3H, m), 3.12 (1H, tt, J=11.9, 3.7 Hz), 3.52–3.61 (2H, m), 4.08–4.16 (2H, m), 4.22 (2H, s), 7.92 (1H, s), 8.36 (1H, d, J=2.2 Hz), 8.43 (1H, d, J=2.2 Hz).
97		7	NMR2: 1.49 (9H, s), 2.47–2.54 (2H, m), 2.65–2.71 (2H, m), 3.69 (2H, t, J=5.8 Hz), 3.99 (2H, t, J=5.4 Hz), 4.11–4.18 (2H, m), 4.35–4.42 (2H, m), 6.30–6.35 (1H, m), 6.64 (1H, s), 8.08 (1H, s), 8.53 (1H, d, J=2.3 Hz), 8.66 (1H, d, J=2.3 Hz).
98		7	NMR2: 1.49 (9H, s), 2.66 (2H, s), 3.67 (2H, m), 4.14 (2H, d, J=3.5 Hz), 6.62 (1H, s), 8.07 (1H, s), 8.45 (1H, d, J=2.2 Hz), 8.78 (1H, d, J=2.2 Hz).
99		6	NMR2: 1.49 (9H, s), 1.65–1.74 (2H, m), 1.92 (2H, d, J=13.5 Hz), 2.58 (4H, t, J=4.8 Hz), 2.80–2.92 (5H, m), 3.75 (4H, t, J=4.7 Hz), 4.09 (2H, t, J=5.5 Hz), 4.22 (2H, s), 6.91 (1H, dd, J=9.6, 2.1 Hz), 7.37 (1H, d, J=9.6 Hz), 7.67 (1H, s), 8.03 (1H, d, J=2.1 Hz).
100		10	NMR2: 1.50 (9H, s), 2.56–2.62 (6H, brm), 2.84 (2H, t, J=5.5 Hz), 3.67 (2H, t, J=5.7 Hz), 3.75 (4H, t, J=4.7 Hz), 4.10 (4H, t, J=5.4 Hz), 5.93 (1H, s), 6.98 (1H, dd, J=9.7, 2.2 Hz), 7.59 (1H, d, J=9.7 Hz), 7.83 (1H, s), 8.04 (1H, d, J=2.2 Hz).

[Table 2-16]

101		101	NMR2: 1.50 (9H, s), 2.56 (2H, brs), 3.67 (2H, t, J = 5.7 Hz), 4.05-4.16 (2H, m), 5.90 (1H, s), 6.75 (1H, brs), 6.95 (1H, dd, J=9.6, 2.2 Hz), 7.56 (1H, d, J=9.6 Hz), 7.80 (1H, s), 8.11 (1H, d, J=2.1 Hz).
102		5	NMR2: 1.68-1.80 (2H, m), 1.92-1.98 (2H, m), 2.80 (2H, td, J=12.2, 2.5 Hz), 2.87-2.97 (1H, m), 3.00 (2H, tt, J=5.6, 1.8 Hz), 3.18-3.24 (2H, m), 4.08 (2H, t, J=5.6 Hz), 4.88 (2H, t, J=1.8 Hz), 7.53-7.61 (2H, m), 7.88 (1H, s), 8.98 (1H, t, J=1.3 Hz). M+H: 341.4
103		6	NMR2: 1.49 (9H, s), 1.66-1.78 (2H, m), 1.94 (2H, d, J=13.2 Hz), 2.88 (2H, s), 2.90-3.03 (3H, m), 4.05-4.12 (2H, m), 4.25 (2H, s), 4.88 (2H, t, J=1.8 Hz), 7.53 (1H, dd, J=9.3, 1.0 Hz), 7.60 (1H, dd, J=9.3, 1.6 Hz), 7.86 (1H, s), 8.99 (1H, t, J=1.6 Hz). M+H: 441.48
104		104	NMR2: 1.51 (9H, s), 2.60 (2H, s), 3.00 (2H, tt, J=5.6, 1.8 Hz), 3.66-3.72 (2H, m), 4.08 (2H, t, J=5.6 Hz), 4.13 (2H, d, J=3.8 Hz), 4.88 (2H, t, J=1.8 Hz), 6.00 (1H, s), 7.66 (1H, dd, J=9.4, 1.6 Hz), 7.73 (1H, dd, J=9.4, 1.0 Hz), 8.00 (1H, s), 8.98-9.02 (1H, m). M+H: 439.4
105		105	NMR2: 2.95-3.03 (2H, m), 4.07 (2H, dt, J=9.9, 5.6 Hz), 4.88 (2H, q, J=2.0 Hz), 7.59 (1H, d, J=9.3 Hz), 7.71 (1H, d, J=9.3 Hz), 7.96 (1H, s), 8.98 (1H, s). M+H: 292.1
106		106	NMR2: 1.36 (12H, s), 7.40-7.53 (2H, m), 7.92 (1H, s), 8.77 (1H, d, J=1.1 Hz). M+H: 279.2
107		5	NMR2: 0.58-0.73 (2H, m), 0.81-0.98 (2H, m), 1.61 (1H, s), 1.65-1.82 (2H, m), 1.86-1.99 (2H, m), 2.79 (2H, td, J=12.2, 2.5 Hz), 2.84-2.99 (2H, m), 3.15-3.26 (2H, m), 6.22 (1H, s), 7.31 (1H, dd, J=9.3, 1.6 Hz), 7.51 (1H, dd, J=9.3, 0.9 Hz), 7.91 (1H, s), 8.88-8.96 (1H, m).

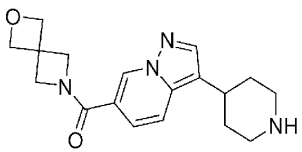
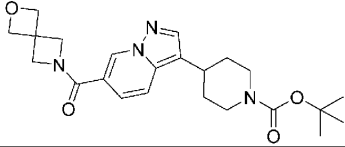
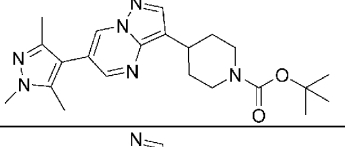
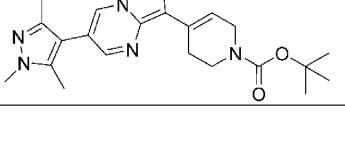
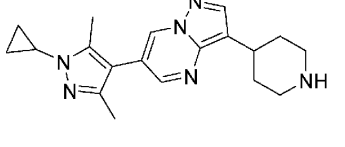
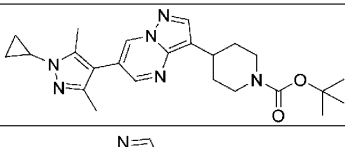
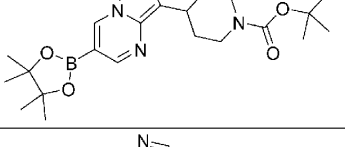
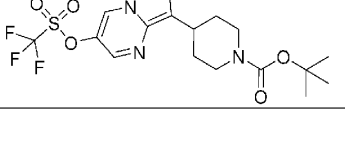
[Table 2-17]

108		108	NMR2: 0.62-0.68 (2H, m), 0.81-0.97 (2H, m), 1.48 (9H, s), 1.62-1.78 (2H, m), 1.82-1.99 (2H, m), 2.76-3.00 (4H, m), 4.25 (2H, brs), 6.25 (1H, brs), 7.33 (1H, dd, J=9.3, 1.0 Hz), 7.49 (1H, dd, J = 9.4, 0.7 Hz), 7.88 (1H, s), 8.93 (1H, s).
109		109	NMR1: 1.41 (9H, s), 1.50-1.66 (2H, m), 1.79-1.90 (2H, m), 2.87 (2H, s), 2.97-3.11 (1H, m), 3.97-4.14 (2H, m), 7.52 (1H, dd, J=9.3, 1.5 Hz), 7.74-7.80 (1H, m), 8.12 (1H, s), 9.02-9.08 (1H, m), 13.23 (1H, brs).
110		6	NMR2: 1.48 (9H, s), 1.60-1.82 (2H, m), 1.93 (2H, d, J=13.4 Hz), 2.74-3.03 (3H, m), 3.95 (3H, s), 4.10-4.39 (2H, m), 7.49 (1H, dd, J=9.3, 0.9 Hz), 7.59 (1H, dd, J=9.3, 1.5 Hz), 7.93 (1H, s), 9.15 (1H, dd, J=1.5, 1.0 Hz).
111		111	NMR2: 1.50 (9H, s), 2.59 (2H, s), 3.65-3.72 (2H, m), 3.96 (3H, s), 4.08-4.16 (2H, m), 5.95-6.06 (1H, m), 7.65 (1H, dd, J=9.4, 1.5 Hz), 7.69 (1H, dd, J=9.5, 0.8 Hz), 8.06 (1H, s), 9.13-9.18 (1H, m).
112		5	NMR2: 1.55-1.80 (3H, m), 1.87-1.99 (2H, m), 2.47 (4H, t, J=4.5 Hz), 2.79 (2H, td, J=12.2, 2.5 Hz), 2.88 (1H, tt, J=12.0, 3.8 Hz), 3.15-3.25 (2H, m), 3.48 (2H, s), 3.71 (4H, t, J=4.6 Hz), 7.09 (1H, dd, J=9.2, 1.3 Hz), 7.46 (1H, d, J=9.2 Hz), 7.77 (1H, s), 8.33 (1H, s).
113		78	NMR2: 1.49 (9H, s), 1.62-1.78 (2H, m), 1.85-1.99 (2H, m), 2.48 (4H, t, J=4.5 Hz), 2.76-3.00 (3H, m), 3.47 (2H, s), 3.71 (4H, t, J=4.6 Hz), 4.16-4.37 (2H, m), 7.11 (1H, dd, J=9.2, 1.5 Hz), 7.44 (1H, dd, J=9.1, 0.8 Hz), 7.75 (1H, s), 8.34 (1H, s).
114		114	NMR2: 1.49 (9H, s), 1.64-1.82 (2H, m), 1.87-2.00 (2H, m), 2.76-3.04 (3H, m), 4.14-4.39 (2H, m), 7.49-7.62 (2H, m), 8.00 (1H, s), 8.88 (1H, t, J = 1.2 Hz), 9.91 (1H, s).
115		115	NMR2: 1.48 (9H, s), 1.62-1.79 (2H, m), 1.79-2.01 (3H, m), 2.75-2.99 (3H, m), 4.16-4.38 (2H, m), 4.70 (2H, d, J = 5.4 Hz), 7.06-7.13 (1H, m), 7.48 (1H, d, J=9.2 Hz), 7.77 (1H, s), 8.42 (1H, s).

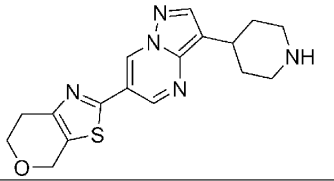
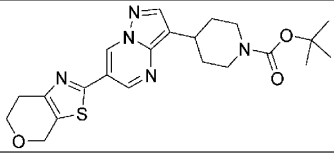
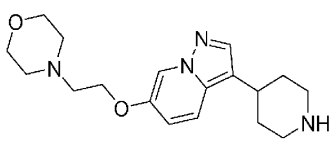
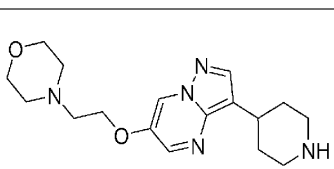
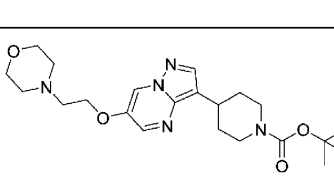
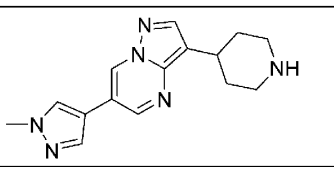
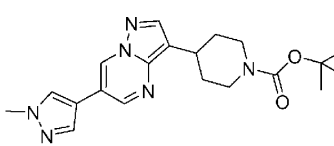
[Table 2-18]

116		1	NMR2: 1.65-1.83 (2H, m), 1.83-2.12 (3H, m), 2.31-2.48 (1H, m), 2.81-3.10 (3H, m), 3.31-3.47 (1H, m), 3.70-3.84 (1H, m), 3.84-4.00 (1H, m), 4.00-4.24 (2H, m), 4.36 (2H, s), 5.34 (2H, s), 7.01 (1H, dd, J=9.2, 1.5 Hz), 7.38 (1H, d, J=2.0 Hz), 7.44 (1H, d, J=9.2 Hz), 7.73 (1H, s), 8.30 (1H, s), 8.82 (1H, d, J=2.0 Hz).
117		5	NMR2: 1.56-1.80 (3H, m), 1.87-2.09 (3H, m), 2.32-2.46 (1H, m), 2.73-2.95 (3H, m), 3.21 (2H, dd, J=9.5, 2.6 Hz), 3.34-3.45 (1H, m), 3.76 (1H, dd, J=8.7, 6.8 Hz), 3.93 (1H, dd, J=16.1, 7.6 Hz), 4.03-4.18 (2H, m), 6.99 (1H, dd, J=9.2, 1.5 Hz), 7.48 (1H, d, J=9.2 Hz), 7.77 (1H, s), 8.29 (1H, s).
118		6	NMR2: 1.49 (9H, s), 1.62-1.79 (2H, m), 1.85-1.96 (2H, m), 1.96-2.10 (1H, m), 2.33-2.47 (1H, m), 2.76-2.99 (3H, m), 3.33-3.45 (1H, m), 3.76 (1H, dd, J=8.7, 6.8 Hz), 3.93 (1H, dd, J=16.1, 7.7 Hz), 4.04-4.16 (2H, m), 4.24 (2H, brs), 7.00 (1H, dd, J=9.2, 1.5 Hz), 7.45 (1H, d, J=9.3 Hz), 7.74 (1H, s), 8.30 (1H, s).
119		7	NMR2: 1.51 (9H, s), 2.59 (2H, brs), 3.68 (2H, t, J=5.7 Hz), 4.01-4.19 (2H, m), 4.83-4.94 (2H, m), 4.94-5.06 (2H, m), 5.97 (1H, s), 6.23-6.34 (1H, m), 7.30 (1H, dd, J=9.4, 1.6 Hz), 7.66 (1H, d, J=9.4 Hz), 7.93 (1H, s), 8.20 (1H, s).
120		5	NMR2: 1.02-1.15 (2H, m), 1.22-1.34 (2H, m), 1.52-1.66 (1H, m), 1.66-1.82 (2H, m), 1.90-2.01 (2H, m), 2.50-2.64 (1H, m), 2.73-2.85 (2H, m), 2.85-2.99 (1H, m), 3.14-3.29 (2H, m), 7.48-7.56 (1H, m), 7.62 (1H, dd, J=9.3, 1.5 Hz), 7.97 (1H, s), 9.14-9.23 (1H, m).
121		27	NMR2: 0.99-1.38 (4H, m), 1.49 (9H, s), 1.63-1.81 (2H, m), 1.87-2.01 (2H, m), 2.51-2.62 (1H, m), 2.76-3.02 (3H, m), 4.26 (2H, brs), 7.51 (1H, dd, J=9.4, 0.9 Hz), 7.64 (1H, dd, J=9.4, 1.5 Hz), 7.95 (1H, s), 9.17-9.22 (1H, m).
122		108	NMR2: 1.49 (9H, s), 1.64-1.82 (2H, m), 1.86-2.02 (2H, m), 2.77-3.04 (3H, m), 3.41 (3H, s), 3.64 (3H, s), 4.13-4.38 (2H, m), 7.43-7.55 (2H, m), 7.89 (1H, s), 9.03-9.09 (1H, m).

[Table 2-19]

123		5	NMR2: 1.60 (1H, m), 1.66-1.80 (2H, m), 1.88-1.98 (2H, m), 2.73-2.84 (2H, m), 2.84-2.97 (1H, m), 3.15-3.25 (2H, m), 4.47 (4H, brs), 4.83 (4H, s), 7.31 (1H, dd, J=9.3, 1.6 Hz), 7.53 (1H, dd, J=9.3, 0.9 Hz), 7.92 (1H, s), 8.72 (1H, dd, J=1.5, 1.0 Hz).
124		108	NMR2: 1.49 (9H, s), 1.63-1.79 (2H, m), 1.87-1.98 (2H, m), 2.76-3.01 (3H, m), 4.27 (2H, brs), 4.47 (4H, brs), 4.83 (4H, s), 7.33 (1H, dd, J=9.3, 1.6 Hz), 7.50 (1H, dd, J=9.3, 0.9 Hz), 7.90 (1H, s), 8.70-8.75 (1H, m).
125		6	NMR2: 1.49 (9H, s), 1.73-1.84 (2H, m), 2.02-2.08 (2H, m), 2.26 (3H, s), 2.28 (3H, s), 2.92 (2H, s), 3.12-3.21 (1H, m), 3.82 (3H, s), 4.25 (2H, s), 7.98 (1H, s), 8.35 (1H, d, J=2.1 Hz), 8.47 (1H, d, J=2.1 Hz).
126		7	NMR2: 1.50 (9H, s), 2.27 (3H, s), 2.28 (3H, s), 2.70 (2H, s), 3.71 (2H, t, J=5.4 Hz), 3.82 (3H, s), 4.13-4.18 (2H, m), 6.67 (1H, s), 8.12 (1H, s), 8.43 (1H, d, J=2.2 Hz), 8.49 (1H, d, J=2.2 Hz).
127		5/127	NMR2: 1.04-1.18 (2H, m), 1.20 (2H, t, J=3.7 Hz), 1.72-1.84 (2H, m), 2.02-2.09 (2H, m), 2.25 (3H, s), 2.36 (3H, s), 2.79-2.88 (2H, m), 3.10-3.20 (1H, m), 3.21 (2H, dt, J=12.3, 3.3 Hz), 3.34 (1H, tt, J=7.3, 3.8 Hz), 8.00 (1H, s), 8.35 (1H, d, J=2.2 Hz), 8.46 (1H, d, J=2.2 Hz).
128		105/ 128	M+H: 437
129		106/ 129	NMR2: 1.37 (12H, s), 1.49 (9H, s), 1.68-1.77 (2H, m), 1.99-2.02 (2H, m), 2.90 (2H, brs), 3.13-3.18 (1H, m), 4.24 (2H, brs), 8.00 (1H, s), 8.16 (1H, d, J=1.7 Hz), 8.93 (1H, m, d, J=1.7 Hz). M+H: 347.1 for B(OH) ₂
130		130	NMR2: 1.48 (9H, s), 1.67-1.87 (2H, m), 1.92-2.10 (2H, m), 2.73-3.05 (2H, m), 3.05-3.24 (1H, m), 4.25 (2H, brs), 8.09 (1H, s), 8.41 (1H, d, J=2.6 Hz), 8.75 (1H, d, J=2.7 Hz).

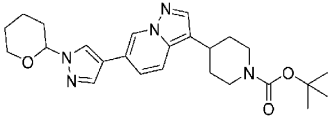
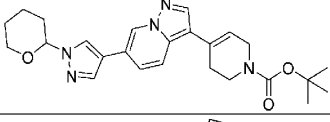
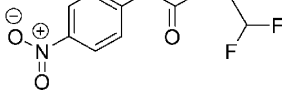
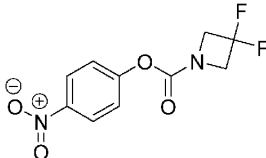
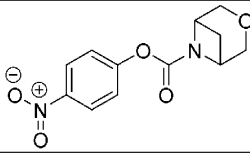
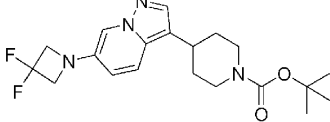
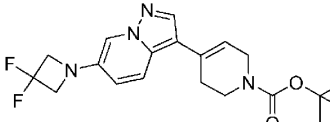
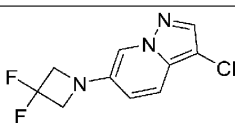
[Table 2-20]

131		5	M+H: 342.3
132		105	M-tBu+2H: 386.3
133		5	NMR2: 1.53-1.79 (3H, m), 1.86-2.00 (2H, m), 2.52-2.64 (4H, m), 2.72-2.92 (5H, m), 3.14-3.25 (2H, m), 3.75 (4H, t, J=4.7 Hz), 4.08 (2H, t, J=5.6 Hz), 6.89 (1H, dd, J=9.6, 2.1 Hz), 7.39 (1H, dd, J=9.6, 0.6 Hz), 7.69 (1H, s), 8.00-8.05 (1H, m).
134		5	NMR2: 1.67-1.79 (2H, m), 1.98-2.06 (2H, m), 2.59 (4H, t, J=4.7 Hz), 2.74-2.93 (4H, m), 3.03-3.13 (1H, m), 3.18 (2H, dt, J=12.3, 3.3 Hz), 3.74 (4H, q, J=5.6 Hz), 4.05-4.16 (2H, m), 7.86 (1H, s), 8.20 (1H, d, J=2.7 Hz), 8.33 (1H, d, J=2.7 Hz).
135		10	NMR2: 1.48 (9H, s), 1.66-1.78 (2H, m), 2.00 (2H, d, J=13.2 Hz), 2.56-2.61 (4H, m), 2.81-2.92 (4H, m), 3.09 (1H, tt, J=12.0, 3.8 Hz), 3.71-3.78 (4H, m), 4.11 (2H, t, J=5.5 Hz), 4.21 (2H, s), 7.83 (1H, s), 8.21 (1H, d, J=2.7 Hz), 8.33 (1H, d, J=2.7 Hz).
136		5/ 136	NMR2: 1.71-1.83 (2H, m), 2.00-2.07 (2H, m), 2.79-2.88 (2H, m), 3.08-3.17 (1H, m), 3.17-3.23 (2H, m), 4.00 (3H, s), 7.66 (1H, d, J=0.9 Hz), 7.76 (1H, d, J=0.9 Hz), 7.97 (1H, s), 8.55 (1H, d, J=2.2 Hz), 8.67 (1H, d, J=2.2 Hz).
137		6/ 137	NMR2: 1.49 (9H, s), 1.70-1.82 (2H, m), 2.03 (2H, d, J=12.6 Hz), 2.91 (2H, s), 3.14 (1H, tt, J=12.0, 3.7 Hz), 4.00 (3H, s), 4.24 (2H, s), 7.67 (1H, d, J=0.9 Hz), 7.76 (1H, d, J=0.9 Hz), 7.94 (1H, s), 8.55 (1H, d, J=2.2 Hz), 8.67 (1H, d, J=2.2 Hz).

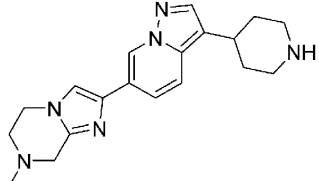
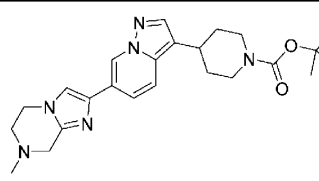
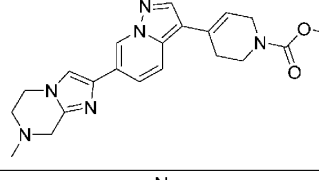
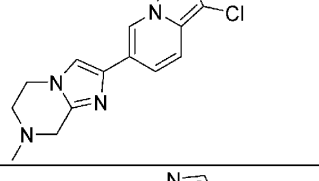
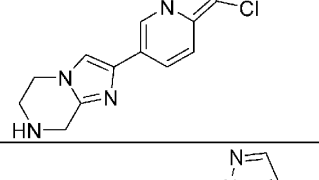
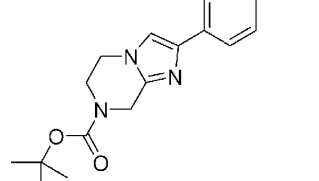
[Table 2-21]

138		104/ 138	NMR2: 1.50 (9H, s), 2.69 (2H, s), 3.70 (2H, s), 4.00 (3H, s), 4.16 (2H, d, J=3.2 Hz), 6.66 (1H, s), 7.69 (1H, d, J=0.9 Hz), 7.78 (1H, d, J=0.9 Hz), 8.08 (1H, s), 8.62 (1H, d, J=2.2 Hz), 8.69 (1H, d, J=2.2 Hz).
139		7/ 139	NMR2: 4.01 (3H, s), 7.71 (1H, s), 7.78 (1H, s), 8.07 (1H, s), 8.67 (2H, s).
140		72	NMR2: 8.07 (1H, s), 8.53 (1H, d, J=2.1 Hz), 8.78 (1H, d, J=2.1 Hz).
141		1	NMR2: 2.07-2.24 (1H, brm), 2.40 – 2.51 (2H, m), 2.62–2.76 (1H, m), 3.88–4.04 (3H, m), 4.02–4.18 (2H, m), 4.19–4.25 (1H, m), 7.33 (2H, dd, J=9.3, 3.3 Hz), 8.24 (2H, dd, J=9.3, 3.0 Hz). M+H: 279.2
142		5/ 142	NMR2: δH(500 MHz, CDCl ₃): 1.04 – 1.10 (2H, m), 1.13 – 1.22 (2H, m), 1.67 – 1.79 (2H, m), 1.91 – 1.99 (2H, m), 2.75 – 2.84 (2H, m), 2.85 – 2.95 (1H, m), 3.21 (2H, dt, J=12.0, 3.1 Hz), 3.65 (1H, tt, J=7.4, 3.8 Hz), 7.16 (1H, dd, J=9.1, 1.6 Hz), 7.51 (1H, d, J=9.1 Hz), 7.69 (1H, s), 7.72 (1H, s), 7.78 (1H, s), 8.53 (1H, s).
143		10/ 143	NMR2: 1.07 (2H, td, J=7.4, 5.4 Hz), 1.11 – 1.22 (2H, m), 1.49 (9H, s), 1.66 – 1.77 (2H, m), 1.94 (2H, d, J=13.1 Hz), 2.88 (2H, s), 2.89 – 2.97 (1H, m), 3.65 (1H, tt, J=7.3, 3.8 Hz), 4.24 (2H, s), 7.18 (1H, d, J=9.2 Hz), 7.48 (1H, d, J=9.2 Hz), 7.70 (1H, s), 7.72 (1H, s), 7.76 (1H, s), 8.53 (1H, s).
144		144	NMR2: 1.50 (9H, s), 1.66–1.78 (2H, m), 1.95 (2H, d, J=13.1 Hz), 2.88 (2H, s), 2.94 (1H, tt, J=12.1, 3.7 Hz), 4.25 (2H, s), 7.22 (1H, dd, J=9.1, 1.5 Hz), 7.51 (1H, dd, J=9.1, 1.0 Hz), 7.78 (1H, s), 7.86 (2H, s), 8.59 (1H, s), 10.24 (1H, s).

[Table 2-22]

145		6/ 145	NMR2: 1.49 (9H, s), 1.60-1.80 (5H, brm), 1.96 (1H, brs), 2.05-2.10 (2H, brm), 2.12-2.20 (2H, brm), 2.87 (2H, s), 2.93 (1H, tt, J=12.0, 3.6 Hz), 3.74 (1H, td, J=11.1, 3.0 Hz), 4.07-4.14 (1H, m), 4.25 (2H, s), 5.43 (1H, dd, J=8.8, 3.7 Hz), 7.20 (1H, dd, J=9.2, 1.6 Hz), 7.49 (1H, d, J=9.1 Hz), 7.76 (1H, s), 7.81 (1H, s), 7.86 (1H, s), 8.56 (1H, s).
146		71/ 146	M+H: 450
147		1	M+H: 273.1
148		1	NMR2: 4.52 (4H, d, J=33.7 Hz), 7.30 – 7.37 (2H, m), 8.22–8.30 (2H, m).
149		1	NMR2: 1.90 (1H, d, J=8.5 Hz), 2.75–2.82 (1H, m), 3.87 (1H, d, J=11.0 Hz), 3.93 (1H, d, J=11.0 Hz), 4.32 (2H, s), 4.37 (2H, s), 7.33 (2H, d, J=9.1 Hz), 8.26 (2H, d, J=9.1 Hz). M+H: 265.2
150		6	NMR2: 1.48 (9H, d, J=6.9 Hz), 1.63-1.75 (2H, m), 1.91 (2H, d, J=13.1 Hz), 2.80-2.91 (3H, m), 4.21 (6H, t, J=11.6 Hz), 6.59 (1H, dd, J=9.5, 2.1 Hz), 7.40 (1H, d, J=9.5 Hz), 7.65 (1H, s), 7.68 (1H, d, J=1.2 Hz).
151		104	NMR2: 1.50 (9H, s), 2.57 (2H, s), 3.67 (2H, t, J=5.7 Hz), 4.11 (2H, s), 4.24 (4H, t, J=11.6 Hz), 5.92 (1H, s), 6.66 (1H, dd, J=9.5, 2.1 Hz), 7.62 (1H, d, J=9.6 Hz), 7.69 (1H, d, J=2.1 Hz), 7.80 (1H, s).
152		170	NMR2: 4.24 (4H, t, J=11.6 Hz), 6.70 (1H, dd, J=9.5, 2.0 Hz), 7.45 (1H, d, J=9.4 Hz), 7.64 (1H, d, J=2.0 Hz), 7.76 (1H, s).

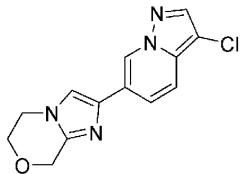
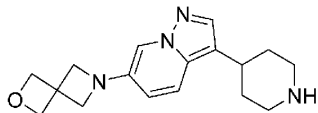
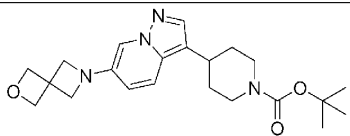
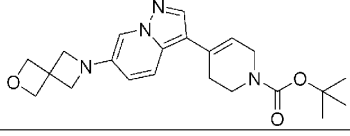
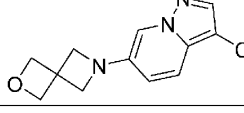
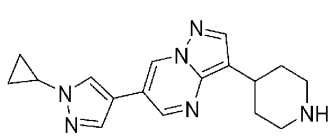
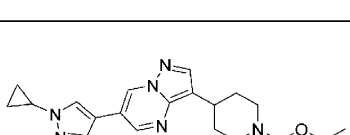
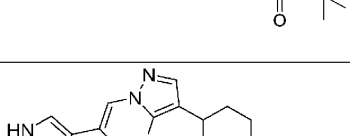
[Table 2-23]

153		5	NMR2: 1.69–1.80 (2H, m), 1.96 (2H, d, J=12.5 Hz), 2.52 (3H, s), 2.80 (2H, td, J=12.3, 2.4 Hz), 2.84–2.95 (3H, m), 3.21 (2H, dt, J=12.3, 3.2 Hz), 3.73 (2H, s), 4.06 (2H, t, J=5.5 Hz), 7.09 (1H, s), 7.42 (1H, d, J=9.2 Hz), 7.49 (1H, d, J=9.2 Hz), 7.78 (1H, s), 8.81 (1H, s). M+H: 337.1
154		6	NMR2: 1.49 (9H, s), 1.65–1.77 (2H, m), 1.94 (2H, d, J=13.2 Hz), 2.53 (3H, s), 2.80–2.97 (5H, brm), 3.73 (2H, s), 4.06 (2H, t, J=5.5 Hz), 4.24 (2H, s), 7.09 (1H, s), 7.42 (1H, d, J=9.2 Hz), 7.47 (1H, d, J=9.2 Hz), 7.75 (1H, s), 8.81 (1H, s). M+H: 437.4
155		104	NMR2: 1.50 (9H, s), 2.53 (3H, s), 2.60 (2H, s), 2.88 (2H, t, J=5.5 Hz), 3.68 (2H, t, J=5.8 Hz), 3.74 (2H, s), 4.07 (2H, t, J=5.5 Hz), 4.12 (2H, s), 5.97 (1H, s), 7.11 (1H, s), 7.48 (1H, d, J=9.3 Hz), 7.68 (1H, d, J=9.3 Hz), 7.91 (1H, s), 8.84 (1H, s). M+H: 435.3
156		78	NMR2: 2.53 (3H, s), 2.88 (2H, t, J=5.5 Hz), 3.73 (2H, s), 4.07 (2H, t, J=5.5 Hz), 7.12 (1H, s), 7.51 (2H, s), 7.86 (1H, s), 8.81 (1H, s). M+H: 288.2
157		5	NMR2: 3.30 (2H, t, J=5.5 Hz), 4.02 (2H, t, J=5.5 Hz), 4.17 (2H, s), 7.12 (1H, s), 7.52 (2H, d, J=1.5 Hz), 7.86 (1H, s), 8.82 (1H, s). M+H: 274.2
158		105	NMR2: 1.51 (9H, s), 3.90 (2H, t, J=5.4 Hz), 4.05 (2H, d, J=5.4 Hz), 4.76 (2H, s), 7.15 (1H, s), 7.52 (2H, s), 7.87 (1H, s), 8.82 (1H, s). M+H: 374.2

[Table 2-24]

159		5	NMR3: 1.71–1.83 (2H, m), 1.97 (2H, d, J=13.0 Hz), 2.76–2.86 (2H, m), 2.96–3.06 (1H, m), 3.17 (2H, d, J=12.8 Hz), 4.17–4.22 (2H, m), 4.22–4.27 (2H, m), 5.08 (2H, s), 7.29 (1H, d, J=9.6 Hz), 7.73 (1H, d, J=9.6 Hz), 7.85 (2H, s), 8.39 (1H, s). M+H: 324.3
160		6	NMR2: 1.49 (9H, s), 1.62–1.78 (2H, m), 1.95 (2H, d, J=14.3 Hz), 2.88 (2H, s), 2.94 (1H, tt, J=11.9, 3.6 Hz), 4.08–4.20 (2H, m), 4.28 (4H, t, J=5.2 Hz), 5.01 (2H, s), 7.09 (1H, dd, J=9.1, 1.6 Hz), 7.51 (1H, d, J=9.1 Hz), 7.72 (1H, s), 7.78 (1H, s), 8.26 (1H, s). M+H: 424.3
161		104	NMR2: 1.51 (9H, s), 2.60 (2H, s), 3.69 (2H, d, J=5.0 Hz), 4.08–4.30 (2H, brm), 4.16–4.18 (2H, brm), 4.25–4.31 (2H, m), 5.02 (2H, s), 5.98 (1H, s), 6.60 (1H, d, J=8.3 Hz), 7.14 (1H, d, J=8.3 Hz), 7.73 (1H, s), 7.93 (1H, s), 8.28 (1H, s). M+H: 422.3
162		105	NMR2: 4.18 (2H, d, J=5.2 Hz), 4.29 (2H, t, J=5.2 Hz), 5.01 (2H, s), 7.21 (1H, dd, J=9.2, 1.5 Hz), 7.56 (1H, d, J=9.2 Hz), 7.73 (1H, s), 7.89 (1H, s), 8.24 (1H, s). M+H: 275.2
163		5	M+H: 324.2
164		6	NMR2: 1.49 (9H, s), 1.66–1.78 (2H, m), 1.91–1.98 (2H, m), 2.87 (2H, s), 2.93 (1H, tt, J=11.9, 3.7 Hz), 4.10 (4H, brs), 4.24 (2H, s), 4.91 (2H, s), 7.14 (1H, s), 7.42 (1H, dd, J=9.2, 1.6 Hz), 7.48 (1H, d, J=9.2 Hz), 7.77 (1H, s), 8.82 (1H, s). M+H: 424.3
165		104	NMR2: 1.50 (9H, s), 2.60 (2H, s), 3.68 (2H, t, J=5.8 Hz), 4.08–4.16 (6H, m), 4.91 (2H, s), 5.97 (1H, s), 7.16 (1H, s), 7.48 (1H, d, J=9.3 Hz), 7.69 (1H, d, J=9.3 Hz), 7.91 (1H, s), 8.84 (1H, s). M+H: 422.3

[Table 2-25]

166		105	NMR2: 4.10 (4H, s), 4.91 (2H, s), 7.16 (1H, s), 7.52 (2H, s), 7.87 (1H, s), 8.81 (1H, s). M+H: 275.1
167		5/ 167	NMR2: 1.69-1.87 (2H, m), 1.87-2.01 (2H, m), 2.76-2.92 (3H, m), 3.19-3.31 (2H, m), 4.00 (4H, s), 4.85 (4H, s), 6.56 (1H, dd, J = 9.5, 2.0 Hz), 7.39 (1H, dd, J = 9.4, 0.7 Hz), 7.59-7.67 (2H, m).
168		6/ 168	NMR2: 1.49 (9H, s), 1.60-1.78 (2H, m), 1.85-1.98 (2H, m), 2.75-2.97 (3H, m), 4.00 (4H, s), 4.22 (2H, brs), 4.85 (4H, s), 6.57 (1H, dd, J=9.5, 2.0 Hz), 7.35 (1H, dd, J=9.4, 0.7 Hz), 7.59-7.65 (2H, m).
169		104/ 169	NMR2: 1.50 (9H, s), 2.56 (2H, brs), 3.66 (2H, t, J=5.6 Hz), 4.02 (4H, s), 4.10 (2H, m), 4.86 (4H, s), 5.91 (1H, brs), 6.63 (1H, dd, J=9.5, 2.1 Hz), 7.57 (1H, d, J=9.4 Hz), 7.62 (1H, d, J=1.3 Hz), 7.77 (1H, s).
170		170	NMR2: 4.02 (4H, s), 4.86 (4H, s), 6.67 (1H, dd, J=9.4, 2.0 Hz), 7.39 (1H, dd, J=9.4, 0.6 Hz), 7.57 (1H, d, J=1.3 Hz), 7.73 (1H, s).
171		5/ 171	NMR2: 1.06-1.18 (2H, m), 1.15-1.29 (2H, m), 1.72-1.82 (2H, m), 1.99-2.07 (2H, m), 2.79-2.88 (2H, m), 3.08-3.17 (1H, m), 3.20 (2H, dt, J=12.4, 3.2 Hz), 3.63-3.71 (1H, m), 7.74 (1H, s), 7.75 (1H, s), 7.97 (1H, s), 8.54 (1H, d, J=2.2 Hz), 8.66 (1H, d, J=2.2 Hz).
172		10/ 172	NMR2: 1.06-1.13 (2H, m), 1.13-1.27 (2H, m), 1.49 (9H, s), 1.70-1.81 (2H, m), 2.03 (2H, d, J=13.3 Hz), 2.91 (2H, s), 3.10-3.18 (1H, m), 3.67 (1H, tt, J=7.5, 3.9 Hz), 4.23 (2H, s), 7.74 (1H, s), 7.75 (1H, s), 7.94 (1H, s), 8.54 (1H, d, J=2.2 Hz), 8.66 (1H, d, J=2.2 Hz).
173		144/ 173	NMR2: 1.49 (9H, s), 1.71-1.83 (2H, m), 2.04 (2H, d, J=13.1 Hz), 2.91 (2H, s), 3.15 (1H, tt, J=12.0, 3.6 Hz), 4.24 (2H, s), 7.91 (2H, s), 7.96 (1H, s), 8.59 (1H, d, J=2.2 Hz), 8.73 (1H, d, J=2.2 Hz), 10.46 (1H, s).

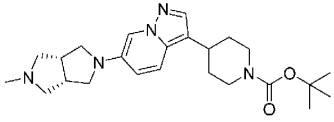
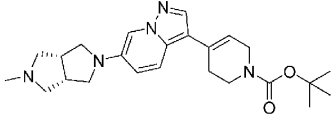
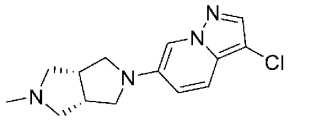
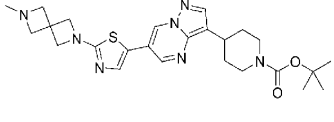
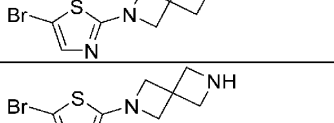
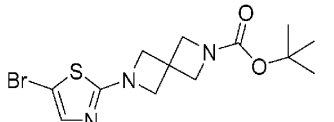
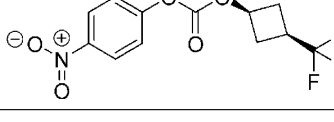
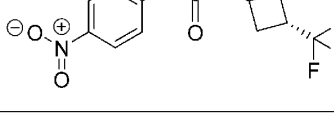
[Table 2-26]

174		7/ 174	NMR2: 1.56 (9H, d, J=0.8 Hz), 1.62 – 1.82 (5H, brm), , 1.98-2.12 (3H, brm), 2.13-2.19 (2H, brm), 2.91 (2H, s), 3.15 (1H, tt, J=12.0, 3.8 Hz), 3.75 (1H, td, J=11.2, 3.0 Hz), 4.08–4.15 (1H, m), 4.23 (2H, brs), 5.41–5.50 (1H, m), 7.82 (1H, s), 7.92 (1H, s), 7.94 (s, 1H), 8.57 (1H, d, J=2.1 Hz), 8.69 (1H, d, J=2.1 Hz).
175		5/ 175	NMR2: 1.73-2.36 (5H, m), 2.68-3.44 (11H, m), 3.68 (2H, dd, J=8.9, 3.5 Hz), 3.99 (2H, dd, J=8.8, 6.8 Hz), 6.88 (1H, dd, J=9.6, 2.0 Hz), 7.42 (1H, d, J=9.5 Hz), 7.64 (1H, s), 7.71-7.81 (1H, m).
176		6/ 176	NMR2: 1.48 (9H, s), 1.60-1.77 (2H, m), 1.82-2.00 (2H, m), 2.75-2.95 (3H, m), 2.97-3.11 (2H, m), 3.15 (2H, dd, J=9.3, 3.1 Hz), 3.34 (2H, dd, J=9.3, 7.4 Hz), 3.68 (2H, dd, J=9.0, 3.9 Hz), 3.99 (2H, dd, J=9.0, 6.8 Hz), 4.08-4.34 (2H, m), 6.87 (1H, dd, J=9.6, 2.1 Hz), 7.34 (1H, d, J=9.0 Hz), 7.61 (1H, s), 7.76 (1H, d, J=1.5 Hz).
177		104/ 177	NMR2: 1.50 (9H, s), 2.50-2.66 (2H, m), 3.00-3.13 (2H, m), 3.18 (2H, dd, J=9.4, 3.1 Hz), 3.38 (2H, dd, J=9.2, 7.5 Hz), 3.61-3.75 (4H, m), 3.99 (2H, dd, J=9.2, 6.8 Hz), 4.05-4.17 (2H, m), 5.91 (1H, brs), 6.93 (1H, dd, J=9.6, 2.1 Hz), 7.57 (1H, d, J=9.5 Hz), 7.73-7.82 (2H, m).
178		170/ 178	NMR2: 2.99-3.13 (2H, m), 3.17 (2H, dd, J=9.3, 3.2 Hz), 3.38 (2H, dd, J=9.3, 7.6 Hz), 3.69 (2H, dd, J=9.0, 3.8 Hz), 3.93-4.05 (2H, m), 6.97 (1H, dd, J=9.6, 2.0 Hz), 7.38 (1H, dd, J=9.6, 0.7 Hz), 7.69 (1H, d, J=1.6 Hz), 7.72 (1H, s).
179		106	NMR2: 0.70 (4H, d, J=5.3 Hz), 1.37 (12H, s), 1.74 (2H, s), 1.90-2.22 (2H, brm), 2.94 (2H, t, J=12.9 Hz), 3.12 – 3.22 (1H, m), 4.05 – 4.16 (2H, m), 4.33 (1H, s), 7.99 (1H, s), 8.62 (1H, d, J=1.4 Hz), 8.94 (1H, d, J=1.4 Hz).
180		180	NMR2: 0.71 (4H, d, J=5.6 Hz), 1.78 (2H, brs), 2.01 (2H, d, J=13.1 Hz), 2.93 (2H, t, J=12.8 Hz), 3.10–3.20 (1H, m), 4.10 (2H, ddd, J=9.5, 6.5, 4.0 Hz), 4.35 (1H, brs), 8.08 (1H, s), 8.41 (1H, d, J=2.6 Hz), 8.75 (1H, d, J=2.6 Hz).

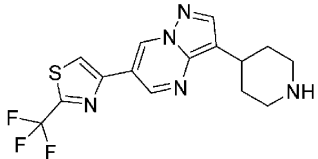
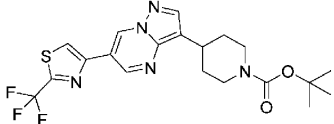
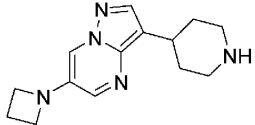
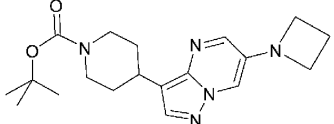
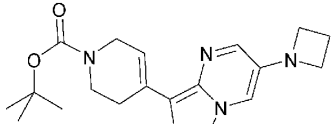
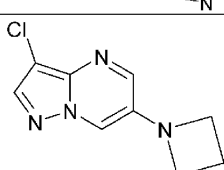
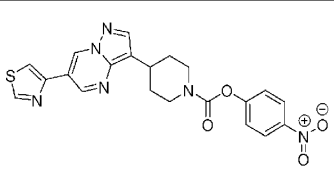
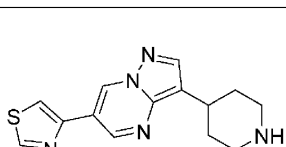
[Table 2-27]

181		6	NMR2: 1.49 (9H, s), 1.66–1.78 (2H, m), 1.94 (2H, d, J=13.3 Hz), 2.87 (2H, s), 2.93 (1H, tt, J=12.0, 3.7 Hz), 3.97 (3H, s), 4.25 (2H, s), 7.18 (1H, dd, J=9.1, 1.6 Hz), 7.49 (1H, d, J=9.1 Hz), 7.61 (1H, s), 7.74 (1H, s), 7.74 (1H, s), 8.53 (1H, s).
182		7	NMR2: 1.51 (9H, s), 2.60 (2H, s), 3.68 (2H, t, J=5.8 Hz), 3.98 (3H, s), 4.08–4.16 (2H, m), 5.97 (1H, s), 7.26 (1H, d, J=9.2 Hz), 7.63 (1H, s), 7.70 (1H, d, J=9.2 Hz), 7.75 (1H, s), 7.91 (1H, s), 8.55 (1H, s).
183		5/183	NMR2: 1.61-1.80 (3H, m), 1.86-1.98 (2H, m), 2.71-2.92 (7H, m), 3.13-3.25 (2H, m), 3.91 (4H, s), 6.56 (1H, dd, J=9.4, 2.0 Hz), 7.38 (1H, dd, J=9.4, 0.7 Hz), 7.61 (1H, dd, J=2.0, 0.7 Hz), 7.64 (1H, s).
184		6/184	NMR2: 1.49 (9H, s), 1.59-1.77 (2H, m), 1.84-1.99 (2H, m), 2.72-2.98 (7H, m), 3.91 (4H, s), 4.24 (2H, brs), 6.57 (1H, dd, J=9.4, 2.1 Hz), 7.35 (1H, dd, J=9.4, 0.7 Hz), 7.58-7.66 (2H, m).
185		104/ 185	NMR2: 1.50 (9H, s), 2.56 (2H, brs), 2.83 (4H, t, J=12.0 Hz), 3.66 (2H, t, J=5.7 Hz), 3.93 (4H, s), 4.10 (2H, brs), 5.91 (1H, brs), 6.64 (1H, dd, J=9.5, 2.1 Hz), 7.57 (1H, d, J=9.5 Hz), 7.62 (1H, d, J=1.3 Hz), 7.78 (1H, s).
186		170/ 186	NMR2: 2.83 (4H, t, J=11.9 Hz), 3.93 (4H, s), 6.67 (1H, dd, J=9.5, 2.0 Hz), 7.39 (1H, dd, J=9.5, 0.8 Hz), 7.57 (1H, dd, J=2.0, 0.7 Hz), 7.73 (1H, s).
187		5	NMR2: 1.64-1.82 (2H, m), 1.87-2.24 (3H, m), 2.34 (3H, s), 2.45 (2H, dd, J=9.3, 3.9 Hz), 2.67-2.91 (5H, m), 2.91-3.06 (2H, m), 3.12 (2H, dd, J=9.2, 3.2 Hz), 3.21 (2H, dd, J=9.5, 2.6 Hz), 3.29 (2H, dd, J=9.0, 7.7 Hz), 6.88 (1H, dd, J=9.6, 2.1 Hz), 7.36 (1H, dd, J=9.6, 0.6 Hz), 7.62 (1H, s), 7.76 (1H, d, J=1.5 Hz).

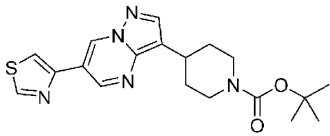
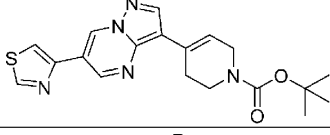
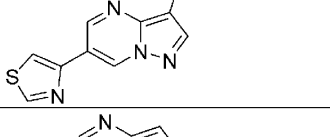
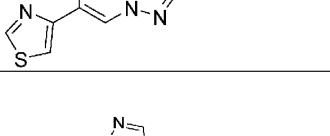
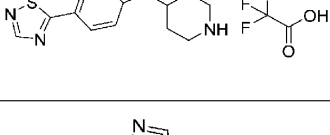
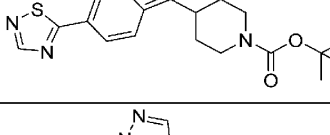
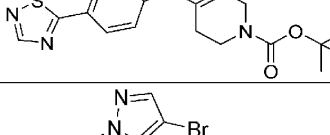
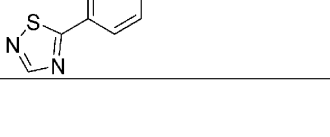
[Table 2-28]

188		6	NMR2: 1.48 (9H, s), 1.60-1.76 (2H, m), 1.86-1.99 (2H, m), 2.34 (3H, s), 2.45 (2H, dd, J=9.3, 3.8 Hz), 2.74 (2H, dd, J=9.3, 7.0 Hz), 2.79-3.05 (5H, m), 3.12 (2H, dd, J=9.2, 3.1 Hz), 3.30 (2H, dd, J=9.0, 7.8 Hz), 4.16-4.36 (2H, m), 6.89 (1H, dd, J=9.6, 2.0 Hz), 7.32 (1H, d, J=9.6 Hz), 7.60 (1H, s), 7.76 (1H, d, J=1.5 Hz).
189		104	NMR2: 1.50 (9H, s), 2.35 (3H, s), 2.44-2.65 (4H, m), 2.66-2.82 (2H, m), 2.92-3.07 (2H, m), 3.14 (2H, dd, J = 9.2, 3.1 Hz), 3.25-3.42 (2H, m), 3.59-3.75 (2H, m), 4.02-4.18 (2H, m), 5.91 (1H, brs), 6.95 (1H, dd, J = 9.7, 2.0 Hz), 7.55 (1H, d, J = 9.8 Hz), 7.71-7.84 (2H, m).
190		170	NMR2: 2.34 (3H, s), 2.45-2.53 (2H, m), 2.65-2.75 (2H, m), 2.92-3.04 (2H, m), 3.10-3.17 (2H, m), 3.29-3.39 (2H, m), 6.99 (1H, dd, J=9.6, 2.0 Hz), 7.37 (1H, dd, J=9.6, 0.7 Hz), 7.68-7.73 (2H, m).
191		105	NMR2: 1.49 (9H, s), 1.69-1.81 (2H, m), 2.01 (2H, d, J=12.9 Hz), 2.32 (3H, s), 2.90 (2H, s), 3.13 (1H, tt, J=12.1, 3.7 Hz), 3.40 (4H, s), 4.21 (4H, s), 4.24 (2H, brs), 7.39 (1H, s), 7.93 (1H, s), 8.54 (1H, d, J=2.2 Hz), 8.56 (1H, d, J=2.2 Hz).
192		78	NMR2: 2.30 (3H, s), 3.37 (4H, s), 4.11 (4H, s), 7.04 (1H, s).
193		5	NMR2: 3.83 (4H, s), 4.15 (4H, s), 7.05 (1H, s).
194		194	NMR2: 1.44 (9H, s), 4.10 (4H, s), 4.15 (4H, s), 7.06 (1H, s).
195		1	NMR2: 2.37-2.48 (2H, m), 2.59-2.76 (3H, m), 4.98-5.07 (1H, m), 7.35-7.42 (2H, m), 8.24-8.32 (2H, m). Stereochemistry was determined by NOESY.
196		1	NMR2: 2.50-2.65 (2H, m), 2.66-2.75 (2H, m), 2.94-3.10 (1H, m), 5.23 (1H, tdd, J=7.6, 6.2, 5.1 Hz), 7.35-7.42 (2H, m), 8.25-8.33 (2H, m). Stereochemistry was determined by NOESY.

[Table 2-29]

197		5	NMR2: 1.73–1.84 (2H, m), 2.01–2.08 (2H, m), 2.79–2.88 (2H, m), 3.15 (1H, tt, J=12.0, 3.8 Hz), 3.21 (2H, dt, J=12.4, 3.3 Hz), 7.78 (1H, s), 8.07 (1H, s), 8.86 (1H, d, J=2.2 Hz), 9.26 (1H, d, J=2.2 Hz).
198		105	NMR2: 1.49 (9H, s), 1.78 (2H, qd, J=12.6, 4.2 Hz), 2.00–2.08 (2H, m), 2.92 (2H, s), 3.17 (1H, tt, J=11.9, 3.6 Hz), 4.25 (2H, s), 7.79 (1H, s), 8.04 (1H, s), 8.87 (1H, d, J=2.2 Hz), 9.26 (1H, d, J=2.2 Hz).
199		5	M+H: 258.2
200		6	M+H: 358.4
201		104	NMR1: 1.43 (9H, s), 2.35 (2H, p, J=7.2 Hz), 2.56 (2H, td, J=5.6, 2.9 Hz), 3.56 (2H, q, J=4.1 Hz), 3.90 (4H, t, J=7.2 Hz), 4.02 (2H, s), 6.60 (1H, s), 8.04 (1H, s), 8.22 (2H, s). M+H: 356.4
202		104	NMR1: 2.36 (2H, p, J=7.2 Hz), 3.91 (4H, t, J=7.3 Hz), 8.11 (1H, s), 8.26 (1H, d, J=2.5 Hz), 8.28 (1H, d, J=2.5 Hz). M+H: 209.2, 211.1
203		1	NMR2: 1.89–2.01 (2H, m), 2.18 (2H, d, J=13.5 Hz), 3.10 (1H, t, J=12.6 Hz), 3.17–3.33 (2H, m), 4.42 (2H, t, J=16.7 Hz), 7.31–7.38 (2H, m), 7.66 (1H, d, J=1.8 Hz), 8.04 (1H, s), 8.24–8.31 (2H, m), 8.94 (1H, d, J=2.1 Hz), 8.96 (1H, d, J=1.8 Hz), 9.27 (1H, d, J=2.1 Hz).
204		5	NMR2: 1.76–1.88 (2H, m), 2.02–2.10 (2H, m), 2.81–2.90 (2H, m), 3.17 (1H, tt, J=12.0, 3.8 Hz), 3.24 (2H, dt, J=12.2, 3.3 Hz), 7.63 (1H, t, J=1.7 Hz), 8.04 (1H, s), 8.91 (1H, d, J=2.1 Hz), 8.95 (1H, d, J=1.7 Hz), 9.25 (1H, d, J=2.1 Hz). M+H: 286.3

[Table 2-30]

205		6	NMR2: 1.49 (9H, s), 1.71–1.83 (2H, m), 2.01–2.09 (2H, m), 2.92 (2H, s), 3.17 (1H, tt, J=11.9, 3.7 Hz), 4.24 (2H, s), 7.63 (1H, d, J=1.9 Hz), 8.01 (1H, s), 8.91 (1H, d, J=2.2 Hz), 8.95 (1H, d, J=1.9 Hz), 9.25 (1H, d, J=2.2 Hz).
206		7	NMR2: 1.50 (9H, s), 2.71 (2H, s), 3.71 (2H, s), 4.17 (2H, d, J=3.7 Hz), 6.69 (1H, s), 7.66 (1H, d, J=1.9 Hz), 8.15 (1H, s), 8.96 (1H, d, J=1.9 Hz), 8.98 (1H, d, J=2.2 Hz), 9.27 (1H, d, J=2.2 Hz).
207		13	NMR2: 7.70 (1H, s), 8.16 (1H, s), 8.96 (1H, s), 9.04 (1H, s), 9.29 (1H, s). M+H:281,283
208		7	NMR2: 6.75 (1H, dd, J=2.4, 0.9 Hz), 7.66 (1H, d, J=1.8 Hz), 8.17 (1H, d, J=2.4 Hz), 8.96 (1H, d, J=1.8 Hz), 8.99 (1H, d, J=2.1 Hz), 9.32 (1H, dd, J=2.1, 0.9 Hz).
209		5	NMR2: 1.82 – 1.95 (2H, m), 2.07 (2H, d, J=13.9 Hz), 3.02–3.09 (2H, s), 3.17 – 3.26 (1H, m), 3.40 (2H, brs), 7.79 (1H, dd, J=9.3, 1.6 Hz), 7.93 (1H, dd, J=9.3, 1.0 Hz), 8.14 (1H, s), 8.38 (1H, brs), 8.59 (1H, brs), 8.99 (1H, s), 9.53 (1H, s). M+H:286
210		6	NMR2: 1.50 (9H, s), 1.67–1.79 (2H, m), 1.95 (2H, d, J=13.1 Hz), 2.88 (2H, brs), 2.97 (1H, tt, J=12.0, 3.7 Hz), 4.27 (2H, brs), 7.54 (1H, dd, J=9.3, 1.6 Hz), 7.61 (1H, dd, J=9.3, 1.0 Hz), 7.94 (1H, s), 8.72 (1H, s), 9.21 (1H, s).
211		7	NMR2: 1.51 (9H, s), 2.61 (2H, s), 3.70 (2H, t, J=5.5 Hz), 4.14 (2H, s), 6.03 (1H, s), 7.60 (1H, dd, J=9.3, 1.6 Hz), 7.81 (1H, d, J=9.3 Hz), 8.08 (1H, s), 8.73 (1H, s), 9.22 (1H, s).
212		13	NMR2: 7.61–7.72 (2H, m), 8.06 (1H, s), 8.74 (1H, s), 9.19–9.24 (1H, m).

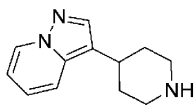
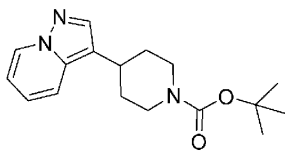
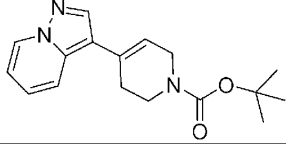
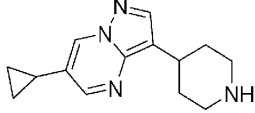
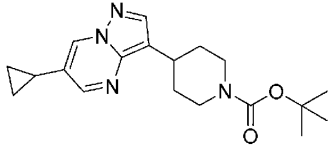
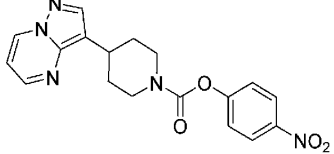
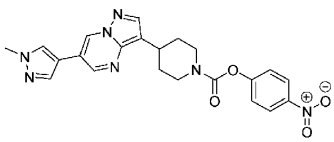
[Table 2-31]

213		213	NMR2: 6.64 (1H, dd, J=2.3, 1.0 Hz), 7.60 (1H, dd, J=9.2, 1.6 Hz), 7.67 (1H, dd, J=9.2, 1.0 Hz), 8.09 (1H, d, J=2.3 Hz), 8.72 (1H, s), 9.24–9.29 (1H, m).
214		5	NMR2: 1.61 (1H, s), 1.69–1.85 (2H, m), 1.94–2.11 (2H, m), 2.75–2.89 (2H, m), 3.00–3.30 (3H, m), 6.56 (1H, t, J=71.8 Hz), 8.02 (1H, s), 8.38 (1H, d, J=2.6 Hz), 8.59 (1H, d, J=2.4 Hz).
215		10	NMR2: 1.49 (9H, s), 1.66–1.84 (2H, m), 1.94–2.10 (2H, m), 2.77–3.02 (2H, m), 3.04–3.20 (1H, m), 4.24 (2H, brs), 6.57 (1H, t, J=71.7 Hz), 7.99 (1H, s), 8.39 (1H, d, J=2.6 Hz), 8.60 (1H, d, J=2.6 Hz).
216		5/ 216	NMR2: 1.72–1.84 (2H, m), 2.00–2.09 (2H, m), 2.79–2.88 (2H, m), 3.09–3.19 (1H, m), 3.21 (2H, dt, J=12.4, 3.3 Hz), 8.04 (1H, s), 8.12 (1H, s), 8.63 (1H, d, J=2.2 Hz), 8.81 (1H, d, J=2.2 Hz), 8.87 (1H, s).
217		105/ 217	NMR2: 1.49 (9H, d, J=1.8 Hz), 1.71–1.85 (2H, m), 2.00–2.06 (2H, m), 2.91 (2H, s), 3.16 (1H, tt, J=12.0, 3.7 Hz), 4.24 (2H, s), 8.02 (1H, s), 8.13 (1H, s), 8.63 (1H, d, J=2.2 Hz), 8.81 (1H, d, J=2.2 Hz), 8.88 (1H, s).
218		5	M+H: 245.4
219		6	NMR2: 1.35 (6H, d, J=6.9 Hz), 1.48 (9H, s), 1.68–1.80 (2H, m), 1.97–2.05 (2H, m), 2.90 (2H, s), 2.95–3.07 (1H, m), 3.12 (1H, tt, J=12.0, 3.7 Hz), 4.22 (2H, s), 7.90 (1H, s), 8.37 (1H, d, J=2.2 Hz), 8.42 (1H, dd, J=2.2, 0.9 Hz). M+H: 345.5
220		105	NMR2: 1.48 (9H, d, J=16.8 Hz), 2.19 (3H, s), 2.65–2.72 (2H, m), 3.66–3.75 (2H, m), 4.15 (2H, d, J=1.0 Hz), 5.27 (1H, q, J=1.5 Hz), 5.57 (1H, s), 6.64 (1H, s), 8.08 (1H, s), 8.60 (1H, d, J=2.3 Hz), 8.73 (1H, d, J=2.3 Hz). M+H: 341.5
221		7	NMR2: 2.19 (3H, d, J=0.5 Hz), 5.31 (1H, d, J=1.5 Hz), 5.58 (1H, s), 8.07 (1H, s), 8.58 (1H, d, J=2.2 Hz), 8.77 (1H, d, J=2.2 Hz). M+H: 194.2

[Table 2-32]

222		6/ 222	NMR2: 1.49 (9H, s), 1.61–1.76 (2H, m), 1.87–1.96 (2H, m), 2.88 (3H, dtt, J=14.3, 10.8, 5.4 Hz), 3.03–3.10 (4H, m), 3.85–3.92 (4H, m), 4.24 (2H, brs), 6.96 (1H, dt, J=9.7, 1.4 Hz), 7.39 (1H, d, J=9.6 Hz), 7.67 (1H, s), 7.92 (1H, d, J=1.4 Hz).
223		104	NMR2: 1.50 (9H, s), 2.57 (2H, s), 3.06–3.11 (4H, m), 3.67 (2H, t, J=5.6 Hz), 3.86–3.92 (4H, m), 4.11 (2H, s), 5.93 (1H, s), 7.03 (1H, dd, J=9.7, 2.1 Hz), 7.60 (1H, d, J=9.7 Hz), 7.82 (1H, s), 7.93 (1H, d, J=2.1 Hz).
224		224	NMR2: 3.05–3.11 (4H, m), 3.86–3.92 (4H, m), 7.08 (1H, dd, J=9.6, 2.0 Hz), 7.43 (1H, d, J=9.6 Hz), 7.78 (1H, s), 7.88 (1H, d, J=2.0 Hz).
225		5	NMR2: 1.73–1.85 (2H, m), 2.04 (2H, ddt, J=11.2, 4.5, 2.3 Hz), 2.79–2.88 (2H, m), 3.11–3.22 (1H, m), 3.22 (2H, dd, J=8.0, 4.6 Hz), 8.13 (1H, s), 8.99 (1H, d, J=2.2 Hz), 9.20 (1H, s), 9.27 (1H, d, J=2.2 Hz).
226		105	NMR2: 1.49 (9H, s), 1.72–1.84 (2H, m), 2.01–2.09 (2H, m), 2.92 (2H, brs), 3.19 (1H, tt, J=12.0, 3.7 Hz), 4.25 (2H, brs), 8.11 (1H, s), 9.00 (1H, d, J=2.2 Hz), 9.20 (1H, s), 9.27 (1H, d, J=2.2 Hz).
227		105	NMR2: 1.49 (9H, s), 1.72–1.84 (2H, m), 2.03 (2H, d, J=12.5 Hz), 2.92 (2H, brs), 3.18 (1H, tt, J=12.0, 3.8 Hz), 4.25 (2H, brs), 8.12 (1H, s), 8.77 (1H, s), 8.90 (1H, d, J=2.2 Hz), 9.33 (1H, d, J=2.2 Hz).
228		5	NMR2: 1.73–1.85 (2H, m), 2.00–2.06 (2H, m), 2.76 (3H, s), 2.83 (2H, td, J=12.3, 2.5 Hz), 3.11–3.25 (3H, m), 8.14 (1H, s), 8.84 (1H, d, J=2.2 Hz), 9.27 (1H, d, J=2.2 Hz).
229		105	NMR2: 1.49 (9H, s), 1.72–1.84 (2H, m), 2.03 (2H, brd, J=13.7 Hz), 2.76 (3H, s), 2.90 (2H, brd, J=12.1 Hz), 3.13–3.23 (1H, m), 4.24 (2H, brs), 8.11 (1H, s), 8.85 (1H, d, J=2.2 Hz), 9.28 (1H, d, J=2.2 Hz).
230		10	NMR2: 1.48 (9H, s), 1.62–1.83 (2H, m), 1.91–2.11 (2H, m), 2.67–3.02 (2H, m), 3.02–3.21 (1H, m), 3.87 (3H, s), 4.22 (2H, brs), 7.83 (1H, s), 8.17 (1H, d, J=2.7 Hz), 8.31 (1H, d, J=2.7 Hz).

[Table 2-33]

231		5	NMR2: 1.69–1.80 (2H, m), 1.91–1.99 (2H, m), 2.75–2.84 (2H, m), 2.86–2.96 (1H, m), 3.21 (2H, dt, J=12.4, 3.4 Hz), 6.70 (1H, td, J=6.8, 1.2 Hz), 7.04 (1H, ddd, J=9.0, 6.8, 1.1 Hz), 7.51 (1H, dt, J=9.0, 1.2 Hz), 7.81 (1H, s), 8.41 (1H, dt, J=6.8, 1.1 Hz).
232		6	NMR2: 1.49 (9H, s), 1.65 – 1.77 (2H, m), 1.94 (2H, d, J=13.2 Hz), 2.87 (2H, s), 2.93 (1H, tt, J=12.1, 3.7 Hz), 4.24 (2H, s), 6.71 (1H, dd, J=6.9, 1.2 Hz), 7.05 (1H, ddd, J=9.0, 6.9, 1.1 Hz), 7.48 (1H, dt, J=9.0, 1.2 Hz), 7.78 (1H, s), 8.42 (1H, dt, J=6.9, 1.1 Hz).
233		7	M+H: 300.3
234		5	NMR2: 0.67-0.81 (2H, m), 0.96-1.10 (2H, m), 1.66-1.82 (3H, m), 1.87-2.07 (3H, m), 2.77-2.88 (2H, m), 3.04-3.15 (1H, m), 3.15-3.24 (2H, m), 7.91 (1H, s), 8.28-8.36 (2H, m).
235		235	NMR2: 0.66-0.81 (2H, m), 0.96-1.14 (2H, m), 1.49 (9H, s), 1.67-1.83 (2H, m), 1.87-2.10 (3H, m), 2.74-3.00 (2H, m), 3.00-3.20 (1H, m), 4.02-4.44 (2H, m), 7.88 (1H, s), 8.28-8.37 (2H, m).
236		1	M+H: 368.4
237		1	NMR2: 1.86–2.01 (2H, m), 2.16 (2H, d, J=13.1 Hz), 3.10 (1H, t, J=12.8 Hz), 3.19 – 3.32 (2H, m), 4.01 (3H, s), 4.41 (2H, t, J=13.7 Hz), 7.29 – 7.38 (2H, m), 7.68 (1H, d, J=0.8 Hz), 7.78 (1H, d, J=0.8 Hz), 7.97 (1H, s), 8.23 – 8.31 (2H, m), 8.58 (1H, d, J=2.2 Hz), 8.69 (1H, d, J=2.2 Hz). M+H: 448.6

[Table 2-34]

238		6	NMR2: 1.49 (9H, s), 1.70–1.81 (2H, m), 2.03 (2H, d, J=13.0 Hz), 2.91 (2H, s), 3.15 (1H, tt, J=12.1, 3.7 Hz), 3.38 (3H, s), 3.80 (2H, d, J=5.1 Hz), 4.24 (2H, s), 4.37 (2H, t, J=5.1 Hz), 7.79 (2H, s), 7.94 (1H, s), 8.57 (1H, d, J=2.2 Hz), 8.69 (1H, d, J=2.2 Hz).
239		104	NMR2: 1.50 (9H, s), 2.69 (2H, s), 3.38 (3H, s), 3.70 (2H, t, J=6.2 Hz), 3.76–3.83 (2H, m), 4.16 (2H, d, J=3.2 Hz), 4.33–4.40 (2H, m), 6.66 (1H, s), 7.81 (2H, s), 8.08 (1H, s), 8.64 (1H, d, J=2.3 Hz), 8.70 (1H, d, J=2.3 Hz).
240		7	NMR2: 3.38 (3H, s), 3.77–3.83 (2H, m), 4.34–4.40 (2H, m), 7.81 (2H, dd, J=6.6, 0.9 Hz), 8.07 (1H, s), 8.68 (1H, d, J=2.1 Hz), 8.69 (1H, d, J=2.1 Hz).
241		1	NMR2: 1.81–1.92 (2H, m), 2.08 (2H, d, J=13.4 Hz), 3.01–3.11 (2H, m), 3.21 (1H, t, J=13.0 Hz), 3.98 (3H, s), 4.42 (2H, t, J=16.2 Hz), 7.22 (1H, dd, J=9.2, 1.5 Hz), 7.31–7.37 (2H, m), 7.51 (1H, d, J=9.2 Hz), 7.62 (1H, d, J=0.8 Hz), 7.75 (1H, d, J=0.8 Hz), 7.80 (1H, s), 8.24–8.31 (2H, m), 8.56 (1H, s). M+H: 447
242		242	NMR2: 1.68–1.80 (2H, m), 1.91–1.99 (2H, m), 2.75–2.84 (2H, m), 2.85–2.95 (1H, m), 3.21 (2H, dt, J=12.4, 3.4 Hz), 3.97 (3H, s), 7.17 (1H, dd, J=9.2, 1.5 Hz), 7.51 (1H, dd, J=9.2, 1.0 Hz), 7.61 (1H, d, J=0.8 Hz), 7.74 (1H, d, J=0.9 Hz), 7.78 (1H, s), 8.53 (1H, dd, J=1.5, 1.0 Hz).
243		7	NMR2: 3.98 (3H, s), 7.31 (1H, dd, J=9.2, 1.5 Hz), 7.54 (1H, dd, J=9.2, 1.0 Hz), 7.63 (1H, d, J=0.9 Hz), 7.75 (1H, d, J=0.9 Hz), 7.87 (1H, s), 8.51 (1H, dd, J=1.5, 1.0 Hz).
244		244	NMR2: 1.51 (9H, s), 2.60 (2H, s), 3.66 – 3.71 (2H, m), 3.98 (3H, s), 4.13 (2H, s), 5.97 (1H, s), 7.26 (1H, d, J=9.2 Hz), 7.63 (1H, s), 7.70 (1H, d, J=9.2 Hz), 7.75 (1H, s), 7.91 (1H, s), 8.55 (1H, s).

[0298] Examples

[0299] Example 3. Synthesis of oxazol-4-ylmethyl4-(5-methoxypyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

5-Methoxy-3-(piperidin-4-yl)pyrazolo[1,5-a]pyridine (28.3 mg)/THF (2 mL) was prepared in a flask. 4-nitrophenyl (oxazol-4-ylmethyl) carbonate (48.5 mg) was added to the mixture at 0°C. DIPEA (64.1 μ L) was added to the mixture at 0°C. The mixture was stirred at room temperature for 3 h. H₂O was added to the reaction mixture at 0°C

to stop the reaction. The mixture was extracted with DCM three times. The organic layer was collected, followed by the evaporation to obtain the crude product. The crude material was purified by basic-silica gel column chromatography (hexane/AcOEt) to obtain the object compound (40.8 mg).

[0300] Example 7. Synthesis of oxazol-4-ylmethyl

4-(6-((1-(difluoromethyl)cyclopropyl)methoxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a solution of tert-butyl

4-[6-[[1-(difluoromethyl)cyclopropyl)methoxy]pyrazolo[1,5-a]pyridin-3-yl]piperidine-1-carboxylate (87 mg) in DCM (2 mL) was added TFA (954 µL) at room temperature. The mixture was stirred for 1 h. The mixture was concentrated.

To a solution of the residue in DCM (2 mL) was added TEA (288 µL) and 4-nitrophenyl (oxazol-4-ylmethyl)carbonate (65.4 mg) at room temperature. The mixture was stirred at room temperature for 3 h. The mixture was concentrated. The residue was purified by basic-silica gel column chromatography (hexane/AcOEt) to obtain the object compound (67 mg).

[0301] Example 47. Synthesis of oxazol-4-ylmethyl

4-(6-(2-methoxyethoxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

A mixture of 6-(2-methoxyethoxy)-3-(piperidin-4-yl)pyrazolo[1,5-a]pyridine (30.8 mg) in a flask. 4-Nitrophenyl(oxazol-4-ylmethyl)carbonate (44.3 mg) was added to the mixture at 0°C. DIPEA (58.6 µl) was added to the mixture at 0°C. The mixture was stirred at room temperature under nitrogen for 3 h. H₂O was added to the reaction mixture at 0°C to stop the reaction. The mixture was extracted with DCM three times. The organic layers were concentrated. The residue was purified basic-silica gel column chromatography (hexane:AcOEt) to obtain the object compound (38.8 mg).

[0302] Example 50. Synthesis of

1-(4-(6-methoxypyrazolo[1,5-a]pyridin-3-yl)piperidin-1-yl)-3-(p-tolyloxy)propan-1-one

To a mixture of the 3-(p-tolyloxy)propanoic acid (18 mg), 6-methoxy-3-(piperidin-4-yl)pyrazolo[1,5-a]pyridine (25 mg), HOBt hydrate (22.95 mg) and TEA (41.8 µl) in DMF (1.5 ml) was stirred at room temperature under nitrogen for 3 h. H₂O was added to the reaction mixture at 0°C. The mixture was extracted with DCM and the organic layer was concentrated. The residue was purified by basic-silica gel column chromatography (hexane/AcOEt) to obtain the object compound (31.4 mg).

[0303] Example 51. Synthesis of oxazol-4-ylmethyl

4-(6-cyclopropoxypyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a solution of tert-butyl

4-(6-cyclopropyloxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (40 mg) in DCM (1.5 ml) was added TFA (0.5 ml) at room temperature. The mixture was stirred at room temperature for 3 h. The mixture was concentrated to give the crude amine. To a mixture of the amine in DCM (2 ml) was added TEA (0.156 ml) and 4-nitrophenyl (oxazol-4-ylmethyl) carbonate (35.5 mg) at room temperature. The mixture was stirred at room temperature for 18 h. The mixture was concentrated. The residue was purified by basic-silica gel column chromatography (hexane/AcOEt) to obtain the object compound (38 mg).

[0304] Example 52. Synthesis of oxazol-4-ylmethyl

4-(6-((1-methylpiperidin-4-yl)oxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a solution of tert-butyl 4-(6-((1-methylpiperidin-4-yl)oxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (83.5 mg) in DCM (10 ml), TFA (1 ml) was added at RT. The mixture was stirred at room temperature for 2 h and then evaporated to obtain the intermediate compound as TFA salt. To a solution of intermediate TFA salt in DCM (10 ml) under nitrogen, TEA (0.3 ml) and 4-nitrophenyl(oxazol-4-ylmethyl)carbonate (73.9 mg) were added at room temperature. The mixture was stirred at room temperature under nitrogen for 2.5 h. AcOEt and H₂O were added at room temperature. The organic layer was concentrated. The residue was purified by basic-silica gel column chromatography (hexane/AcOEt to AcOEt/MeOH) to obtain the object compound (35 mg).

[0305] Example 54. Synthesis of thiazol-4-ylmethyl

4-(6-(2-morpholinoethyl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

A mixture of benzyl 4-(6-(2-morpholinoethyl)pyrazolo[1,5-a]pyrimidin-3-yl)-3,6-dihydropyridine-1(2H)-carboxylate (195 mg) and 10% Pd/C (170 mg) in AcOEt/EtOH (1/1) (10 mL) was stirred at 50°C under hydrogen for 1 h. The reaction mixture was filtered through Celite. The filtrate was concentrated to obtain the intermediate compound. A solution of the intermediate compound, TEA (121 µL) and tert-butyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (139 mg) in DCM (10 mL) was stirred at room temperature for 3 days. The mixture was concentrated. The residue was purified by basic-silica gel column chromatography (hexane/AcOEt) to obtain the object compound (108 mg).

[0306] Example 55. Synthesis of

1-(4-(6-methoxy)pyrazolo[1,5-a]pyridin-3-yl)piperidin-1-yl)-2-((2-methylbenzyl)oxy)ethan-1-one

A mixture of 2-methylbenzyl alcohol (45.02 mg), NaH (12.86 mg) in DMF (1.5 mL) was slightly sonicated, then stirred at room temperature for a few hours. To this

mixture, a solution of

2-chloro-1-(4-(6-methoxypyrazolo[1,5-a]pyridin-3-yl)piperidin-1-yl)ethan-1-one (37.8 mg) in DMF (0.5 mL) was added at 0°C. The mixture was stirred at room temperature under nitrogen. Then, sodium iodide (9.20 mg) was added to the mixture. The mixture was stirred at 60°C under nitrogen overnight. Sat. NH₄Cl aq. was added to the mixture at 0°C. The mixture was extracted with DCM. The organic layer was concentrated. The residue was purified by basic-silica gel column chromatography (hexane/AcOEt) to obtain the object compound (18.1 mg).

[0307] Example 56. Synthesis of thiazol-4-ylmethyl

4-(6-(2-morpholino-2-oxoethyl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

To a solution of

2-(3-(1-((thiazol-4-ylmethoxy)carbonyl)piperidin-4-yl)pyrazolo[1,5-a]pyrimidin-6-yl)acetic acid (30 mg) in DMF (2 ml) were added HATU (36.9 mg), DIPEA (26.1 µl, 0.149 mmol) and morpholine (13.03 µl, 0.149 mmol) at room temperature. The mixture was stirred overnight. The reaction mixture was diluted with sat. NaHCO₃ aq. and H₂O and extracted with AcOEt. The organic layer was concentrated. The residue was purified by column chromatography to obtain the object compound (13 mg).

[0308] Example 57. Synthesis of thiazol-4-ylmethyl

4-(6-(2-methoxyethoxy)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

To a solution of 6-(2-methoxyethoxy)-3-(piperidin-4-yl)pyrazolo[1,5-a]pyrimidine (82.5 mg) in DCM (10 mL) under nitrogen, TEA (125 µL) and 4-nitrophenyl (thiazol-4-ylmethyl) carbonate (131 mg) were added at RT. The mixture was stirred at room temperature under nitrogen for 3.5 h. H₂O was added at room temperature. The water layer was extracted with AcOEt. The organic layer was concentrated. The residue was purified by amino silica gel column chromatography (hexane/AcOEt). The obtained product was triturated in IPE (solid appeared) at room temperature. The solid was collected to obtain the object compound (92.1 mg).

[0309] Example 65. Synthesis of oxazol-4-ylmethyl

4-(6-(morpholinomethyl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate hydrochloride

To a solution of 4-((3-(piperidin-4-yl)pyrazolo[1,5-a]pyridin-6-yl)methyl)morpholine (41 mg) in THF (3 mL) were added DIPEA (36 µL) and 4-nitrophenyl(oxazol-4-ylmethyl)carbonate (54 mg), and the mixture was stirred at room temperature for 30 min. Sat. NaHCO₃ aq. and AcOEt were added to the mixture. The organic layer was separated by phase separator (Whatman, filter paper 1PS), and the solvent was removed. The residue was purified by amino silica gel column chromatography (heptane: AcOEt). The obtained product was dissolved in AcOEt (3 mL),

and 4N HCl/AcOEt (22 μ L) was added to the mixture. The reaction mixture was stirred at room temperature for 30 min. The precipitates were collected on a filter to obtain the object compound (20 mg).

[0310] Example 67. Synthesis of oxazol-4-ylmethyl

4-(6-(2,2-difluoroethoxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a solution of 6-(2,2-difluoroethoxy)-3-(piperidin-4-yl)pyrazolo[1,5-a]pyridine (35 mg) in THF (3 mL) were added DIPEA (33 μ L) and 4-nitrophenyl(oxazol-4-ylmethyl)carbonate (49 mg), and the mixture was stirred at room temperature for 30 min. Sat. NaHCO_3 aq. and AcOEt were added to the mixture. The organic layer was separated by phase separator (Whatman, filter paper 1PS), and the solvent was removed. The residue was purified by basic-silica gel column chromatography (heptane/AcOEt). The obtained solid was washed by trituration with diisopropyl ether, and then collected on a filter to obtain the object compound (36 mg).

[0311] Example 68. Synthesis of thiazol-4-ylmethyl

4-(6-(2,2-difluoroethoxy)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a solution of 6-(2,2-difluoroethoxy)-3-(piperidin-4-yl)pyrazolo[1,5-a]pyridine (35 mg) in THF (3 mL) were added DIPEA (33 μ L) and 4-nitrophenyl(thiazol-4-ylmethyl)carbonate (52 mg), and the mixture was stirred at room temperature for 30 min. Sat. NaHCO_3 aq. and AcOEt were added to the mixture. The organic layer was separated by phase separator (Whatman, filter paper 1PS), and the solvent was removed. The residue was purified by basic-silica gel column chromatography (heptane/AcOEt). The obtained solid was washed by trituration with diisopropyl ether, and then collected on a filter to obtain the object compound (43 mg).

[0312] Example 76. Synthesis of oxazol-4-ylmethyl

4-(6-(1-cyclopropyl-3,5-dimethyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

To a solution of 6-(1-cyclopropyl-3,5-dimethyl-1H-pyrazol-4-yl)-3-(piperidin-4-yl)pyrazolo[1,5-a]pyrimidine (80 mg) in DCM (5 mL) were added TEA (66.3 μ L) and 4-nitrophenyl(oxazol-4-ylmethyl)carbonate (75 mg) at room temperature. The mixture was stirred for 3 h. The mixture was concentrated. The residue was purified by basic-silica gel column chromatography (hexane/AcOEt) to obtain the object compound (100 mg).

[0313] Example 82. Synthesis of

(4-(6-(1-cyclopropyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidin-1-yl)(3,3-difluoroazetidin-1-yl)methanone

To a mixture of 6-(1-cyclopropyl-1H-pyrazol-4-yl)-3-(piperidin-4-yl)pyrazolo[1,5-a]pyridine (35 mg)

and 4-nitrophenyl 3,3-difluoroazetidine-1-carboxylate (38.2 mg) in THF (2.5 mL), DIPEA (80 μ L) was added. The mixture was stirred under reflux overnight under nitrogen. H₂O was added to the reaction mixture at 0°C to stop the reaction. The mixture was extracted with DCM. The organic layer was concentrated. The residue was purified by basic-silica gel column chromatography (hexane/AcOEt) to obtain the object compound (44 mg).

[0314] Example 85. Synthesis of oxazol-4-ylmethyl

4-(6-(1-cyclopropyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a solution of 6-(1-cyclopropyl-1H-pyrazol-4-yl)-3-(piperidin-4-yl)pyrazolo[1,5-a]pyridine (50 mg) in DCM (5 ml) was added 4-nitrophenyl(oxazol-4-ylmethyl)carbonate (47.3 mg) at RT. The mixture was stirred for 3 h. The mixture was concentrated. The residue was purified by basic-silica gel column chromatography (hexane/AcOEt) and silica gel column chromatography (AcOEt/MeOH) and triturated with hexane/AcOEt to obtain the object compound (46 mg).

[0315] Example 93. Synthesis of cyclopropyl

4-(6-(1-cyclopropyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

To a solution of 6-(1-cyclopropyl-1H-pyrazol-4-yl)-3-(piperidin-4-yl)pyrazolo[1,5-a]pyrimidine (65 mg) in DCM (4 mL) were added TEA (58.8 μ L) and cyclopropyl(4-nitrophenyl)carbonate (56.4 mg) at room temperature. The mixture was stirred for 3 h. The mixture was concentrated. The residue was purified by basic-silica gel column chromatography (hexane/AcOEt) to obtain the object compound (60 mg).

[0316] Example 94. Synthesis of cyclopropyl

4-(6-(tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a solution of tert-butyl 4-(6-((3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (70 mg) in THF (5 ml), DIPEA (58.7 μ L) and cyclopropyl(4-nitrophenyl)carbonate (75 mg) were added at room temperature. The mixture was stirred at room temperature overnight. Sat. NaHCO₃ aq. was added. The reaction mixture was extracted with AcOEt. The organic layer was concentrated. The residue was purified by basic-silica gel chromatography (heptane/AcOEt/MeOH). The obtained solid was triturated in IPE (5 mL). And the solid was collected to obtain the object compound (53 mg).

[0317] Example 95. Synthesis of cyclopropyl

4-(6-(5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-2-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

A mixture of cyclopropyl

4-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate (173 mg), 2-bromo-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazine (50 mg), Pd(OAc)₂ (15 mg), Xantphos (50 mg) and K₂CO₃ (180 mg) in dioxane/ H₂O (6/1) (5 mL) was stirred at 80°C under nitrogen for 3h. The mixture was diluted with AcOEt. To the mixture was added Na₂SO₄. The mixture was filtered through Celite. The filtrate was concentrated. The residue was purified by column chromatography to obtain the object compound (10 mg).

[0318] Example 102. Synthesis of thiazol-4-ylmethyl

4-(6-(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

A mixture of

6-(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)-3-(piperidin-4-yl)pyrazolo[1,5-a]pyridine (50 mg) in THF (1.5 mL) was prepared in a flask.

4-nitrophenyl(thiazol-4-ylmethyl)carbonate (54.8 mg) was added to the mixture at 0°C. DIPEA (52.5 µL) was added to the mixture at 0°C. The mixture was stirred for 3 h at room temperature under nitrogen. H₂O was added to the reaction mixture at 0°C to stop the reaction. The mixture was extracted with DCM three times. The organic layer was collected, followed by the evaporation to obtain the crude product. The crude was purified by basic-silica gel column chromatography (hexane/AcOEt) to obtain the object compound (65.1 mg).

[0319] Example 110. Synthesis of cyclopropyl

4-(6-(1-cyclopropyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate

To a solution of tert-butyl

4-(6-(1-cyclopropyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carboxylate (72 mg) in DCM (5 mL) was added TFA (0.5 mL) at room temperature. The mixture was stirred for 3 h. The mixture was concentrated. The residue was co-evaporated with toluene (3 times) and dried in vacuo to give the intermediate. To a solution of the intermediate in DCM (4 mL) were added TEA (0.148 mL) and cyclopropyl(4-nitrophenyl)carbonate (51.3 mg) at room temperature. The mixture was stirred for 3 h. The mixture was diluted with H₂O and extracted with DCM. The organic layer was concentrated. The residue was purified by basic-silica gel column chromatography (hexane/AcOE) to obtain the object compound (65 mg).

[0320] Example 112. Synthesis of cyclopropyl

4-(6-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyrazolo[1,5-a]pyridin-3-yl)piperidine-1-carbo

xylate

To a solution of

6-(3-(piperidin-4-yl)pyrazolo[1,5-a]pyridin-6-yl)-2-oxa-6-azaspiro[3.3]heptane 81 mg) in THF (5 mL) were added DIPEA (71 μ L) and cyclopropyl (4-nitrophenyl) carbonate (79 mg), and the mixture was stirred at room temperature for 5 h. Sat. NaHCO_3 aq. and AcOEt were added to the mixture. The organic layer was separated by phase separator (Whatman, filter paper 1PS), and the solvent was removed. The obtained crude product was purified by basic-silica gel column chromatography (heptane : AcOEt). The product was triturated with IPE and collected on a filter to obtain the object compound (65 mg).

[0321] Example 113. Synthesis of

(1-methylcyclopropyl)methyl-4-(6-(thiazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

4-Nitrophenyl

4-(6-(thiazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate (70 mg) was placed in a flask. DMF (1 mL) was added to the flask to make the mixture.

1-methylcyclopropyl)methanol (25.2 μ L) was added to the mixture at room temperature. KOTBu (26.2 mg) was added to the mixture at 0°C. Then the mixture was stirred under nitrogen for 3 h at room temperature. The flask was cooled at 0°C, and H_2O was added to the reaction mixture. The mixture was extracted by AcOEt. The combined organic layers were concentrated. The residue was purified by basic-silica gel column chromatography (hexane: AcOEt:MeOH) to obtain the object compound (13.9 mg).

[0322] Example 117. Synthesis of thiazol-4-ylmethyl

4-(6-(thiazol-5-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

To a solution of 5-(3-(piperidin-4-yl)pyrazolo[1,5-a]pyrimidin-6-yl)thiazole (60 mg) in DCM (4 mL) were added TEA (58.6 μ L) and

4-nitrophenyl(thiazol-4-ylmethyl)carbonate (70.7 mg) at room temperature. The mixture was stirred for 3 h. The mixture was diluted with H_2O and extracted with DCM. The organic layer was concentrated. The residue was purified by basic-silica gel column chromatography (hexane/AcOEt) and triturated with AcOEt to obtain the object compound (74 mg).

[0323] Example 138. Synthesis of 1-fluoro-2-methylpropan-2-yl

4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperidine-1-carboxylate

To a solution of

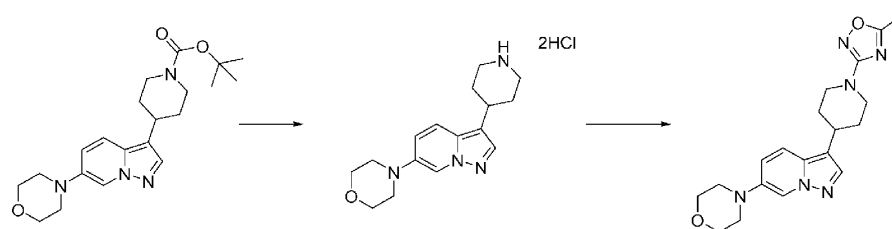
1-(((1-fluoro-2-methylpropan-2-yl)oxy)carbonyl)-3-methyl-1H-imidazol-3-ium iodide (244.1 mg) in DCM (20 mL) under nitrogen,

6-(1-methyl-1H-pyrazol-4-yl)-3-(piperidin-4-yl)pyrazolo[1,5-a]pyrimidine (98 mg) and TEA (242 μ l) were added at RT. The mixture was stirred at room temperature for 1 h 5 min. H₂O was added at RT. The water layer was extracted with DCM. The combined organic layer was dried over Na₂SO₄. Filtration and concentration gave the crude which was purified by silica gel chromatography (hexane/AcOEt). The product was triturated in IPE to obtain the object compound (75.1 mg).

[0324] Example 143. Synthesis of

4-{3-[1-(5-methyl-1,2,4-oxadiazol-3-yl)piperidin-4-yl]pyrazolo[1,5-a]pyridin-6-yl}morpholine.

[Chem.34]



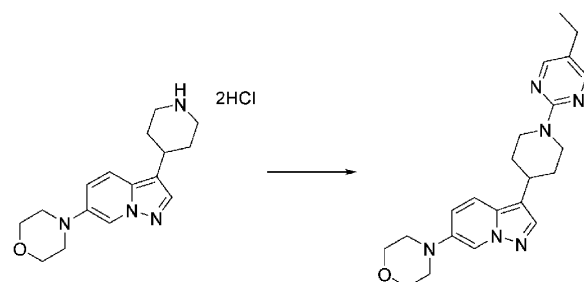
A solution of tert-butyl

4-[6-(morpholin-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperidine-1-carboxylate (909 mg) in 4N HCl in dioxane (5 mL) and dioxane (5 mL) was stirred at room temperature for 4 h. The reaction was concentrated to obtain the intermediate compound (910 mg). A solution of the intermediate compound (100 mg), 3-chloro-5-methyl-1,2,4-oxadiazole (70 mg) and TEA (0.16 mL) in EtOH (1 mL) was stirred at 80°C overnight. The reaction mixture was partitioned between DCM and water. The organic layer was separated and concentrated. The residue was purified by silica gel column chromatography (petrol/AcOEt) to obtain the object compound (25 mg).

[0325] Example 144. Synthesis of

4-{3-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]pyrazolo[1,5-a]pyridin-6-yl}morpholine

[Chem.35]

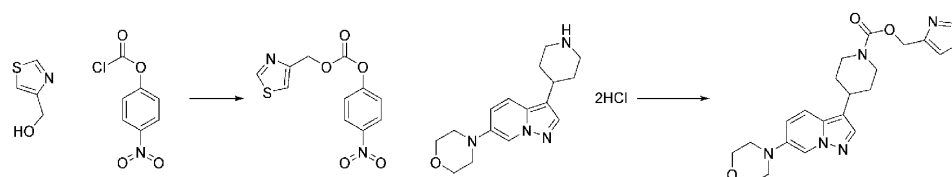


A solution of 4-[3-(piperidin-4-yl)pyrazolo[1,5-a]pyridin-6-yl]morpholine dihydrochloride salt (100 mg), 2-chloro-5-ethylpyrimidine (48 mg) and triethylamine (0.16

mL) in EtOH (1 mL) was stirred at 80°C overnight. The reaction mixture was partitioned between DCM and water. The organic phase was concentrated in vacuo and the residue was purified by column chromatography (SiO₂, AcOEt:petrol) to give the desired product (25 mg).

LCMS: [M+H]⁺ = 393.

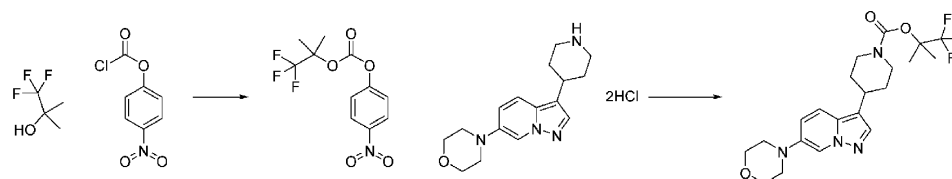
[0326] Example 145. Synthesis of (1,3-thiazol-4-yl)methyl 4-[6-(morpholin-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperidine-1-carboxylate
[Chem.36]



A solution of (1,3-thiazol-4-yl)methanol (32 mg), 4-nitrophenyl chloroformate (60 mg) and triethylamine (0.12 mL) in DCM (3 mL) was stirred at room temperature for 2 hours. Then, a solution of 4-[3-(piperidin-4-yl)pyrazolo[1,5-a]pyridin-6-yl]morpholine dihydrochloride salt (100 mg) and triethylamine (0.12 mL) in DCM (2 mL) was added and the resulting mixture was stirred at room temperature overnight. The reaction mixture was partitioned between DCM and NaHCO₃. The organic phase was washed NaHCO₃ and then concentrated in vacuo. The residue was purified by column chromatography (SiO₂, AcOEt:petrol) to give the desired product (67 mg).

LCMS: [M+H]⁺ = 393.

[0327] Example 146. Synthesis of 1,1,1-trifluoro-2-methylpropan-2-yl 4-[6-(morpholin-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperidine-1-carboxylate
[Chem.37]



Step 1: synthesis of 4-nitrophenyl 1,1,1-trifluoro-2-methylpropan-2-yl carbonate.

4-Nitrophenyl chloroformate (1.9 g) was added to a solution of 1,1,1-trifluoro-2-methylpropan-2-ol (1.0 g) and pyridine (1.3 mL) in DCM (20 mL) and the solution was stirred at room temperature overnight. The reaction was quenched with 1M HCl and extracted with DCM. The organic phase was concentrated in vacuo and the residue was purified by column chromatography (SiO₂, DCM:petrol) to give the desired product (1.1 g).

¹H NMR (400 MHz, DMSO-d₆): 8.38-8.28 (m, 2H), 7.67-7.58 (m, 2H), 1.75 (s, 6H).

[0328] Step 2: synthesis of 1,1,1-trifluoro-2-methylpropan-2-yl

4-[6-(morpholin-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperidine-1-carboxylate.

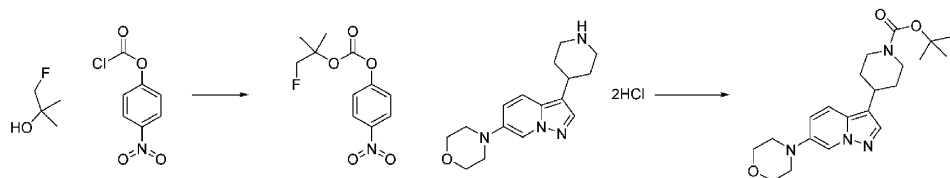
A solution of 4-[3-(piperidin-4-yl)pyrazolo[1,5-a]pyridin-6-yl]morpholine dihydrochloride salt (100 mg), 4-nitrophenyl 1,1,1-trifluoro-2-methylpropan-2-yl carbonate (82 mg) and triethylamine (0.16 mL) in DCM (3 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between DCM and NaHCO₃. The organic phase was washed with NaHCO₃ and then concentrated in vacuo. The residue was purified by column chromatography (SiO₂, AcOEt:petrol) to give the desired product (65 mg).

LCMS: [M+H]⁺ = 441.

[0329] Example 147. Synthesis of 1-fluoro-2-methylpropan-2-yl

4-[6-(morpholin-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperidine-1-carboxylate

[Chem.38]



Step 1: synthesis of 1-fluoro-2-methylpropan-2-yl 4-nitrophenyl carbonate.

4-Nitrophenyl chloroformate (654 mg) was added to a solution of 1-fluoro-2-methylpropan-2-ol (250 mg) and pyridine (0.44 mL) in DCM (10 mL) and the reaction was stirred at room temperature overnight. The reaction mixture was partitioned between DCM and 1M HCl and the organic phase was concentrated in vacuo. The residue was purified by column chromatography (SiO₂, DCM:petrol) to give the desired product (202 mg).

¹H NMR (400 MHz, DMSO-d₆): 8.36-8.26 (m, 2H), 7.63-7.50 (m, 2H), 4.62 (s, 1H), 4.51 (s, 1H), 1.51 (d, J = 2.3 Hz, 6H).

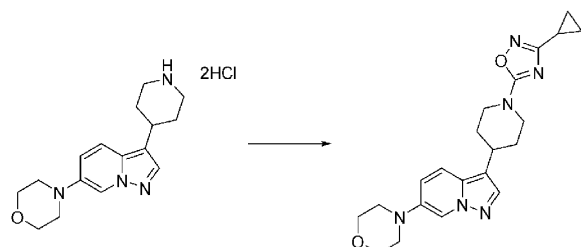
[0330] Step 2: synthesis of 1-fluoro-2-methylpropan-2-yl

4-[6-(morpholin-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperidine-1-carboxylate.

A solution of 1-fluoro-2-methylpropan-2-yl 4-nitrophenyl carbonate (72 mg), 4-[3-(piperidin-4-yl)pyrazolo[1,5-a]pyridin-6-yl]morpholine dihydrochloride salt (100 mg) and triethylamine (0.16 mL) in DCM (3 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between DCM and NaHCO₃ and the organic phase was concentrated in vacuo. The residue was purified by column chromatography (SiO₂, AcOEt:petrol) to give the desired product (53 mg).

LCMS: [M+H]⁺ = 405.

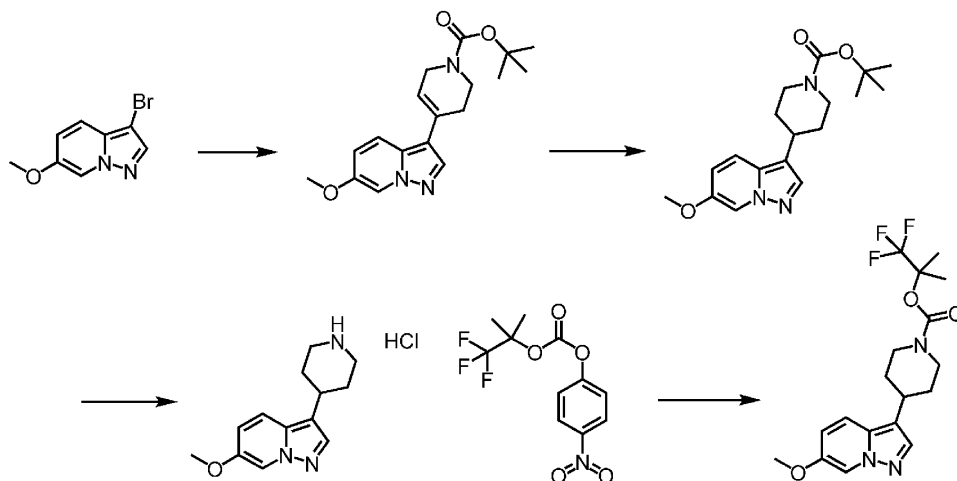
- [0331] Example 148. Synthesis of
4-{3-[1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl]pyrazolo[1,5-a]pyridin-6-yl}
morpholine
 [Chem.39]



A solution of 4-[3-(piperidin-4-yl)pyrazolo[1,5-a]pyridin-6-yl]morpholine dihydrochloride salt (100 mg), 5-chloro-3-cyclopropyl-1,2,4-oxadiazole (48 mg) and triethylamine (0.16 mL) in EtOH (1 mL) was stirred at 80°C overnight. The reaction mixture was partitioned between DCM and water and the organic phase was concentrated in vacuo. The residue was purified by column chromatography (SiO₂, AcOEt:petrol) to give the desired product (23 mg).

LCMS: [M+H]⁺ = 395.

- [0332] Example 149. Synthesis of 1,1,1-trifluoro-2-methylpropan-2-yl
4-{6-methoxypyrazolo[1,5-a]pyridin-3-yl}piperidine-1-carboxylate
 [Chem.40]



Step 1: synthesis of tert-butyl

4-{6-methoxypyrazolo[1,5-a]pyridin-3-yl}-1,2,3,6-tetrahydropyridine-1-carboxylate.

A suspension of 3-bromo-6-methoxypyrazolo[1,5-a]pyridine (600 mg), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate (860 mg), Pd(PPh₃)₄ (153 mg) and 1M Na₂CO₃ (5.3 mL) in DME (17 mL) was

stirred at reflux for 2 hours. The reaction mixture was partitioned between AcOEt and water and the organic phase was concentrated in vacuo. The residue was purified by column chromatography (SiO₂, AcOEt:petrol) to give the desired product (744 mg).
LCMS: [M+H]⁺ = 330.

[0333] Step 2: synthesis of tert-butyl

4-{6-methoxypyrazolo[1,5-a]pyridin-3-yl}piperidine-1-carboxylate.

A mixture of tert-butyl

4-{6-methoxypyrazolo[1,5-a]pyridin-3-yl}-1,2,3,6-tetrahydropyridine-1-carboxylate (700 mg) and PtO₂ (150 mg) in AcOEt (12 mL) was stirred under H₂ at room temperature overnight. The reaction mixture was filtered through Celite and the solvent was removed in vacuo to give the desired product (618 mg).

LCMS: [M-tBu]⁺ = 276.

[0334] Step 3: synthesis of 4-{6-methoxypyrazolo[1,5-a]pyridin-3-yl}piperidine hydrochloride salt.

4M HCl in dioxane (6 mL) was added to a solution of tert-butyl

4-{6-methoxypyrazolo[1,5-a]pyridin-3-yl}piperidine-1-carboxylate (618 mg) in dioxane (6 mL) and the resulting mixture was stirred at room temperature for 4 hours. The reaction was concentrated in vacuo to give the desired product (520 mg).

LCMS: [M+H]⁺ = 232

[0335] Step 4: synthesis of 1,1,1-trifluoro-2-methylpropan-2-yl

4-{6-methoxypyrazolo[1,5-a]pyridin-3-yl}piperidine-1-carboxylate.

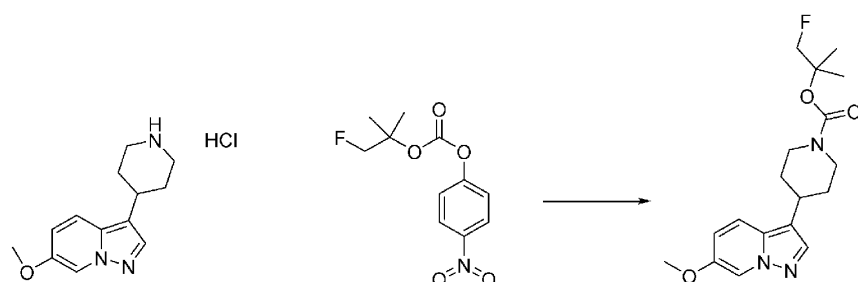
A solution of 4-{6-methoxypyrazolo[1,5-a]pyridin-3-yl}piperidine hydrochloride salt (100 mg), 4-nitrophenyl 1,1,1-trifluoro-2-methylpropan-2-yl carbonate (121 mg) and triethylamine (0.2 mL) in DCM (2 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between DCM and NaHCO₃. The organic phase was washed NaHCO₃ and then concentrated in vacuo. The residue was purified by column chromatography (SiO₂, AcOEt:petrol) to give the desired product (42 mg).

LCMS: [M+H]⁺ = 386.

[0336] Example 150. Synthesis of 1-fluoro-2-methylpropan-2-yl

4-{6-methoxypyrazolo[1,5-a]pyridin-3-yl}piperidine-1-carboxylate

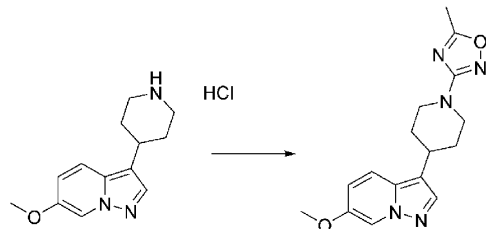
[Chem.41]



A solution of 4-{6-methoxypyrazolo[1,5-a]pyridin-3-yl}piperidine hydrochloride salt (100 mg), 1-fluoro-2-methylpropan-2-yl 4-nitrophenyl carbonate (106 mg) and triethylamine (0.2 mL) in DCM (2 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between DCM and NaHCO_3 . The organic phase was washed with NaHCO_3 and then concentrated in vacuo. The residue was purified by column chromatography (SiO_2 , AcOEt:petrol) to give the desired product (41 mg). LCMS: $[\text{M}+\text{H}]^+ = 350$.

[0337] Example 151. Synthesis of
4-{6-methoxypyrazolo[1,5-a]pyridin-3-yl}-1-(5-methyl-1,2,4-oxadiazol-3-yl)piperidin
e

[Chem.42]

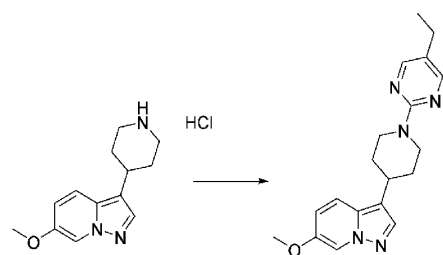


A solution of 4-{6-methoxypyrazolo[1,5-a]pyridin-3-yl}piperidine hydrochloride salt (78 mg), 3-chloro-5-methyl-1,2,4-oxadiazole (52 mg) and triethylamine (0.16 mL) in EtOH (1 mL) was stirred at 80°C overnight. The reaction mixture was partitioned between DCM and water. The organic phase was concentrated in vacuo and the residue was purified by column chromatography (SiO_2 , AcOEt:petrol) to give the desired product (7 mg).

LCMS: $[\text{M}+\text{H}]^+ = 314$.

[0338] Example 152. Synthesis of
5-ethyl-2-(4-{6-methoxypyrazolo[1,5-a]pyridin-3-yl}piperidin-1-yl)pyrimidine

[Chem.43]



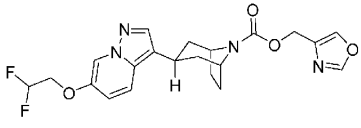
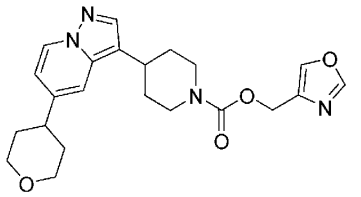
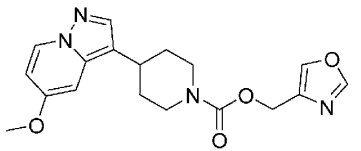
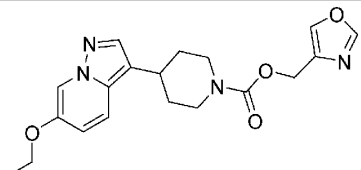
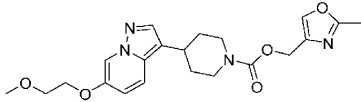
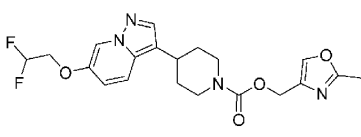
A solution of 4-{6-methoxypyrazolo[1,5-a]pyridin-3-yl}piperidine hydrochloride salt (100 mg), 2-chloro-5-ethylpyrimidine (64 mg) and triethylamine (0.2 mL) in EtOH (1 mL) was stirred at 80°C overnight. The reaction mixture was partitioned between DCM and water. The organic phase was concentrated in vacuo and the residue was purified by column chromatography (SiO₂, AcOEt:petrol) to give the desired product (28 mg).

LCMS: [M+H]⁺ = 338.

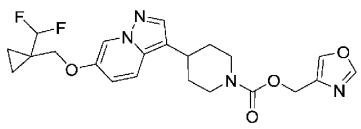
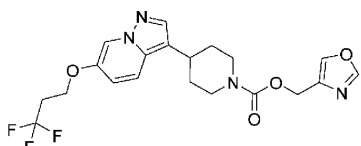
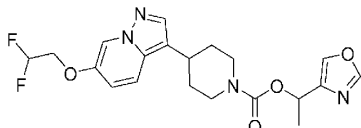
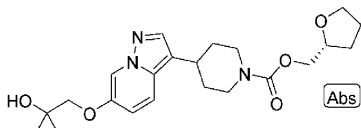
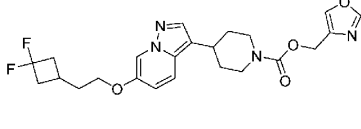
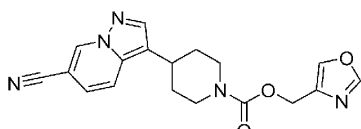
[0339] The compounds of Examples were manufactured in the same manner as in any of the above Examples. Structural formulae and physicochemical data of the compounds of Examples 1 to 152 are shown in the following table.

[0340]

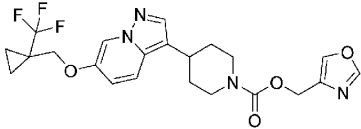
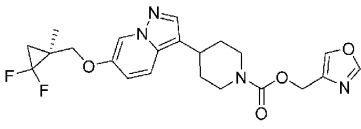
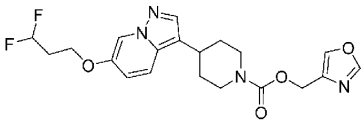
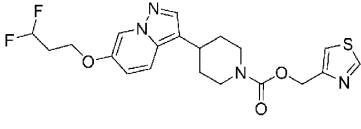
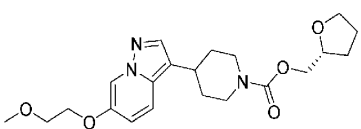
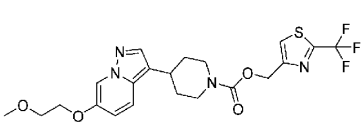
[Table 3-1]

EX	STR	Prop	Physicochemical Data
1		7	NMR2: 1.80–1.88 (5H, m), 2.02 (1H, d, J=9.5 Hz), 2.08 (2H, dd, J=8.6, 4.3 Hz), 3.34 (1H, tt, J=11.9, 5.5 Hz), 4.16 (2H, td, J=13.0, 4.0 Hz), 4.38 (1H, s), 4.43 (1H, s), 5.14 (2H, brd, J=11.6 Hz), 6.11 (1H, dd, J=54.9, 4.0 Hz), 6.90 (1H, dd, J=9.7, 2.2 Hz), 7.33 (1H, d, J=9.7 Hz), 7.66 (1H, s), 7.74 (1H, d, J=0.9 Hz), 7.88 (1H, s), 8.04 (1H, d, J=2.2 Hz).
2		3	NMR2: 1.72 (2H, d, J=13.5 Hz), 1.78–1.89 (4H, m), 1.94 (2H, brs), 2.79 (1H, tq, J=10.1, 5.5 Hz), 2.88–2.98 (3H, m), 3.55 (2H, ddt, J=13.2, 11.2, 7.7 Hz), 4.08–4.16 (2H, m), 4.27–4.33 (2H, brs), 5.11 (2H, brs), 6.61 (1H, dd, J=7.2, 1.9 Hz), 7.20–7.24 (1H, m), 7.72–7.76 (2H, m), 7.89 (1H, d, J=0.9 Hz), 8.35 (1H, dd, J=7.2, 0.9 Hz). M+H: 411.6
3		3	NMR2: 1.70 (2H, d, J=13.3 Hz), 1.93 (2H, brs), 2.86 (1H, tt, J=12.0, 3.7 Hz), 2.94 (2H, s), 3.87 (3H, s), 4.26–4.33 (2H, brs), 5.11 (2H, s), 6.42 (1H, dd, J=7.6, 2.6 Hz), 6.59 (1H, d, J=2.7 Hz), 7.68 (1H, s), 7.72–7.77 (1H, m), 7.89 (1H, s), 8.23 (1H, d, J=7.6 Hz). M+H: 357.5
4		7	NMR2: 1.45 (3H, t, J=6.9 Hz), 1.70 (2H, brs), 1.93 (2H, brs), 2.89–2.93 (3H, m), 4.00 (2H, d, J=6.9 Hz), 4.25 (1H, s), 4.32 (1H, s), 5.11 (2H, s), 6.88 (1H, dd, J=9.6, 2.1 Hz), 7.34 (1H, d, J=9.6 Hz), 7.65 (1H, s), 7.73 (1H, s), 7.88 (1H, s), 8.00 (1H, d, J=2.1 Hz).
5		3	NMR2: 1.70 (2H, brd, J=13.1 Hz), 1.92 (2H, brs), 2.46 (3H, s), 2.90 (3H, ddt, J=11.9, 8.3, 3.7 Hz), 3.47 (3H, s), 3.75–3.80 (2H, m), 4.07–4.13 (2H, m), 4.27 (2H, brm), 5.03 (2H, s), 6.94 (1H, dd, J=9.6, 2.1 Hz), 7.35 (1H, dd, J=9.6, 0.8 Hz), 7.58 (1H, s), 7.65 (1H, s), 8.04 (1H, d, J=2.1 Hz).
6		3	NMR2: 1.62–1.81 (2H, m), 1.82–2.03 (2H, m), 2.46 (3H, s), 2.78–3.06 (3H, m), 4.17 (2H, td, J= 12.9, 4.0 Hz), 4.30 (2H, brs), 5.03 (2H, s), 6.11 (1H, tt, J= 54.9, 4.0 Hz), 6.93 (1H, dd, J= 9.7, 2.1 Hz), 7.40 (1H, dd, J= 9.6, 0.6 Hz), 7.58 (1H, s), 7.69 (1H, s), 8.03–8.09 (1H, m).

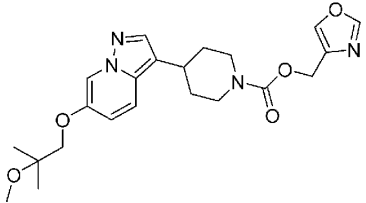
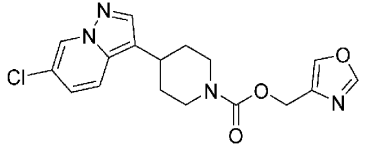
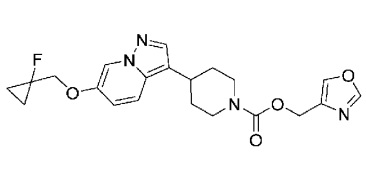
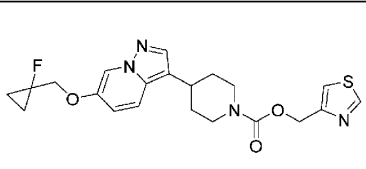
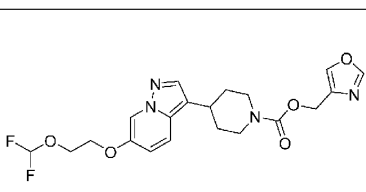
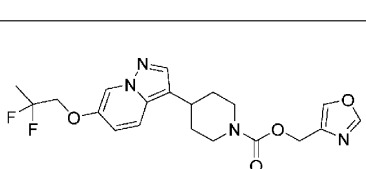
[Table 3-2]

7		7	NMR2: 0.72–0.84 (2H, m), 0.96–1.05 (2H, m), 1.61–1.79 (2H, m), 1.86–2.01 (2H, m), 2.81–3.06 (3H, m), 4.16–4.44 (2H, m), 5.09–5.13 (2H, m), 5.97 (1H, t, J=57.7 Hz), 6.90 (2H, dd, J=9.6, 2.1 Hz), 7.37 (1H, d, J=9.6 Hz), 7.66 (2H, s), 7.73 (1H, d, J=0.9 Hz), 7.88 (1H, s), 7.98 (1H, d, J=2.1 Hz). M+H: 447
8		7	NMR2: 1.67–1.73 (2H, m), 1.93 (2H, brs), 2.66 (2H, qt, J=10.5, 6.4 Hz), 2.86–2.96 (3H, m), 4.18 (2H, t, J=6.4 Hz), 4.25–4.32 (2H, m), 5.11 (2H, brs), 6.89 (1H, dd, J=9.6, 2.1 Hz), 7.38 (1H, d, J=9.6 Hz), 7.67 (1H, s), 7.73 (1H, d, J=1.0 Hz), 7.88 (1H, s), 8.03 (1H, d, J=2.1 Hz).
9		3	NMR2: 1.58–1.80 (5H, m), 1.84–2.03 (2H, m), 2.80–3.05 (3H, m), 4.17 (2H, td, J = 12.9, 4.0 Hz), 4.31 (2H, brs), 5.89 (1H, q, J= 6.6 Hz), 6.11 (1H, tt, J= 54.9, 4.0 Hz), 6.93 (1H, dd, J= 9.6, 2.2 Hz), 7.40 (1H, d, J= 9.6 Hz), 7.64 (1H, t, J= 0.8 Hz), 7.70 (1H, s), 7.86 (1H, s), 8.06 (1H, d, J = 1.7 Hz).
10		3	NMR2: 1.37 (6H, s), 1.60–1.76 (3H, m), 1.84–1.98 (4H, m), 1.99–2.08 (1H, m), 2.19 (1H, brs), 2.91 (3H, tt, J=12.0, 3.7 Hz), 3.78 (2H, s), 3.82 (1H, ddd, J=8.3, 7.2, 6.0 Hz), 3.90 (1H, dt, J=8.3, 6.8 Hz), 4.05 (1H, t, J=9.0 Hz), 4.11–4.22 (2H, m), 4.30 (2H, s), 6.93 (1H, dd, J=9.6, 2.1 Hz), 7.38 (1H, dd, J=9.6, 0.8 Hz), 7.67 (1H, s), 8.03 (1H, dd, J=2.1, 0.8 Hz). M+H: 418.7
11		3	NMR2: 1.67–1.73 (2H, m), 1.93 (2H, s), 1.98–2.06 (2H, m), 2.21–2.41 (3H, m), 2.68–2.81 (2H, m), 2.90 (3H, tt, J=11.9, 3.7 Hz), 3.93 (2H, t, J=6.0 Hz), 4.25 (1H, s), 4.31 (1H, s), 5.11 (2H, s), 6.85 (1H, dd, J=9.6, 2.1 Hz), 7.35 (1H, dd, J=9.6, 0.8 Hz), 7.65 (1H, s), 7.74 (1H, d, J=1.0 Hz), 7.88 (1H, d, J=1.0 Hz), 7.98 (1H, dd, J=2.1, 0.8 Hz). M+H: 461.5
12		7	NMR2: 1.65–1.82 (2H, m), 1.84–2.00 (2H, m), 2.85–3.02 (3H, m), 4.20–4.44 (2H, m), 5.11 (2H, s), 7.13 (1H, dd, J=9.3, 1.5 Hz), 7.55 (1H, d, J=9.4 Hz), 7.74 (1H, s), 7.89 (1H, s), 7.96 (1H, s), 8.81 (1H, s). M+H: 352

[Table 3-3]

13		7	NMR2: 0.87–1.00 (2H, m), 1.15–1.21 (2H, m), 1.63–1.77 (2H, m), 1.85–2.03 (2H, m), 2.83–3.03 (3H, m), 4.04 (2H, s), 4.18–4.39 (2H, m), 5.04–5.17 (2H, m), 6.91 (1H, dd, J=9.6, 2.1 Hz), 7.37 (1H, d, J=9.7 Hz), 7.66 (1H, s), 7.68–7.76 (1H, m), 7.88 (1H, s), 7.99 (1H, d, J=2.1 Hz). M+H: 465
14		7	NMR2: 1.18–1.28 (1H, m), 1.33–1.43 (4H, m), 1.63–1.80 (2H, m), 1.85–2.02 (2H, m), 2.81–3.05 (3H, m), 3.82–3.93 (1H, m), 3.93–4.03 (1H, m), 4.15–4.44 (2H, m), 5.11 (2H, s), 6.92 (1H, dd, J=9.6, 2.1 Hz), 7.37 (1H, d, J=9.6 Hz), 7.66 (1H, s), 7.70–7.76 (1H, m), 7.88 (1H, s), 7.99 (1H, d, J=2.1 Hz). M+H: 447
15		3	NMR2: 1.60–1.81 (2H, m), 1.84–2.04 (2H, m), 2.26–2.47 (2H, m), 2.80–3.08 (3H, m), 4.09 (2H, t, J=6.0 Hz), 4.29 (2H, s), 5.11 (2H, s), 6.09 (1H, tt, J=56.4, 4.7 Hz), 6.87 (1H, dd, J=9.6, 2.2 Hz), 7.37 (1H, dd, J=9.6, 0.7 Hz), 7.67 (1H, s), 7.71–7.75 (1H, m), 7.88 (1H, s), 8.01–8.05 (1H, m).
16		3	NMR2: 1.62–1.82 (2H, m), 1.85–2.04 (2H, m), 2.28–2.45 (2H, m), 2.82–3.08 (3H, m), 4.11 (2H, t, J=6.0 Hz), 4.33 (2H, brs), 5.33 (2H, s), 6.09 (1H, tt, J=56.4, 4.7 Hz), 6.87 (1H, dd, J=9.6, 2.2 Hz), 7.34–7.42 (2H, m), 7.67 (1H, s), 8.03 (1H, d, J=1.5 Hz), 8.82 (1H, d, J=2.0 Hz).
17		3	NMR2: 1.63–1.67 (1H, m), 1.60–1.77 (2H, m), 1.84–1.99 (4H, m), 1.97–2.07 (1H, m), 2.86–2.95 (3H, m), 3.47 (3H, s), 3.78 (2H, dd, J=5.5, 3.4 Hz), 3.81 (1H, q, J=7.1 Hz), 3.86–3.94 (1H, m), 4.05 (1H, t, J=9.0 Hz), 4.08–4.15 (2H, m), 4.12–4.20 (2H, m), 4.29 (2H, brs), 6.95 (1H, dd, J=9.6, 2.1 Hz), 7.37 (1H, d, J=9.6 Hz), 7.66 (1H, s), 8.04 (1H, d, J=2.1 Hz). M+H: 404.6
18		3	NMR2: 1.68–1.79 (2H, brm), 1.95 (2H, brs), 2.97 (3H, m), 3.47 (3H, brs), 3.75–3.80 (2H, m), 4.07–4.13 (2H, m), 4.30 (2H, brs), 5.32 (2H, d, J=4.6 Hz), 6.95 (1H, dd, J=9.6, 2.1 Hz), 7.36 (1H, dd, J=9.6, 0.8 Hz), 7.59 (1H, s), 7.66 (1H, s), 8.04 (1H, d, J=2.1 Hz).

[Table 3-4]

19		7	NMR2: 1.32 (6H, s), 1.66–1.72 (2H, m), 1.93 (2H, brs), 2.85–2.95 (3H, m), 3.31 (3H, s), 3.80 (2H, s), 4.25 (1H, brs), 4.32 (1H, brs), 5.11 (2H, brs), 6.95 (1H, dd, J=9.7, 2.2 Hz), 7.35 (1H, d, J=9.7 Hz), 7.65 (1H, s), 7.73 (1H, d, J=0.9 Hz), 7.88 (1H, d, J=0.9 Hz), 8.03 (1H, d, J=2.1 Hz).
20		7	NMR2: 1.62–1.80 (2H, m), 1.85–2.01 (2H, m), 2.85–3.01 (2H, m), 4.17–4.41 (3H, m), 5.11 (2H, s), 7.04 (1H, dd, J=9.5, 1.8 Hz), 7.37–7.47 (1H, m), 7.71 – 7.79 (2H, m), 7.88 (1H, s), 8.44–8.48 (1H, m). M+H: 361
21		3	NMR2: 0.80–0.89 (2H, m), 1.17–1.31 (2H, m), 1.61–1.80 (2H, m), 1.85–2.04 (2H, m), 2.83–3.02 (3H, m), 4.12–4.43 (4H, m), 5.11 (2H, s), 6.97 (1H, dd, J=9.6, 2.1 Hz), 7.38 (1H, d, J=9.6 Hz), 7.67 (1H, s), 7.73 (1H, d, J=0.9 Hz), 7.88 (1H, s), 8.05 (1H, d, J=1.8 Hz).
22		3	NMR2: 0.78–0.91 (2H, m), 1.17–1.30 (2H, m), 1.62–1.80 (2H, m), 1.95 (2H, d, J=11.2 Hz), 2.82–3.08 (3H, m), 4.19 (2H, d, J=20.8 Hz), 4.33 (2H, s), 5.33 (2H, s), 6.97 (1H, dd, J=9.6, 2.1 Hz), 7.35–7.42 (2H, m), 7.67 (1H, s), 8.05 (1H, d, J=2.1 Hz), 8.82 (1H, d, J=2.0 Hz).
23		3	NMR2: 1.70 (2H, brs), 1.93 (2H, brs), 2.86–2.95 (3H, m), 4.16 (2H, dd, J=5.7, 3.4 Hz), 4.23 (2H, dd, J=5.7, 3.4 Hz), 4.30 (2H, brs), 5.11 (2H, brs), 6.32 (1H, t, J=73.8 Hz), 6.93 (1H, dd, J=9.6, 2.1 Hz), 7.38 (1H, d, J=9.6 Hz), 7.67 (1H, s), 7.74 (1H, s), 7.88 (1H, s), 8.04 (1H, d, J=2.1 Hz). M+H: 437.4
24		7	NMR2: 1.70 (2H, brd, J=12.9 Hz), 1.80 (3H, t, J=18.8 Hz), 1.93 (2H, s), 2.86–2.96 (3H, m), 4.09 (2H, t, J=11.3 Hz), 4.25 (1H, s), 4.32 (1H, s), 5.11 (2H, s), 6.94 (1H, dd, J=9.7, 2.2 Hz), 7.39 (1H, d, J=9.7 Hz), 7.69 (1H, s), 7.73 (1H, d, J=0.9 Hz), 7.88 (1H, s), 8.05 (1H, d, J=2.2 Hz).

[Table 3-5]

25		3	NMR2: 1.68–1.75 (2H, m), 1.94 (2H, s), 2.87–2.97 (3H, m), 4.15–4.17 (2H, m), 4.22–4.24 (2H, m), 4.32 (2H, brs), 5.33 (2H, brs), 6.32 (1H, d, J=73.9 Hz), 6.93 (1H, dd, J=9.6, 2.2 Hz), 7.34 – 7.41 (2H, m), 7.67 (1H, s), 8.04 (1H, d, J=2.2 Hz), 8.82 (1H, d, J=2.0 Hz). M+H: 453.4
26		3	NMR2: 1.65–1.80 (2H, m), 1.94 (2H, brs), 2.90–3.05 (3H, m), 4.18–4.19 (2H, m), 4.25–4.40 (4H, m), 5.33 (2H, brs), 6.93 (1H, dd, J=9.7, 2.0 Hz), 7.38 – 7.39 (2H, m), 7.68 (1H, s), 8.03 (1H, d, J=2.0 Hz), 8.82 (1H, d, J=1.8 Hz). M+H: 471.4
27		7	NMR2: 0.34–0.41 (2H, m), 0.64–0.71 (2H, m), 1.26–1.33 (1H, m), 1.66–1.72 (2H, m), 1.93 (2H, brs), 2.86–2.94 (3H, m), 3.77 (2H, d, J=6.9 Hz), 4.24 (1H, brs), 4.31 (1H, brs), 5.10 (2H, s), 6.92 (1H, d, J=9.6 Hz), 7.35 (1H, d, J=9.6 Hz), 7.64 (1H, s), 7.73 (1H, s), 7.88 (1H, s), 7.98 (1H, s).
28		3	NMR2: 1.62–1.81 (2H, m), 1.85–2.03 (2H, m), 2.82–3.05 (3H, m), 4.17–4.42 (4H, m), 4.67–4.78 (2H, m), 4.90 (2H, dd, J=18.8, 8.8 Hz), 5.11 (2H, s), 6.94 (1H, dd, J=9.6, 2.1 Hz), 7.39 (1H, dd, J=9.6, 0.6 Hz), 7.69 (1H, s), 7.71–7.75 (1H, m), 7.88 (1H, d, J=0.9 Hz), 8.08 (1H, dd, J=2.2, 0.6 Hz).
29		3	NMR2: 1.62–1.82 (2H, m), 1.86–2.03 (2H, m), 2.84–3.08 (3H, m), 4.19–4.45 (4H, m), 4.66–4.78 (2H, m), 4.90 (2H, dd, J=18.8, 8.8 Hz), 5.33 (2H, s), 6.94 (1H, dd, J=9.6, 2.2 Hz), 7.34–7.45 (2H, m), 7.69 (1H, s), 8.08 (1H, dd, J=2.1, 0.7 Hz), 8.82 (1H, d, J=2.1 Hz).
30		7	NMR2: 1.64–1.80 (2H, m), 1.86–2.00 (2H, m), 2.86–3.05 (4H, m), 3.20–3.26 (2H, m), 3.50 (2H, t, J=7.6 Hz), 3.76–3.87 (1H, m), 4.09 (2H, d, J=6.4 Hz), 4.17–4.43 (2H, m), 4.53–4.60 (2H, m), 4.71 (2H, t, J=6.7 Hz), 5.11 (2H, s), 6.89 (1H, dd, J=9.6, 2.1 Hz), 7.36 (1H, d, J=9.6 Hz), 7.66 (1H, s), 7.71–7.76 (1H, m), 7.88 (1H, s), 8.02 (1H, d, J=2.3 Hz). M+H: 468

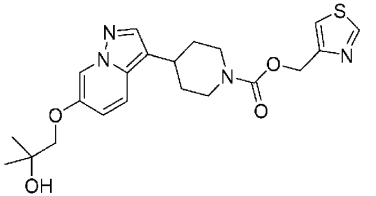
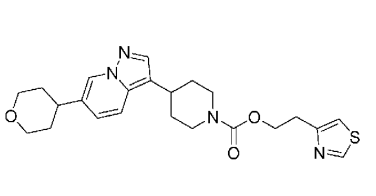
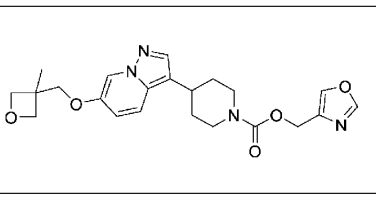
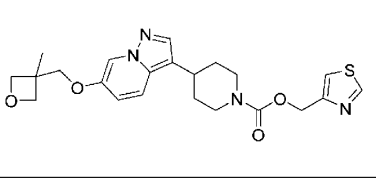
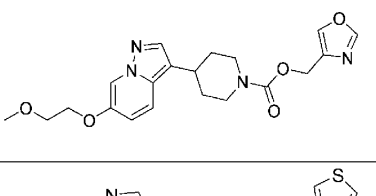
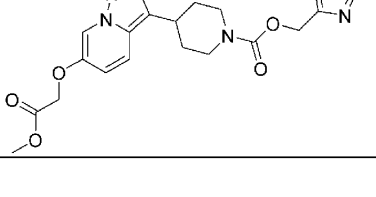
[Table 3-6]

31		7	NMR2: 1.65–1.79 (2H, m), 1.88–2.00 (2H, m), 2.87–3.05 (4H, m), 3.20–3.26 (2H, m), 3.50 (2H, t, J=7.6 Hz), 3.76–3.84 (1H, m), 4.09 (2H, d, J=6.4 Hz), 4.32 (2H, s), 4.53–4.59 (2H, m), 4.71 (2H, t, J=6.7 Hz), 5.33 (2H, s), 6.89 (1H, dd, J=9.6, 2.1 Hz), 7.35 (1H, s), 7.37–7.40 (1H, m), 7.66 (1H, s), 8.02 (1H, d, J=2.2 Hz), 8.82 (1H, d, J=2.0 Hz). M+H: 484
32		7	NMR2: 1.65–1.78 (2H, br), 1.94 (2H, s), 2.94 (3H, tt, J=12.0, 3.7 Hz), 4.33 (2H, s), 5.31–5.35 (2H, m), 7.03 (1H, ddd, J=9.8, 7.7, 2.2 Hz), 7.38 (1H, d, J=2.0 Hz), 7.41–7.48 (1H, m), 7.76 (1H, s), 8.35–8.40 (1H, m), 8.82 (1H, d, J=2.0 Hz).
33		7	NMR2: 1.66–1.72 (2H, m), 1.93 (2H, brs), 2.70 (4H, t, J=12.1 Hz), 2.85 (2H, t, J=5.3 Hz), 2.91–2.95 (3H, m), 3.40 (4H, s), 3.94 (2H, t, J=5.3 Hz), 4.25 (1H, brs), 4.31 (1H, brs), 5.11 (2H, brs), 6.89 (1H, dd, J=9.6, 2.1 Hz), 7.34 (1H, d, J=9.6 Hz), 7.65 (1H, s), 7.73 (1H, d, J=1.0 Hz), 7.88 (1H, d, J=1.0 Hz), 7.99 (1H, d, J=2.1 Hz).
34		3	NMR2: 1.25–1.37 (1H, m), 1.57–1.81 (3H, m), 1.84–2.01 (2H, m), 2.01–2.18 (1H, m), 2.81–3.04 (3H, m), 4.02 (2H, d, J=7.2 Hz), 4.30 (2H, brs), 5.11 (2H, s), 6.90 (1H, dd, J=9.6, 2.2 Hz), 7.37 (1H, dd, J=9.6, 0.6 Hz), 7.67 (1H, s), 7.73 (1H, d, J=0.9 Hz), 7.88 (1H, s), 7.99–8.03 (1H, m).
35		3	NMR2: 1.25–1.39 (1H, m), 1.57–1.82 (3H, m), 1.86–2.02 (2H, m), 2.02–2.18 (1H, m), 2.84–3.09 (3H, m), 4.02 (2H, d, J=7.0 Hz), 4.20–4.44 (2H, m), 5.33 (2H, s), 6.91 (1H, dd, J=9.6, 2.1 Hz), 7.34–7.42 (2H, m), 7.67 (1H, s), 8.01 (1H, d, J=1.7 Hz), 8.82 (1H, d, J=2.1 Hz).
36		7	NMR2: 1.62–1.76 (4H, m), 1.86–2.00 (4H, m), 2.85 – 2.95 (3H, m), 2.99 (1H, t, J=3.2 Hz), 3.88 (2H, s), 4.20 (2H, s), 4.27 (2H, s), 5.11 (2H, brs), 6.95 (1H, dd, J=9.7, 2.2 Hz), 7.35 (1H, d, J=9.7 Hz), 7.65 (1H, s), 7.73 (1H, q, J=0.9 Hz), 7.88 (1H, s), 8.05 (1H, d, J=2.2 Hz).

[Table 3-7]

37		7	NMR2: 1.58–1.75 (4H, m), 1.87–1.94 (4H, m), 2.86–2.96 (3H, m), 2.99 (1H, t, J=3.2 Hz), 3.88 (2H, s), 4.20 (2H, s), 4.31 (2H, s), 5.33 (2H, s), 6.95 (1H, dd, J=9.7, 2.1 Hz), 7.35 (1H, d, J=9.7 Hz), 7.37 (1H, d, J=2.1 Hz), 7.66 (1H, s), 8.05 (1H, d, J=2.1 Hz), 8.81 (1H, d, J=2.1 Hz).
38		7	NMR2: 1.61–1.69 (2H, m), 1.75 (2H, s), 1.87–1.96 (2H, m), 2.02 (2H, s), 2.96 (2H, s), 3.02 (1H, t, J=3.2 Hz), 3.11 (1H, tt, J=12.0, 3.7 Hz), 3.88 (2H, s), 4.16–4.38 (2H, brm), 4.30 (2H, brs), 5.10 (2H, brd, J=5.6 Hz), 7.73 (1H, s), 7.81 (1H, s), 7.88 (1H, s), 8.27 (1H, d, J=2.7 Hz), 8.36 (1H, d, J=2.7 Hz).
39		7	NMR2: 1.61–1.69 (2H, m), 1.76 (2H, s), 1.87–1.96 (2H, m), 2.02 (2H, s), 2.98 (2H, s), 3.02 (1H, t, J=3.2 Hz), 3.12 (1H, tt, J=12.0, 3.7 Hz), 3.88 (2H, s), 4.24 (2H, s), 4.31 (2H, brs), 5.33 (2H, brd, J=6.1 Hz), 7.37 (1H, d, J=2.1 Hz), 7.82 (1H, s), 8.27 (1H, d, J=2.7 Hz), 8.36 (1H, d, J=2.7 Hz), 8.81 (1H, d, J=2.1 Hz).
40		7	NMR2: 1.71 (2H, brs), 1.93 (2H, brs), 2.85–2.95 (3H, m), 3.30–3.36 (2H, m), 3.81–3.92 (3H, m), 4.25 (1H, brs), 4.32 (1H, brs), 4.56 (2H, dd, J=6.7, 5.2 Hz), 4.73 (2H, t, J=6.7 Hz), 4.79 (1H, d, J=5.2 Hz), 5.11 (2H, brs), 6.86 (1H, dd, J=9.6, 2.1 Hz), 7.38 (1H, d, J=9.6 Hz), 7.66 (1H, s), 7.73 (1H, d, J=1.0 Hz), 7.81 (1H, d, J=2.1 Hz), 7.88 (1H, s).
41		3	NMR2: 1.62–1.82 (2H, m), 1.82–2.09 (2H, m), 2.77–3.07 (3H, m), 3.37–3.55 (1H, m), 4.17 (2H, d, J=6.5 Hz), 4.28 (2H, brs), 4.59 (2H, t, J=6.1 Hz), 4.90 (2H, dd, J=7.9, 6.3 Hz), 5.11 (2H, s), 6.90 (1H, dd, J=9.6, 2.2 Hz), 7.37 (1H, d, J=9.2 Hz), 7.67 (1H, s), 7.73 (1H, d, J=0.9 Hz), 7.88 (1H, s), 8.04 (1H, d, J=1.6 Hz).
42		7	NMR2: 1.37 (6H, s), 1.67–1.73 (3H, m), 1.93 (2H, brs), 2.86–2.96 (3H, m), 3.78 (2H, s), 4.25 (1H, brs), 4.32 (1H, brs), 5.11 (2H, br s), 6.93 (1H, dd, J=9.6, 2.2 Hz), 7.37 (1H, dd, J=9.6, 0.7 Hz), 7.66 (1H, s), 7.74 (1H, d, J=1.0 Hz), 7.89 (1H, d, J=1.0 Hz), 8.03 (1H, d, J=1.8 Hz).

[Table 3-8]

43		7	NMR2: 1.37 (6H, s), 1.68–1.75 (2H, m), 1.94 (2H, brs), 2.16 (1H, s), 2.87–2.97 (3H, m), 3.78 (2H, s), 4.32 (2H, brs), 5.32 (2H, brs), 6.93 (1H, dd, J=9.6, 2.1 Hz), 7.35–7.40 (2H, m), 7.67 (1H, s), 8.03 (1H, d, J=2.1 Hz), 8.82 (1H, d, J=2.1 Hz).
44		3	NMR2: 1.68 (2H, s), 1.75–1.86 (4H, m), 1.92 (2H, s), 2.72–2.81 (1H, m), 2.85–2.97 (3H, m), 3.22 (2H, d, J=6.7 Hz), 3.49–3.59 (2H, m), 4.11 (2H, dt, J=11.4, 3.2 Hz), 4.31 (2H, s), 4.47 (2H, t, J=6.7 Hz), 6.99 (1H, dd, J=9.2, 1.6 Hz), 7.07 (1H, d, J=1.9 Hz), 7.43 (1H, d, J=9.2 Hz), 7.72 (1H, s), 8.26 (1H, s), 8.77 (1H, d, J=1.9 Hz).
45		3	NMR2: 1.46 (3H, s), 1.61–1.81 (2H, m), 1.85–2.04 (2H, m), 2.83–3.03 (3H, m), 4.00 (2H, s), 4.29 (2H, brs), 4.48 (2H, d, J=6.0 Hz), 4.64 (2H, d, J=6.0 Hz), 5.11 (2H, s), 6.93 (1H, dd, J=9.6, 2.2 Hz), 7.38 (1H, dd, J=9.6, 0.5 Hz), 7.67 (1H, s), 7.72–7.76 (1H, m), 7.89 (1H, s), 8.03–8.08 (1H, m).
46		3	NMR2: 1.46 (3H, s), 1.60–1.81 (2H, m), 1.84–2.05 (2H, m), 2.81–3.05 (3H, m), 4.00 (2H, s), 4.32 (2H, brs), 4.48 (2H, d, J=6.0 Hz), 4.64 (2H, d, J=6.0 Hz), 5.33 (2H, s), 6.93 (1H, dd, J=9.6, 2.2 Hz), 7.34–7.42 (2H, m), 7.67 (1H, s), 8.05 (1H, d, J=1.6 Hz), 8.82 (1H, d, J=2.1 Hz).
47		3/47	NMR2: 1.68–1.74 (2H, m), 1.94 (2H, brs), 2.88–3.00 (3H, m), 3.47 (3H, s), 3.75–3.80 (2H, m), 4.07–4.13 (2H, m), 4.31 (2H, brs), 5.33 (2H, brs), 6.95 (1H, dd, J=9.6, 2.2 Hz), 7.33–7.40 (2H, m), 7.66 (1H, s), 8.04 (1H, d, J=2.2 Hz), 8.82 (1H, d, J=2.2 Hz). M+H: 401.6
48		7	NMR2: 1.65–1.74 (2H, m), 1.93 (2H, brs), 2.87–2.97 (3H, m), 3.83 (3H, s), 4.32 (2H, brs), 4.62 (2H, brs), 5.33 (2H, brs), 6.99 (1H, dd, J=9.6, 2.2 Hz), 7.36–7.42 (2H, m), 7.68 (1H, s), 8.02 (1H, d, J=2.1 Hz), 8.82 (1H, d, J=2.2 Hz).

[Table 3-9]

49		3	NMR2: 1.68–1.74 (2H, m), 1.94 (2H, brs), 2.86–2.96 (3H, m), 3.47 (3H, s), 3.75–3.80 (2H, m), 4.07–4.13 (2H, m), 4.31 (2H, brs), 5.33 (2H, brs), 6.95 (1H, dd, J=9.6, 2.2 Hz), 7.33–7.40 (2H, m), 7.66 (1H, s), 8.04 (1H, d, J=2.2 Hz), 8.82 (1H, d, J=2.1 Hz). M+H: 417.5
50		50	NMR2: 1.64–1.80 (2H, m), 2.01 (2H, t, J=14.5 Hz), 2.28 (3H, s), 2.69–2.78 (1H, m), 2.79–2.96 (2H, m), 3.00 (1H, tt, J=11.9, 3.8 Hz), 3.17–3.27 (1H, m), 3.83 (3H, s), 4.08 (1H, d, J=13.6 Hz), 4.32 (2H, qt, J=9.4, 4.5 Hz), 4.75–4.83 (1H, m), 6.83 (2H, d, J=8.2 Hz), 6.88 (1H, dd, J=9.6, 2.2 Hz), 7.08 (2H, d, J=8.2 Hz), 7.35 (1H, d, J=9.6 Hz), 7.65 (1H, s), 8.02 (1H, d, J=2.2 Hz). M+H: 394.5
51		7/51	NMR2: 0.79–0.85 (4H, m), 1.66–1.79 (2H, m), 1.82–2.05 (2H, m), 2.83–3.04 (3H, m), 3.70–3.77 (1H, m), 4.12–4.44 (2H, m), 5.11 (2H, s), 6.85 (1H, dd, J=9.6, 2.1 Hz), 7.31–7.37 (1H, m), 7.66 (1H, s), 7.71–7.76 (1H, m), 7.88 (1H, s), 8.29–8.34 (1H, m). M+H: 383
52		7/52	NMR2: 1.83 – 1.91 (2H, m), 1.93 (4H, brs), 2.03 (2H, brs), 2.26 (2H, brs), 2.31 (3H, s), 2.71 (2H, brs), 2.86 – 2.95 (3H, m), 4.18 (1H, brs), 4.25 (1H, brs), 4.31 (1H, brs), 5.11 (2H, brs), 6.90 (1H, dd, J=9.6, 2.1 Hz), 7.36 (1H, d, J=9.6 Hz), 7.66 (1H, s), 7.73 (1H, s), 7.88 (1H, s), 8.06 (1H, d, J=2.1 Hz).
53		3	NMR2: 1.64-2.03 (10H, m), 2.45-2.59 (1H, m), 2.84-3.04 (5H, m), 3.47-3.57 (1H, m), 4.30 (2H, s), 4.61-4.73 (4H, m), 5.11 (2H, s), 7.00 (1H, dd, J=9.2, 1.5 Hz), 7.42 (1H, d, J=9.2 Hz), 7.70-7.76 (2H, m), 7.88 (1H, s), 8.26 (1H, s).
54		54	NMR2: 1.78 (2H, brd, J=12.8 Hz), 2.04 (2H, brs), 2.52 (4H, brd, J=4.7 Hz), 2.65 (2H, t, J=7.2 Hz), 2.82 (2H, t, J=7.2 Hz), 2.99 (2H, brs), 3.10–3.20 (1H, m), 3.73 (4H, t, J=4.7 Hz), 4.31 (2H, brs), 5.28–5.35 (2H, brm), 7.38 (1H, d, J=1.8 Hz), 7.90 (1H, s), 8.34 (1H, d, J=2.0 Hz), 8.54 (1H, d, J=1.8 Hz), 8.81 (1H, d, J=2.0 Hz).

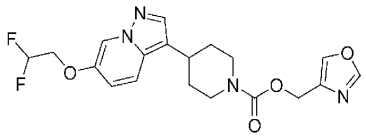
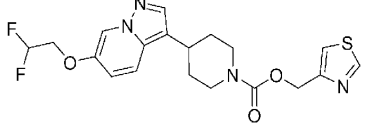
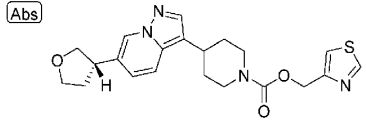
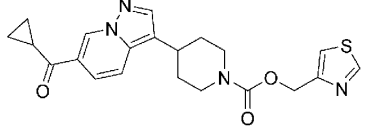
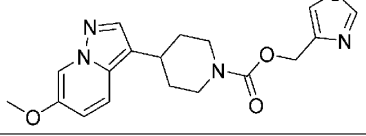
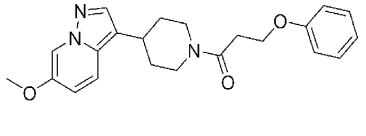
[Table 3-10]

55		55	NMR2: 1.63–1.75 (2H, m), 1.93–2.06 (2H, m), 2.37 (3H, s), 2.71–2.79 (1H, m), 2.93–3.03 (1H, m), 3.15 (1H, t, J=12.5 Hz), 3.83 (3H, s), 4.03 (1H, d, J=13.5 Hz), 4.19–4.30 (2H, m), 4.59–4.68 (2H, m), 4.71 (1H, d, J=13.4 Hz), 6.88 (1H, dd, J=9.6, 2.0 Hz), 7.15–7.22 (2H, m), 7.19–7.27 (1H, m), 7.30–7.37 (2H, m), 7.63 (1H, s), 8.01 (1H, d, J=2.0 Hz). M+H: 394.5
56		56	NMR2: 1.78 (2H, brs), 2.03 (2H, brs), 2.99 (2H, brs), 3.16 (1H, tt, J=12.0, 3.7 Hz), 3.55–3.61 (2H, m), 3.64–3.69 (2H, m), 3.69–3.76 (6H, m), 4.31 (2H, brs), 5.33 (2H, brd, J=5.6 Hz), 7.38 (1H, d, J=2.0 Hz), 7.92 (1H, s), 8.32 (1H, d, J=2.2 Hz), 8.51 (1H, d, J=2.2 Hz), 8.81 (1H, d, J=2.0 Hz). M+H: 471
57		3/57	NMR2: 1.76 (2H, brs), 2.02 (2H, brs), 2.98 (2H, brs), 3.12 (1H, tt, J=11.9, 3.7 Hz), 3.47 (3H, s), 3.77–3.82 (2H, m), 4.11–4.17 (2H, m), 4.30 (2H, brs), 5.33 (2H, brs), 7.37 (1H, d, J=2.0 Hz), 7.82 (1H, s), 8.23 (1H, d, J=2.6 Hz), 8.36 (1H, d, J=2.6 Hz), 8.81 (1H, d, J=2.0 Hz).
58		7	NMR2: 1.77 (2H, brd, J=12.4 Hz), 2.02 (2H, brs), 2.98 (2H, brs), 3.13 (1H, tt, J=11.9, 3.7 Hz), 4.22 (2H, td, J=12.8, 3.9 Hz), 4.31 (2H, brs), 5.33 (2H, brd, J=6.3 Hz), 6.14 (1H, tt, J=54.7, 3.9 Hz), 7.38 (1H, d, J=2.0 Hz), 7.86 (1H, s), 8.25 (1H, d, J=2.7 Hz), 8.36 (1H, d, J=2.7 Hz), 8.81 (1H, d, J=2.1 Hz).
59		7	NMR2: 1.72 (2H, s), 1.82 (4H, h, J=4.1 Hz), 1.94 (2H, s), 2.76 (1H, h, J=7.5 Hz), 2.88–2.98 (3H, m), 3.50–3.59 (2H, m), 4.10 (2H, dt, J=11.4, 3.2 Hz), 4.26 (1H, s), 4.32 (1H, s), 5.11 (2H, s), 6.99 (1H, d, J=9.2 Hz), 7.43 (1H, d, J=9.2 Hz), 7.72 (1H, s), 7.74 (1H, s), 7.88 (1H, s), 8.25 (1H, s).
60		7	NMR2: 1.70–1.91 (6H, m), 2.02 (2H, brs), 2.82–2.91 (1H, m), 2.97 (2H, s), 3.14 (1H, tt, J=11.9, 3.7 Hz), 3.52–3.61 (2H, m), 4.07–4.16 (2H, m), 4.24 (1H, brs), 4.32 (1H, brs), 5.10 (2H, brd, J=6.2 Hz), 7.73 (1H, d, J=0.75 Hz), 7.88 (1H, s), 7.91 (1H, s), 8.36 (1H, d, J=2.2 Hz), 8.43 (1H, dd, J=2.2, 0.55 Hz).

[Table 3-11]

61		7	NMR2: 1.68–1.74 (2H, m), 1.94 (2H, brs), 2.59 (4H, brs), 2.83 (2H, t, J=5.5 Hz), 2.87–2.96 (3H, m), 3.75 (4H, t, J=4.7 Hz), 4.09 (2H, t, J=5.5 Hz), 4.31 (2H, brs), 5.33 (2H, brs), 6.91 (1H, dd, J=9.7, 1.9 Hz), 7.33–7.40 (2H, m), 7.66 (1H, s), 8.03 (1H, s), 8.82 (1H, s).
62			NMR2: 1.79–1.85 (2H, m), 2.07 (2H, brs), 2.26 (3H, s), 2.27 (s, 3H), 3.01 (2H, s), 3.19 (1H, tt, J=11.9, 3.7 Hz), 4.33 (2H, s), 5.34 (2H, brd, J=6.2 Hz), 7.39 (1H, d, J=2.1 Hz), 7.96 (1H, s), 8.35 (1H, d, J=2.1 Hz), 8.47 (1H, d, J=2.1 Hz), 8.82 (1H, d, J=2.1 Hz).
63		3	NMR2: 0.71 (4H, d, J=5.9 Hz), 1.73 (2H, brs), 1.95 (2H, brs), 2.87–3.03 (5H, m), 4.09 (4H, q, J=8.4 Hz), 4.35 (1H, brs), 4.88 (2H, brs), 7.52 (1H, d, J=9.3 Hz), 7.60 (1H, d, J=9.3 Hz), 7.85 (1H, s), 8.99 (1H, s). M+H: 425.4
64		3	NMR2: 0.59-0.70 (2H, m), 0.85-0.96 (2H, m), 1.64-1.83 (2H, m), 1.85-2.04 (2H, m), 2.83-3.06 (4H, m), 4.34 (2H, brs), 5.33 (2H, s), 6.22 (1H, brs), 7.33 (1H, dd, J = 9.3, 1.6 Hz), 7.38 (1H, d, J = 2.1 Hz), 7.48 (1H, dd, J = 9.3, 0.9 Hz), 7.87 (1H, s), 8.82 (1H, d, J = 2.1 Hz), 8.89-8.94 (1H, m).
65		65	NMR1: 1.49-1.70 (2H, m), 1.76-1.94 (2H, m), 2.80-3.21 (5H, m), 3.21-3.44 (2H, m), 3.64-3.82 (2H, m), 3.95 (2H, d, J=12.0 Hz), 4.10 (2H, brs), 4.28-4.46 (2H, m), 4.99 (2H, s), 7.35 (1H, d, J=9.0 Hz), 7.80 (1H, d, J=9.5 Hz), 7.99 (1H, s), 8.16 (1H, d, J = 0.9 Hz), 8.39 (1H, d, J=0.7 Hz), 8.83 (1H, s), 10.79 (1H, brs).
66		65	NMR1: 1.51-1.72 (2H, m), 1.76-1.97 (2H, m), 2.78-3.21 (5H, m), 3.21-3.54 (2H, m), 3.61-3.87 (2H, m), 3.95 (2H, d, J=11.8 Hz), 4.06-4.26 (2H, m), 4.36 (2H, d, J=4.5 Hz), 5.20 (2H, s), 7.37 (1H, d, J = 9.4 Hz), 7.71 (1H, d, J=2.0 Hz), 7.81 (1H, d, J=9.2 Hz), 8.00 (1H, s), 8.84 (1H, s), 9.11 (1H, d, J=2.0 Hz), 10.98 (1H, brs).

[Table 3-12]

67		3/67	NMR2: 1.63-1.80 (2H, m), 1.83-2.03 (2H, m), 2.83-3.03 (3H, m), 4.17 (2H, td, J=12.9, 4.0 Hz), 4.30 (2H, brs), 5.11 (2H, s), 6.11 (1H, tt, J=54.9, 4.0 Hz), 6.93 (1H, dd, J=9.6, 2.2 Hz), 7.40 (1H, dd, J=9.7, 0.7 Hz), 7.69 (1H, s), 7.71-7.77 (1H, m), 7.88 (1H, s), 8.06 (1H, dd, J=2.1, 0.7 Hz).
68		3/68	NMR2: 1.62-1.82 (2H, m), 1.83-2.02 (2H, m), 2.79-3.10 (3H, m), 4.17 (2H, td, J = 12.9, 4.0 Hz), 4.33 (2H, brs), 5.33 (2H, s), 6.11 (1H, tt, J = 54.9, 4.0 Hz), 6.93 (1H, dd, J=9.6, 2.1 Hz), 7.33-7.46 (2H, m), 7.70 (1H, s), 8.06 (1H, d, J=2.0 Hz), 8.82 (1H, d, J=2.0 Hz).
69		3	NMR2: 1.66-1.80 (2H, m), 1.85-2.05 (3H, m), 2.36-2.43 (1H, m), 2.88-3.04 (3H,m), 3.37-3.43 (1H, m), 3.75-3.78 (1H, m), 3.90-3.96 (1H, m), 4.07-4.14 (2H, m), 4.32 (2H, s), 5.33 (2H, s), 7.01 (1H, dd, J=9.2, 1.5 Hz), 7.38 (1H, d, J=2.0 Hz), 7.44 (1H, d, J=9.2 Hz), 7.73 (1H, s), 8.30 (1H, s), 8.82 (1H, d, J=2.0 Hz). Chiral separation using SFC: CHIRALPAK IH, CO2/IPA (7/3)
70		3	NMR2: 1.03-1.16 (2H, m), 1.22-1.37 (2H, m), 1.65-1.85 (2H, m), 1.86-2.06 (2H, m), 2.50-2.62 (1H, m), 2.85-3.08 (3H, m), 4.34 (2H, brs), 5.34 (2H, s), 7.36-7.42 (1H, m), 7.50 (1H, dd, J=9.3, 0.9 Hz), 7.64 (1H, dd, J=9.4, 1.6 Hz), 7.93 (1H, s), 8.82 (1H, d, J=2.1 Hz), 9.20 (1H, dd, J=1.5, 1.0 Hz).
71		3	NMR2: 1.71 (2H, d, J=13.1 Hz), 1.94 (2H, s), 2.80-3.10 (3H, m), 3.82 (3H, s), 4.32 (2H, s), 5.33 (2H, s), 6.88 (1H, d, J=9.6 Hz), 7.35(1H, d, J=9.6 Hz), 7.38 (1H,s), 7.66 (1H, s), 8.01 (1H, s), 8.82 (1H, s). M+H: 373.5
72		50	NMR2: 1.64-1.81 (2H, m), 1.96-2.06 (2H, m), 2.70-2.79 (1H, m), 2.81-3.05 (3H, m), 3.23 (1H, t, J=12.8 Hz), 3.83 (3H, s), 4.08 (1H, d, J=13.7 Hz), 4.36 (2H, q, J=6.7 Hz), 4.79 (1H, d, J=13.3 Hz), 6.85-6.91 (1H, m), 6.94 (3H, t, J=7.7 Hz), 7.29 (2H, t, J=7.7 Hz), 7.35 (1H, d, J=9.6 Hz), 7.66 (1H, s), 8.02 (1H, d, J=2.1 Hz). M+H: 380.4

[Table 3-13]

73		3	NMR2: 1.66-1.85 (2H, m), 1.86-2.05 (2H, m), 2.85-3.10 (3H, m), 4.19-4.66 (6H, m), 4.83 (4H, s), 5.33 (2H, s), 7.34 (1H, dd, J = 9.3, 1.6 Hz), 7.37-7.41 (1H, m), 7.49 (1H, dd, J=9.3, 0.9 Hz), 7.88 (1H, s), 8.69-8.75 (1H, m), 8.82 (1H, d, J=2.0 Hz).
74			NMR2: 1.73-1.80 (2H, m), 2.02 (2H, s), 2.98 (2H, s), 3.12 (1H, tt, J=12.1, 3.7 Hz), 4.31 (2H, s), 5.33 (2H, s), 7.37 (1H, dt, J=2.0, 0.8 Hz), 7.81 (1H, s), 8.16 (1H, d, J=2.7 Hz), 8.31 (1H, d, J=2.7 Hz), 8.81 (1H, d, J=2.0 Hz).
75		7	NMR 2: 1.79 - 1.86 (2H, m), 2.07 (2H, brs), 2.26 (3H, s), 2.27 (3H, s), 3.01 (2H, brs), 3.18 (1H, ddt, J=12.0, 7.5, 3.8 Hz), 3.81 (3H, s), 4.34 (2H, brs), 5.34 (2H, brs), 7.38 (1H, d, J=2.0 Hz), 7.96 (1H, s), 8.35 (1H, d, J=2.1 Hz), 8.47 (1H, d, J=2.1 Hz), 8.82 (1H, d, J=2.0 Hz).
76		3/76	NMR2: 1.06- 1.17 (2H, m), 1.17-1.24 (2H, m), 1.81 (2H, s), 2.05 (2H, d, J=7.9 Hz), 2.24 (3H, s), 2.36 (3H, s), 2.99 (2H, s), 3.18 (1H, tt, J=11.8, 3.6 Hz), 3.34 (1H, tt, J=7.4, 3.8 Hz), 4.26 (1H, s), 4.34 (1H, s), 5.09 - 5.14 (2H, m), 7.74 (1H, s), 7.88 (1H, s), 7.96 (1H, s), 8.35 (1H, d, J=2.1 Hz), 8.47 (1H, d, J=2.1 Hz).
77		3	NMR2: 0.70 (4H, d, J=5.1 Hz), 1.78 (2H, brs), 2.04 (2H, d, J=9.9 Hz), 2.95 (2H, t, J=12.8 Hz), 2.99-3.04 (2H, m), 3.17 (1H, ddt, J=12.1, 7.4, 3.8 Hz), 4.09 (4H, q, J=5.4 Hz), 4.35 (1H, brs), 4.90 (2H, s), 8.02 (1H, s), 8.91 (1H, d, J=2.2 Hz), 9.12 (1H, d, J=2.2 Hz). M+H: 426.4
78		3	NMR2: 0.58-0.81 (4H, m), 1.63-1.83 (2H, m), 1.83-2.04 (2H, m), 2.58 (4H, t, J = 4.6 Hz), 2.74-2.99 (5H, m), 3.75 (4H, t, J = 4.7 Hz), 3.95-4.57 (5H, m), 6.91 (1H, dd, J = 9.6, 2.2 Hz), 7.36 (1H, d, J = 9.6 Hz), 7.66 (1H, s), 8.03 (1H, d, J = 1.6 Hz).
79		65	NMR1: 1.63-1.75 (2H, m), 1.92 (2H, d, J=12.9 Hz), 2.97 (2H, s), 3.02-3.11 (1H, m), 3.18 - 3.22 (2H, brm), 3.59-3.62 (4H, m), 3.76-3.79 (2H, m), 3.98 (2H, brs), 4.07-4.14 (2H, m), 4.49 (2H, s), 5.20 (2H, s), 7.70 (1H, s), 8.02 (1H, s), 8.45 (1H, d, J=2.6 Hz), 8.96 (1H, d, J=2.6 Hz), 9.11 (1H, s), 10.56 (1H, s).

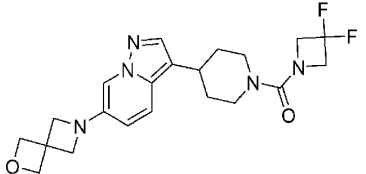
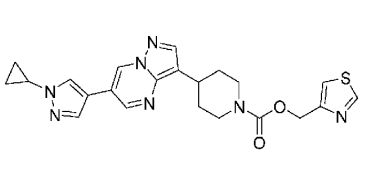
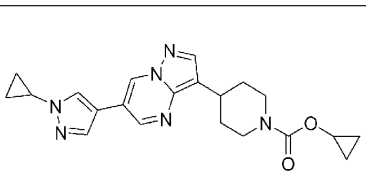
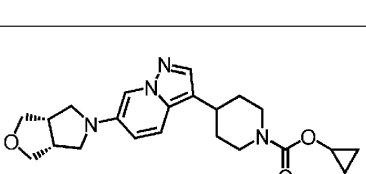
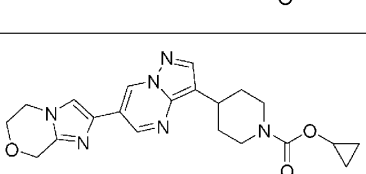
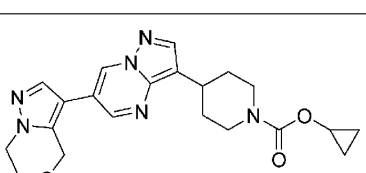
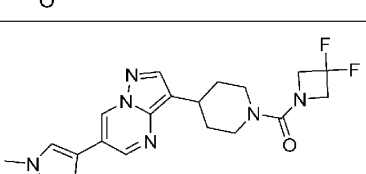
[Table 3-14]

80		3	NMR2: 1.79 (2H, pd, J=12.6, 3.9 Hz), 1.93 (1H, dt, J=12.7, 7.7 Hz), 2.05 (2H, d, J=13.1 Hz), 2.27 (1H, ddd, J=11.0, 8.9, 5.5 Hz), 2.40 (1H, ddd, J=11.0, 8.8, 6.6 Hz), 2.86 – 2.98 (3H, m), 3.17 (1H, tt, J=12.0, 3.7 Hz), 3.80 (1H, d, J=9.2 Hz), 3.89 – 4.06 (5H, m), 4.00 (3H, s), 4.11 (1H, q, J=7.7 Hz), 4.19 (1H, d, J=9.1 Hz), 7.67 (1H, s), 7.76 (1H, s), 7.94 (1H, s), 8.55 (1H, d, J=2.2 Hz), 8.67 (1H, d, J=2.2 Hz). M+H: 422.4
81		3	NMR2: 1.08 (2H, q, J=6.5 Hz), 1.18 (2H, brs), 1.65–1.81 (2H, m), 1.98 (2H, d, J=13.2 Hz), 2.31 (1H, s), 2.41 – 2.46 (1H, m), 2.87–2.99 (3H, m), 3.65 (1H, dq, J=7.6, 3.8 Hz), 3.87 (1H, q, J=7.6 Hz), 3.98–4.08 (3H, m), 4.67–4.72 (1H, m), 5.93 (1H, d, J=56.4 Hz), 7.19 (1H, d, J=9.1 Hz), 7.47 (1H, d, J=9.1 Hz), 7.70 (1H, s), 7.72 (1H, s), 7.76 (1H, s), 8.53 (1H, s). M+H: 441.3
82		3/82	NMR2: 1.08 (2H, td, J=7.4, 5.3 Hz), 1.19 (2H, s), 1.68–1.80 (2H, m), 1.99 (2H, d, J=12.1 Hz), 2.93–3.02 (3H, m), 3.65 (1H, tt, J=7.2, 3.8 Hz), 3.99 (2H, d, J=13.3 Hz), 4.32 (4H, t, J=12.4 Hz), 7.19 (1H, d, J=9.1 Hz), 7.47 (1H, d, J=9.1 Hz), 7.70 (1H, s), 7.72 (1H, s), 7.75 (1H, s), 8.53 (1H, s). M+H: 427.3
83		3	NMR2: 1.04–1.16 (2H, m), 1.16–1.22 (2H, m), 1.67–1.81 (2H, m), 1.89–1.99 (3H, m), 2.23–2.32 (1H, m), 2.36–2.45 (1H, m), 2.83–3.00 (4H, m), 3.61–3.69 (1H, m), 3.80 (1H, d, J=9.2 Hz), 3.93 (1H, td, J=8.0, 4.9 Hz), 3.96–4.06 (4H, m), 4.11 (1H, q, J=7.7 Hz), 4.19 (1H, d, J=9.2 Hz), 7.18 (1H, d, J=9.2 Hz), 7.48 (1H, d, J=9.2 Hz), 7.70 (1H, s), 7.72 (1H, s), 7.76 (1H, s), 8.53 (1H, s). M+H: 447.6
84		3	NMR2: 1.08 (2H, p, J=7.8 Hz), 1.15–1.22 (2H, m), 1.68–1.80 (2H, m), 1.87 (1H, d, J=8.2 Hz), 1.97 (2H, d, J=13.1 Hz), 2.69 (1H, q, J=6.9 Hz), 2.90–3.01 (3H, m), 3.65 (1H, tt, J=7.4, 3.7 Hz), 3.83 (2H, d, J=10.4 Hz), 4.06 (2H, d, J=13.4 Hz), 4.18 (2H, d, J=6.2 Hz), 4.40 (2H, d, J=10.4 Hz), 7.18 (1H, d, J=9.1 Hz), 7.48 (1H, d, J=9.1 Hz), 7.70 (1H, s), 7.72 (1H, s), 7.75 (1H, s), 8.53 (1H, s). M+H: 433.3

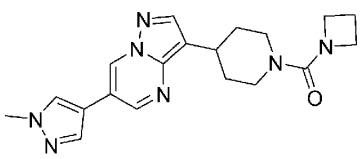
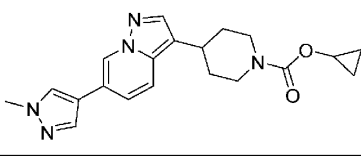
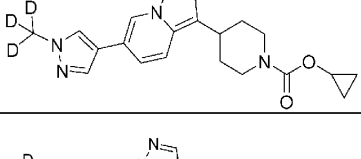
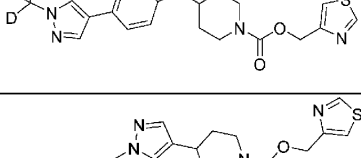
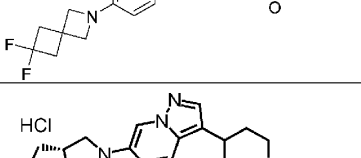
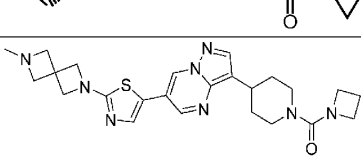
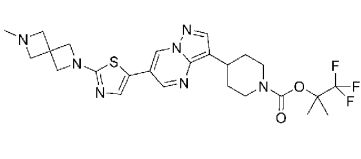
[Table 3-15]

85		3/85	NMR2: 1.05–1.10 (2H, m), 1.17–1.21 (2H, m), 1.73 (2H, d, J=13.3 Hz), 1.95 (2H, s), 2.90–3.00 (3H, m), 3.65 (1H, tt, J=7.3, 3.8 Hz), 4.31 (2H, s), 5.11 (2H, s), 7.18 (1H, dd, J=9.2, 1.5 Hz), 7.47 (1H, dd, J=9.2, 1.0 Hz), 7.70 (1H, s), 7.72 (1H, d, J=0.9 Hz), 7.74–7.75 (2H, m), 7.89 (1H, s), 8.53 (1H, dd, J=1.5, 0.9 Hz).
86		3	NMR2: 1.08 (2H, ddd, J=7.2, 4.4, 2.8 Hz), 1.11 – 1.22 (2H, m), 1.73 (2H, qd, J=12.4, 4.0 Hz), 1.95 (2H, dd, J=12.8, 3.5 Hz), 2.25 (2H, p, J=7.7 Hz), 2.86 – 3.00 (3H, m), 3.61 – 3.69 (1H, m), 3.96 – 4.05 (6H, m), 7.17 (1H, dd, J=9.1, 1.6 Hz), 7.48 (1H, d, J=9.1 Hz), 7.70 (1H, s), 7.72 (1H, s), 7.75 (1H, s), 8.53 (1H, s) M+H: 391.31
87		7	NMR2: 1.70 (2H, brd, J=12.9 Hz), 1.93 (2H, s), 2.85 – 2.95 (3H, m), 4.21 (4H, t, J=11.6 Hz), 4.31 (2H, s), 5.11 (2H, s), 6.59 (1H, dd, J=9.4, 2.1 Hz), 7.39 (1H, d, J=9.4 Hz), 7.63 (1H, s), 7.68 (1H, d, J=2.1 Hz), 7.73 (1H, s), 7.88 (1H, s).
88		3	NMR2: 0.70 (4H, d, J=5.1 Hz), 1.72 (2H, brs), 1.92–1.96 (2H, m), 2.53 (3H, s), 2.84 – 2.98 (5H, m), 3.73 (2H, s), 4.03–4.15 (4H, m), 4.34 (1H, brs), 7.09 (1H, s), 7.39–7.48 (2H, m), 7.74 (1H, s), 8.81 (1H, s). M+H: 421.3
89		3	NMR2: 0.71 (4H, d, J=6.0 Hz), 1.73 (2H, brs), 1.94 (2H, brs), 2.87 – 3.00 (3H, m), 4.07 – 4.18 (2H, m), 4.16 – 4.20 (2H, m), 4.25 – 4.31 (2H, m), 4.36 (1H, brs), 5.01 (2H, s), 7.09 (1H, dd, J=9.2, 1.6 Hz), 7.50 (1H, d, J=9.2 Hz), 7.72 (1H, s), 7.77 (1H, s), 8.26 (1H, s). M+H: 408.3
90		3	NMR2: 0.71 (4H, brs), 1.72 (2H, brs), 1.95 (2H, brs), 2.86–2.98 (3H, m), 4.10 (6H, brs), 4.35 (1H, brs), 4.91 (2H, s), 7.14 (1H, s), 7.42 (1H, d, J=9.2 Hz), 7.47 (1H, d, J=9.2 Hz), 7.76 (1H, s), 8.82 (1H, s). M+H: 408.3

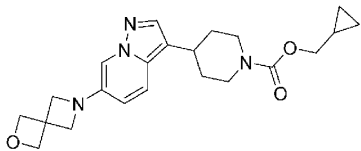
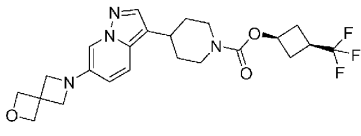
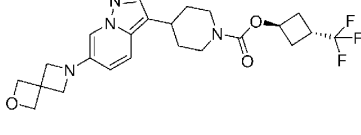
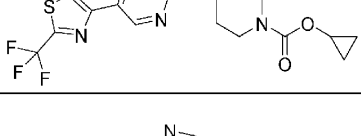
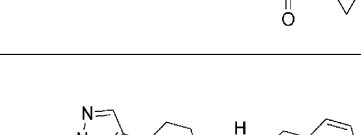
[Table 3-16]

91		3	NMR2: 1.65–1.76 (2H, m), 1.95 (2H, d, J=13.2 Hz), 2.91–3.00 (3H, m), 3.94–4.00 (2H, m), 4.00 (4H, s), 4.31 (4H, t, J=12.4 Hz), 4.85 (4H, s), 6.58 (1H, d, J=9.4 Hz), 7.33 (1H, d, J=9.4 Hz), 7.61 (2H, s). M+H: 418.3
92		3	NMR2: 1.06–1.29 (4H, m), 1.80 (2H, s), 2.06 (2H, brs), 3.00 (2H, s), 3.13–3.21 (1H, m), 3.67 (1H, tt, J=7.5, 3.7 Hz), 4.32 (2H, s), 5.33 (2H, s), 7.38 (1H, d, J=2.0 Hz), 7.74 (1H, s), 7.75 (1H, s), 7.92 (1H, s), 8.54 (1H, d, J=2.2 Hz), 8.66 (1H, d, J=2.2 Hz), 8.82 (1H, d, J=2.0 Hz).
93		3/93	NMR2: 0.70 (4H, d, J=5.1 Hz), 1.06–1.17 (2H, m), 1.14–1.22 (2H, m), 1.77 (2H, s), 2.03 (2H, d, J=12.8 Hz), 2.95 (2H, t, J=12.7 Hz), 3.11–3.20 (1H, m), 3.67 (1H, tt, J=7.4, 3.8 Hz), 4.06–4.15 (2H, m), 4.34 (1H, s), 7.74 (1H, s), 7.75 (1H, s), 7.93 (1H, s), 8.54 (1H, d, J=2.2 Hz), 8.66 (1H, d, J=2.2 Hz).
94		3/94	NMR2: 0.60–0.79 (4H, m), 1.61–1.82 (2H, m), 1.82–2.06 (2H, m), 2.75–2.98 (3H, m), 2.98–3.10 (2H, m), 3.15 (2H, dd, J=9.3, 2.9 Hz), 3.34 (2H, dd, J=9.2, 7.4 Hz), 3.68 (2H, dd, J=8.9, 3.8 Hz), 3.89–4.52 (5H, m), 6.87 (1H, dd, J=9.6, 2.1 Hz), 7.33 (1H, d, J=9.6 Hz), 7.60 (1H, s), 7.76 (1H, d, J=1.6 Hz).
95		95	NMR2: 0.70 (4H, d, J=5.0 Hz), 1.76 (2H, s), 2.03 (2H, s), 2.94 (2H, t, J=12.9 Hz), 3.11–3.21 (1H, m), 4.00–4.20 (6H, brm), 4.34 (1H, s), 4.92 (2H, s), 7.23 (1H, s), 7.93 (1H, s), 8.72 (1H, d, J=2.1 Hz), 8.99 (1H, d, J=2.1 Hz).
96		95	NMR2: 0.70 (4H, d, J=4.9 Hz), 1.78 (2H, s), 2.03 (2H, s), 2.95 (2H, t, J=12.8 Hz), 3.11–3.20 (1H, m), 4.06–4.15 (2H, m), 4.19 (2H, dd, J=6.1, 4.4 Hz), 4.30 (2H, t, J=5.2 Hz), 4.35 (1H, brs), 5.00 (2H, s), 7.75 (1H, s), 7.95 (1H, s), 8.44 (1H, d, J=2.1 Hz), 8.47 (1H, J=2.1 Hz).
97		3	NMR2: 1.74–1.86 (2H, m), 2.04–2.11 (2H, m), 2.96–3.05 (2H, m), 3.20 (1H, tt, J=11.9, 3.7 Hz), 3.97 (2H, brs), 4.00 (3H, s), 4.31 (4H, t, J=12.4 Hz), 7.67 (1H, s), 7.76 (1H, s), 7.93 (1H, s), 8.55 (1H, d, J=2.2 Hz), 8.67 (1H, d, J=2.2 Hz). M+H: 402.3

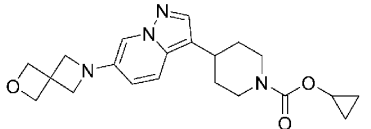
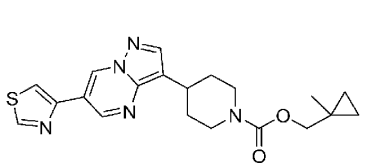
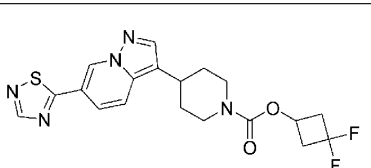
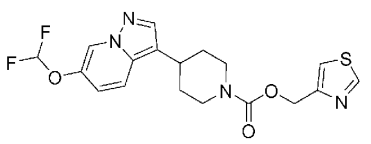
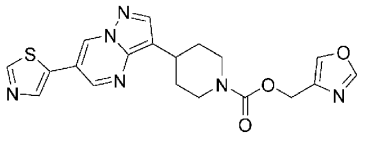
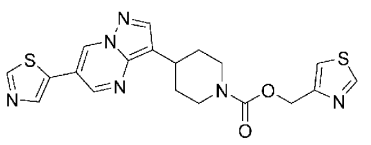
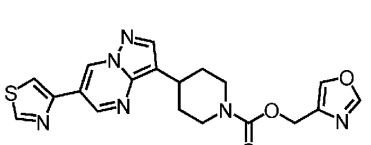
[Table 3-17]

98		3	NMR2: 1.77 (2H, qd, J=12.6, 3.9 Hz), 2.01-2.07 (2H, m), 2.24 (2H, p, J=7.6 Hz), 2.94 (2H, td, J=12.9, 2.5 Hz), 3.12-3.22 (1H, m), 3.98-4.07 (6H, m), 4.00 (s, 3H), 7.67 (1H, s), 7.76 (1H, s), 7.93 (1H, s), 8.55 (1H, d, J=2.2 Hz), 8.67 (1H, d, J=2.2 Hz) M+H: 366.2
99		7	NMR2: 0.71 (4H, d, J=5.8 Hz), 1.73 (2H, brs), 1.94 (2H, s), 2.87-2.99 (3H, m), 3.97 (3H, s), 4.07-4.14 (2H, m), 4.35 (1H, brs), 7.19 (1H, dd, J=9.1, 1.6 Hz), 7.48 (1H, d, J=9.1 Hz), 7.61 (1H, s), 7.74 (1H, s), 7.75 (1H, s), 8.53 (1H, s).
100			NMR2: 0.70 (4H, d, J=5.4 Hz), 1.72 (2H, s), 1.95 (2H, s), 2.87-2.99 (3H, m), 4.07-4.15 (2H, m), 4.35 (1H, s), 7.19 (1H, dd, J=9.2, 1.2 Hz), 7.48 (1H, d, J=9.2 Hz), 7.61 (1H, s), 7.74 (1H, s), 7.75 (1H, s), 8.53 (1H, s).
101			NMR2: 1.74 (2H, d, J=13.2 Hz), 1.97 (2H, s), 2.96 (3H, tt, J=11.9, 3.7 Hz), 4.33 (2H, s), 5.34 (2H, s), 7.19 (1H, dd, J=9.2, 1.6 Hz), 7.38 (1H, d, J=2.0 Hz), 7.48 (1H, d, J=9.2 Hz), 7.61 (1H, s), 7.74 (1H, s), 7.75 (1H, s), 8.53 (1H, s), 8.82 (1H, d, J=2.0 Hz).
102		3/ 102	NMR2: 1.65 - 1.77 (2H, m), 1.93 (2H, brs), 2.82 (4H, t, J=12.0 Hz), 2.86 - 3.02 (3H, m), 3.91 (4H, s), 4.31 (2H, s), 5.33 (2H, s), 6.57 (1H, dd, J=9.4, 2.1 Hz), 7.31-7.39 (2H, m), 7.59-7.63 (2H, m), 8.82 (1H, d, J=2.1 Hz). M+H: 474.8
103		65	NMR1: 0.53-0.73 (4H, m), 1.43-1.63 (2H, m), 1.76-1.93 (2H, m), 2.69-4.29 (19H, m), 7.07 (1H, dd, J=9.6, 1.8 Hz), 7.59 (1H, d, J=9.6 Hz), 7.67 (1H, s), 7.88 (1H, s), 10.49 (1H, s).
104		7	M+H: 479.37
105		7	NMR2: 1.72 (6H, s), 1.79 (2H, dt, J=12.5, 6.6 Hz), 2.01-2.08 (2H, m), 2.32 (3H, s), 2.92 (2H, s), 3.14 (1H, ddd, J=12.0, 8.3, 3.7 Hz), 3.41 (4H, s), 4.11-4.26 (2H, m), 4.21 (4H, s), 7.39 (1H, s), 7.93 (1H, s), 8.52-8.59 (2H, m). M+H: 550.3

[Table 3-18]

106		3	NMR2: 0.26–0.36 (2H, m), 0.51–0.59 (2H, m), 1.15 (1H, dddd, J=16.8, 9.0, 7.3, 3.8 Hz), 1.73 (2H, dd, J=12.4, 4.2 Hz), 1.93 (2H, d, J=12.6 Hz), 2.85 – 2.94 (3H, m), 3.94 (2H, d, J=7.2 Hz), 4.00 (4H, s), 4.29 (2H, brd, J=13.5 Hz), 4.85 (4H, s), 6.57 (1H, dd, J=9.5, 2.0 Hz), 7.35 (1H, d, J=9.5 Hz), 7.61 (2H, s). M+H: 397.6
107		3	NMR2: 1.69 (2H, qd, J=12.5, 4.3 Hz), 1.94 (2H, d, J=13.3 Hz), 2.25 (2H, s), 2.53–2.66 (3H, m), 2.85–2.94 (3H, m), 4.00 (4H, s), 4.23 (2H, brs), 4.85 (4H, s), 4.87 – 4.98 (1H, m), 6.58 (1H, dd, J=9.7, 2.0 Hz), 7.34 (1H, d, J=9.7 Hz), 7.62 (2H, s). M+H: 465.2 stereochemistry was determined by NOESY
108		3	NMR2: 1.63 – 1.75 (2H, m), 1.91 – 1.97 (2H, m), 2.34 – 2.44 (2H, m), 2.57 – 2.66 (2H, m), 2.85 – 2.97 (4H, m), 4.00 (4H, s), 4.25 (2H, brs), 4.85 (4H, s), 5.07 – 5.16 (1H, m), 6.55 – 6.60 (1H, m), 7.34 (1H, d, J=9.4 Hz), 7.61 (2H, s). M+H: 465.23 stereochemistry was determined by NOESY
109		3	NMR2: 0.71 (4H, d, J=4.8 Hz), 1.79 (2H, brs), 2.02–2.08 (2H, brm), 2.91–3.00 (2H, m), 3.18 (1H, tt, J=11.9, 3.7 Hz), 4.06–4.14 (2H, m), 4.35 (1H, brs), 7.79 (1H, s), 8.03 (1H, s), 8.87 (1H, d, J=2.2 Hz), 9.26 (1H, d, J=2.2 Hz).
110		7/ 110	NMR2: 0.69-0.72 (4H, m), 1.02-1.14 (2H, m), 1.12-1.22 (2H, m), 1.72 (2H, s), 1.92-1.96 (2H, m), 2.87-2.99 (3H, m), 3.65 (1H, tt, J=7.4, 3.8 Hz), 4.07-4.14 (2H, m), 4.35 (1H, s), 7.18 (1H, dd, J=9.2, 1.6 Hz), 7.47 (1H, d, J=9.2 Hz), 7.70 (1H, s), 7.72 (1H, s), 7.75 (1H, s), 8.53 (1H, s).
111		3	NMR2: 1.67–1.79 (2H, m), 2.01 (2H, d, J=12.5 Hz), 2.42–2.52 (2H, m), 2.85 (2H, t, J=6.9 Hz), 2.92 (2H, td, J=12.8, 2.6 Hz), 3.08 (1H, tt, J=11.8, 3.7 Hz), 3.52 (2H, q, J=6.5 Hz), 3.91-3.98 (6H, m), 4.48 (1H, t, J=5.6 Hz), 7.22 (3H, dd, J=7.5, 5.3 Hz), 7.31 (2H, t, J=7.5 Hz), 7.72–7.77 (2H, m), 8.01 (1H, d, J=2.7 Hz).

[Table 3-19]

112		3/ 112	NMR2: 0.62-0.75 (4H, m), 1.62-1.78 (2H, m), 1.83-2.01 (2H, m), 2.77-3.01 (3H, m), 3.93-4.49 (7H, m), 4.85 (4H, s), 6.57 (1H, dd, J=9.5, 2.0 Hz), 7.34 (1H, dd, J=9.5, 0.7 Hz), 7.57-7.66 (2H, m).
113		113	NMR2: 0.33 - 0.39 (2H, m), 0.50 (2H, t, J=2.9 Hz), 1.15 (3H, s), 1.81 (2H, qd, J=12.6, 4.3 Hz), 2.03-2.11 (2H, m), 2.99 (2H, s), 3.20 (1H, tt, J=12.0, 3.7 Hz), 3.91 (2H, s), 4.32 (2H, s), 7.64 (1H, d, J=2.1 Hz), 8.01 (1H, s), 8.92 (1H, d, J= 2.0 Hz), 8.95 (1H, d, J= 2.0 Hz), 9.25 (1H, d, J=2.1 Hz) M+H: 398.3
114		3	NMR2: 1.70 - 1.82 (2H, m), 1.99 (2H, d, J=13.1 Hz), 2.67-2.73 (2H, m), 2.93 (1H, s), 3.03 (4H, dddd, J=24.4, 12.3, 8.2, 4.3 Hz), 4.24 (1H, brs), 4.34 (1H, brs), 4.92-4.94 (1H, m), 7.56 (1H, dd, J=9.3, 1.5 Hz), 7.61 (1H, d, J=9.3 Hz), 7.94 (1H, s), 8.72 (1H, s), 9.21 (1H, s).
115		3	NMR2: 1.63-2.09 (4H, m), 2.81-3.10 (3H, m), 4.33 (2H, brs), 5.33 (2H, s), 6.49 (1H, t, J=72.8 Hz), 7.02 (1H, dd, J=9.6, 2.1 Hz), 7.36-7.41 (1H, m), 7.46 (1H, dd, J=9.6, 0.7 Hz), 7.79 (1H, s), 8.40 (1H, d, J=1.3 Hz), 8.82 (1H, d, J=2.0 Hz).
116		3	NMR2: 1.76-1.84 (2H, brm), 2.00-2.10 (2H, brm), 2.99 (2H, brs), 3.18 (1H, tt, J=12.0, 3.7 Hz), 4.30 (2H, s), 5.11 (2H, s), 7.74 (1H, d, J=1.0 Hz), 7.89 (1H, d, J=1.0 Hz), 8.00 (1H, s), 8.13 (1H, d, J=0.7 Hz), 8.63 (1H, d, J=2.3 Hz), 8.81 (1H, d, J=2.3 Hz), 8.88 (1H, d, J=0.7 Hz).
117		3/ 117	NMR2: 1.75-1.87 (2H, brm), 2.05-2.07 (2H, brm), 3.01 (2H, s), 3.19 (1H, tt, J=12.0, 3.7 Hz), 4.33 (2H, s), 5.34 (2H, s), 7.38 (1H, d, J=2.5 Hz), 8.00 (1H, s), 8.13 (1H, s), 8.63 (1H, d, J=2.8 Hz), 8.81 (1H, d, J=2.8 Hz), 8.82 (1H, d, J=2.5 Hz), 8.88 (1H, d, J=0.7 Hz).
118		3	NMR2: 1.80 (2H, d, J=12.9 Hz), 2.07 (2H, brs), 2.99 (2H, brs), 3.19 (1H, tt, J=12.0, 3.7 Hz), 4.31 (2H, brs), 5.11 (2H, brs), 7.63 (1H, d, J=2.1 Hz), 7.74 (1H, d, J=1.0 Hz), 7.88 (1H, d, J=1.1 Hz), 7.99 (1H, s), 8.91 (1H, d, J=2.0 Hz), 8.95 (1H, d, J=2.0 Hz), 9.24 (1H, d, J=2.1 Hz). M+H: 411.4

[Table 3-20]

119		3	NMR2: 1.35 (6H, d, J=7.0 Hz), 1.78 (2H, brs), 2.04 (2H, brs), 2.93 – 3.08 (3H, m), 3.10 – 3.19 (1H, m), 4.24 (1H, brs), 4.32 (1H, brs), 5.11 (2H, brs), 7.75 (1H, s), 7.89 (2H, d, J=3.7 Hz), 8.37 (1H, s), 8.43 (1H, s). M+H: 370.5.
120		7	NMR2: 1.66–1.74 (2H, m), 1.93 (2H, s), 2.84–2.96 (3H, m), 3.03–3.10 (4H, m), 3.85–3.92 (4H, m), 4.28 (2H, s), 5.08–5.13 (2H, m), 6.96 (1H, dd, J=9.6, 2.1 Hz), 7.37 (1H, dd, J=9.6, 0.8 Hz), 7.65 (1H, s), 7.73 (1H, s), 7.86–7.95 (2H, m).
121		3	NMR2: 2.05 (2H, brs), 2.06 (2H, d, J=12.8 Hz), 2.99 (2H, brs), 3.20 (1H, tt, J=12.0, 3.7 Hz), 4.27 (1H, brs), 4.34 (1H, brs), 5.12 (2H, brs), 7.74 (1H, d, J=0.9 Hz), 7.89 (1H, s), 8.09 (1H, s), 9.00 (1H, d, J=2.2 Hz), 9.21 (1H, s), 9.27 (1H, d, J=2.2 Hz).
122		3	NMR2: 1.78 (2H, brs), 2.04 (2H, brs), 2.98 (2H, brs), 3.17 (1H, tt, J=12.0, 3.7 Hz), 4.25 (1H, brs), 4.32 (1H, brs), 5.11 (2H, brs), 6.78 (1H, dd, J=7.1, 4.0 Hz), 7.74 (1H, s), 7.88 (1H, s), 7.96 (1H, s), 8.42 (1H, dd, J=4.0, 1.8 Hz), 8.63 (1H, dd, J=7.0, 1.8 Hz).
123		7	NMR2: 1.81 (2H, brs), 2.06 (2H, brs), 2.99 (2H, s), 3.20 (1H, tt, J=12.0, 3.7 Hz), 4.26–4.34 (2H, brm), 5.12 (2H, s), 7.74 (1H, d, J=1.0 Hz), 7.89 (1H, s), 8.11 (1H, s), 8.77 (1H, s), 8.90 (1H, d, J=2.2 Hz), 9.33 (1H, d, J=2.2 Hz).
124		3	NMR2: 1.80 (2H, brs), 2.05 (2H, brs), 2.76 (3H, s), 2.99 (2H, s), 3.19 (1H, tt, J=12.1, 3.7 Hz), 4.27 (1H, s), 4.34 (1H, brs), 5.11 (2H, brs), 7.74 (1H, d, J=1.0 Hz), 7.89 (1H, s), 8.09 (1H, s), 8.85 (1H, d, J=2.2 Hz), 9.27 (1H, d, J=2.2 Hz).
125		3	NMR2: 1.83 (2H, brs), 2.05 (2H, brs), 3.01 (2H, brs), 3.20 (1H, tt, J=12.1, 3.8 Hz), 4.33 (2H, brs), 5.34 (2H, brs), 7.38 (1H, d, J=2.1 Hz), 7.63 (1H, d, J=1.9 Hz), 7.99 (1H, s), 8.82 (1H, d, J=2.1 Hz), 8.91 (1H, d, J=2.1 Hz), 8.95 (1H, d, J=2.1 Hz), 9.25 (1H, d, J=2.1 Hz). M+H: 427.4

[Table 3-21]

126		7	NMR2: 1.79–1.85 (2H, m), 2.05–2.07 (2H, brm), 3.01 (2H, s), 3.21 (1H, tt, J=12.0, 3.7 Hz), 4.34 (2H, brs), 5.34 (2H, s), 7.39 (1H, d, J=2.1 Hz), 8.11 (1H, s), 8.77 (1H, s), 8.82 (1H, d, J=2.1 Hz), 8.90 (1H, d, J=2.2 Hz), 9.33 (1H, d, J=2.2 Hz).
127		3	NMR1: 1.60–1.72 (2H, m), 1.92 (2H, d, J=12.9 Hz), 2.34 (2H, p, J=7.2 Hz), 2.97 (2H, s), 3.04 (1H, tt, J=11.8, 3.7 Hz), 3.87 (4H, t, J=7.2 Hz), 4.09 (2H, d, J=12.7 Hz), 5.20 (2H, s), 7.70 (1H, d, J=2.0 Hz), 7.84 (1H, s), 8.10–8.16 (2H, m), 9.11 (1H, d, J=2.0 Hz). M+H: 399.4
128		3	NMR2: 1.35 (6H, d, J=6.95 Hz), 1.76–1.84 (2H, m), 2.01–2.09 (2H, m), 3.01 (3H, tdd, J=14.2, 7.7, 4.3 Hz), 3.14 (1H, tt, J=11.8, 2.6 Hz), 4.31 (2H, s), 5.33 (2H, d, J=6.3 Hz), 7.38 (1H, t, J=2.0 Hz), 7.88 (1H, d, J=1.6 Hz), 8.36 (1H, t, J=2.1 Hz), 8.40–8.45 (1H, m), 8.81 (1H, d, J=2.0 Hz). M+H: 386.4
129		3	NMR2: 1.66–1.93 (2H, m), 1.93–2.15 (2H, m), 2.82–3.09 (2H, m), 3.09–3.24 (1H, m), 4.33 (2H, brs), 5.33 (2H, s), 6.56 (1H, t, J=71.7 Hz), 7.35–7.40 (1H, m), 7.98 (1H, s), 8.39 (1H, d, J=2.4 Hz), 8.60 (1H, d, J=2.6 Hz), 8.81 (1H, d, J=2.1 Hz).
130		7	NMR2: 1.73–1.80 (2H, m), 2.03 (2H, d, J=13.0 Hz), 2.98 (2H, s), 3.12 (1H, tt, J=11.9, 3.7 Hz), 3.87 (3H, s), 4.30 (2H, s), 5.33 (2H, s), 7.37 (1H, dd, J=2.0, 1.0 Hz), 7.81 (1H, s), 8.17 (1H, d, J=2.7 Hz), 8.31 (1H, d, J=2.7 Hz), 8.81 (1H, d, J=2.0 Hz).
131		3	NMR2: 1.73 (2H, d, J=12.9 Hz), 1.95 (2H, s), 2.90 – 3.00 (3H, m), 4.26 (1H, s), 4.33 (1H, s), 5.11 (2H, s), 6.72 (1H, td, J=7.0, 1.4 Hz), 7.06 (1H, ddd, J=9.0, 6.7, 1.1 Hz), 7.47 (1H, dt, J=9.0, 1.2 Hz), 7.74 (1H, d, J=0.65 Hz), 7.77 (s, 1H), 7.89 (1H, s), 8.42 (1H, d, J=7.0 Hz).
132		3	NMR2: 0.63–0.83 (2H, m), 0.97–1.14 (2H, m), 1.67–1.87 (2H, m), 1.87–2.14 (3H, m), 2.84–3.08 (2H, m), 3.08–3.23 (1H, m), 4.16–4.45 (2H, m), 5.33 (2H, s), 7.33–7.42 (1H, m), 7.87 (1H, s), 8.25–8.38 (2H, m), 8.81 (1H, d, J=2.0 Hz).

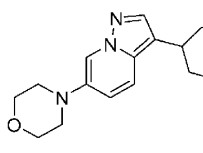
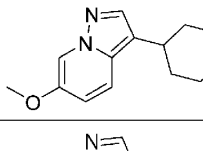
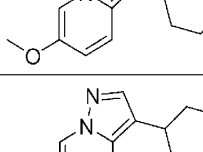
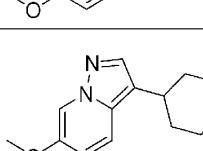
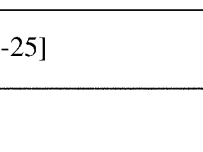
[Table 3-22]

133		113	NMR2: 1.79 (2H, d, J=12.1 Hz), 2.04 (2H, s), 3.00 (2H, s), 3.18 (1H, tt, J=12.0, 3.7 Hz), 4.32 (2H, s), 5.33 (2H, s), 6.78 (1H, dd, J=7.0, 4.0 Hz), 7.38 (1H, d, J=2.1 Hz), 7.96 (1H, s), 8.42 (1H, dd, J=4.0, 1.8 Hz), 8.63 (1H, dd, J=7.1, 1.8 Hz), 8.81 (1H, d, J=2.1 Hz).
134		113	NMR2: 1.79 (3H, s), 1.92 (5H, t, J=5.2 Hz), 1.96 – 2.10 (4H, m), 2.98 (2H, s), 3.17 (1H, tt, J=12.0, 3.7 Hz), 4.00 (3H, s), 4.20 (1H, s), 4.32 (1H, s), 4.89 – 4.94 (1H, m), 7.68 (1H, s), 7.77 (1H, d, J=0.8 Hz), 7.94 (1H, s), 8.56 (1H, d, J=2.2 Hz), 8.68 (1H, d, J=2.2 Hz).
135		7	NMR2: 1.72 (6H, brs), 1.76–1.84 (2H, m), 2.06 (2H, s), 2.88–2.97 (1H, m), 2.97–3.06 (1H, m), 3.16 (1H, tt, J=11.9, 3.7 Hz), 3.38 (3H, s), 3.80 (2H, d, J=5.1 Hz), 4.14 (1H, d, J=13.4 Hz), 4.27 (1H, d, J=13.4 Hz), 4.37 (2H, t, J=5.1 Hz), 7.79 (2H, s), 7.94 (1H, s), 8.57 (1H, d, J=2.2 Hz), 8.69 (1H, d, J=2.2 Hz).
136		113	NMR2: 1.79 (2H, s), 2.04 (2H, s), 2.98 (2H, s), 3.16 (1H, tt, J=11.9, 3.7 Hz), 4.00 (3H, s), 4.30 (2H, s), 5.11 (2H, s), 7.67 (1H, d, J=0.8 Hz), 7.73 – 7.75 (1H, m), 7.76 (1H, d, J=0.68 Hz), 7.88 (1H, s), 7.92 (1H, s), 8.55 (1H, d, J=2.2 Hz), 8.67 (1H, d, J=2.2 Hz). M+H: 408.6
137		113	NMR2: 1.68–1.80 (2H, m), 1.99 (2H, brd, J=13.3 Hz), 2.69 (2H, d, J=14.6 Hz), 2.92 – 3.11 (5H, m), 3.97 (3H, s), 4.22 (1H, brs), 4.30 (1H, brs), 4.93 (1H, qtd, J=7.5, 5.6, 3.7 Hz), 7.20 (1H, dd, J=9.2, 1.6 Hz), 7.48 (1H, dd, J=9.2, 1.1 Hz), 7.61 (1H, s), 7.74 (1H, d, J=0.6 Hz), 7.76 (1H, s), 8.54 (1H, s).
138		3/ 138	NMR1: 1.42 (6H, d, J=2.1 Hz), 1.62–1.74 (2H, m), 1.93 (2H, d, J=12.1 Hz), 2.92 (2H, s), 3.08 (1H, ddd, J=11.9, 8.2, 3.8 Hz), 3.89 (3H, s), 4.06 (2H, d, J=12.6 Hz), 4.52 (2H, d, J=47.6 Hz), 8.04 (1H, d, J=0.8 Hz), 8.09 (1H, s), 8.31 (1H, s), 8.78 (1H, d, J=2.2 Hz), 9.31 (1H, d, J=2.2 Hz).
139		7	NMR1: 1.58 (2H, tt, J=12.6, 6.3 Hz), 1.66 (6H, s), 1.90 (2H, d, J=12.4 Hz), 2.92 (1H, s), 3.03 (2H, ddd, J=11.9, 8.4, 3.5 Hz), 3.87 (3H, s), 3.97 (1H, brs), 4.07 (1H, brs), 7.41 (1H, dd, J=9.3, 1.6 Hz), 7.72 (1H, dd, J=9.3, 1.0 Hz), 7.87 (1H, s), 7.97 (1H, s), 8.23 (1H, s), 8.90 (1H, s).

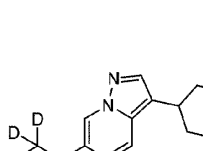
[Table 3-23]

140		7	NMR1: 1.66 (6H, s), 1.67 – 1.76 (2H, m), 1.96 (2H, d, J=13.0 Hz), 2.93 (1H, s), 3.00 – 3.14 (2H, m), 3.89 (3H, s), 3.94 (1H, s), 4.06 (1H, s), 8.04 (1H, s), 8.10 (1H, s), 8.31 (1H, s), 8.79 (1H, d, J=2.2 Hz), 9.31 (1H, d, J=2.2 Hz).
141		7	NMR1: 1.67 (6H, s), 2.59 (2H, brs), 3.60 (2H, t, J=5.8 Hz), 3.87 (3H, s), 4.06 (2H, q, J=2.9 Hz), 6.09 (1H, s), 7.52 (1H, dd, J=9.4, 1.6 Hz), 7.90 (1H, d, J=9.4 Hz), 8.01 (1H, s), 8.08 (1H, s), 8.27 (1H, s), 8.97 (1H, s).
142		7	NMR1: 2.58 (2H, s), 3.66 (2H, s), 3.87 (3H, s), 4.10 (1H, s), 4.14 (1H, s), 5.13 (2H, s), 6.09 (1H, s), 7.33 (1H, s), 7.32–7.41 (4H, m), 7.48–7.54 (1H, m), 7.88 (1H, d, J=9.2 Hz), 8.01 (1H, s), 8.08 (1H, s), 8.26 (1H, s), 8.97 (1H, s).
143		143	NMR1: 1.61–1.76 (2H, m), 1.88–1.92(2H, m), 2.45 (3H, s), 2.97–3.10 (7H, m), 3.73–3.79 (4H, m), 3.90–3.98 (2H, m), 7.15–7.23 (1H, m), 7.58–7.65 (1H, m), 7.72 (1H, s), 7.97–8.02(1H, m).
144		143/ 144	NMR1: 1.10–1.21 (3H, m), 1.51–1.66 (2H, m), 1.89–1.97 (2H, m), 2.39–2.49 (2H, m), 2.93–3.05 (2H, m), 3.01–3.14 (5H, m), 3.72–3.79 (4H, m), 4.72–4.79 (2H, m), 7.14–7.21 (1H, m), 7.58–7.65 (1H, m), 7.70 (s, 1H), 7.95–8.02(1H, m), 8.25 (2H, s).
145		7/ 145	NMR1: 1.50–1.64 (2H, m), 1.83–1.90 (2H, m), 2.93–3.11 (7H, m), 3.72–3.79 (4H, m), 4.08–4.16 (2H, m), 5.21 (2H, s), 7.14–7.23 (1H, m), 7.56–7.63 (1H, m), 7.66–7.74 (2H, m), 7.97–8.02 (1H, m), 9.11 (1H, d, J = 2.0 Hz).
146		7/ 146	NMR1: 1.49-1.64 (2H, m), 1.66 (6H, s), 1.72-1.94 (2H, m), 2.92-3.25 (7H, m), 3.72-3.79 (4H, m), 4.05 (2H, s), 7.14-7.25 (1H, m), 7.54-7.63 (1H, m), 7.73 (1H, s), 7.93-8.02 (1H, m).
147		7/ 147	NMR1: 1.37-1.48 (6H, m), 1.48-1.61 (2H, m), 1.83-1.97 (2H, m), 2.79-3.10 (7H, m), 3.69-3.81 (4H, m), 3.94-4.17 (2H, m), 4.39-4.62 (2H, m), 7.11-7.22 (1H, m), 7.55-7.64 (1H, m), 7.72 (1H, s), 7.96-8.03 (1H, m).

[Table 3-24]

148		143/ 148	NMR1: 0.80-0.90 (2H, m), 0.90-1.01 (2H, m), 1.63-1.80 (2H,m), 1.80-1.90 (1H, m), 1.93 (2H, m), 3.05 (5H, t, J=5.1 Hz), 3.13-3.29 (2H, m), 3.75 (4H, t, J=4.8 Hz), 4.02 (2H, d, J=13.3 Hz), 7.19 (1H, dd, J=9.8, 2.2 Hz), 7.62 (1H, d, J=9.7 Hz), 7.73 (1H, s), 8.00 (1H, d, J=2.0 Hz).
149		7/ 149	NMR1: 1.46-1.63 (2H, m) 1.66 (6H, s), 1.83-1.94 (2H, m), 2.77-3.12 (3H, m), 3.80 (3H, s), 3.86-4.14 (2H, m), 6.91-7.02 (1H, m), 7.53-7.67 (1H, m), 7.77 (1H, s), 8.23-8.37 (1H, m).
150		7/ 150	NMR1: 1.34-1.47 (6H, m), 1.47-1.63 (2H, m), 1.80-1.92 (2H,m), 2.77-3.04 (3H, m), 3.80 (3H, s), 3.99-4.17 (2H, m), 4.52 (2H, d, J=47.6 Hz), 6.93-7.00 (1H, m), 7.52-7.68 (1H, m), 7.76 (1H, s), 8.25-8.33 (1H, m).
151		143/ 151	NMR1: 1.61-1.80 (2H, m), 1.86-1.99 (2H, m), 2.45 (3H, s), 2.97-3.10 (3H, m), 3.80 (3H, s), 3.90-4.01 (2H, m), 6.88-7.02 (1H, m), 7.59-7.69 (1H, m), 7.76 (1H, s), 8.26-8.35 (1H, m).
152		143/ 152	NMR1: 1.08-1.19 (3H, m), 1.53-1.67 (2H, m), 1.87-1.98 (2H, m), 2.38-2.48 (2H, m), 2.93-3.04 (2H,m), 3.04-3.15 (1H, m), 3.80 (3H, s), 4.65-4.81 (2H, m), 6.92-6.99 (1H, m), 7.61-7.67 (1H, m), 7.74 (s, 1H), 8.25 (2H, s), 8.27-8.31 (1H, m).

[Table 3-25]

153			NMR2: 1.69-1.71 (2H, brm), 1.93 (2H, brs), 2.88-2.93 (3H, brm), 4.27-4.31 (2H, brd), 5.11 (2H, brs), 6.88 (1H, dd, J = 9.6, 2.1 Hz), 7.35 (1H, d, J = 9.6 Hz), 7.65 (1H, s), 7.73 (1H, s), 7.88 (1H, s), 8.01 (1H, J = 1.5 Hz).
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[0341] Biological Activity

Test Example 1: CSF1R kinase assay

Example Compounds were serially diluted (half log scale; 10 concentrations) in DMSO. Serially diluted compounds were prepared with the assay buffer (0.25 M EPPS pH7.5, 50 mM MgCl₂, 2.5 mM EGTA, 0.05% Brij-35) to reach 4 times concentration in 4% (v/v) DMSO. Each compound concentration was added at 5 μ L/well in a 384-wells plate. The ATP/peptide solution (0.372 mM ATP, 0.4 μ M Fluorescein-polyGT (PV3610, Life Technologies)) was added at 5 μ L in all wells. The CSF1R (PV3249, Life Technologies) diluted solution (0.28 nM) was added at 10 μ L in wells of each compound concentration and compound free control designated as 0% in-

hibition. On the other hand, assay buffer without enzyme was added at 10 μ L in wells of 0% response control designated as 100% inhibition. The plates were incubated for 80 min at room temperature with orbital shaker at 750 rpm. The stop solution (20 mM EDTA, 2 nM Tb-PY20 (PV3528, Life Technologies) antibody diluted with TR-FRET dilution buffer (PV3574, Life Technologies)) was added at 20 μ L in all wells. The plates were incubated for 30 min at room temperature with orbital shaker at 750 rpm. The plates were read using LanthaScreen™ Assay Mode of Infinite M1000 (Tecan). The value of signal is calculated with the ratio of 520 nm/490 nm emission using an excitation light at 337 nm. The IC₅₀ value was calculated by plotting the percentage of inhibition against the concentration of compound in curve fitting of a non-linear regression using GraphPad Prism 7 software.

[0342] Results are shown in the following table.

[Table 4]

EX	IC ₅₀ (nM)	EX	IC ₅₀ (nM)	EX	IC ₅₀ (nM)	EX	IC ₅₀ (nM)
1	15.40	41	56.3% inhibition at 0.3 nM	81	92.92	121	2.13
2	5.61	42	0.32	82	12.12	122	4.57
3	9.32	43	0.26	83	19.60	123	3.02
4	0.41	44	113.10	84	34.07	124	3.51
5	1.24	45	0.51	85	0.17	125	0.25
6	0.69	46	0.35	86	6.09	126	1.41
7	0.68	47	0.47	87	0.46	127	0.59
8	0.54	48	1.35	88	1.47	128	10.13
9	2.10	49	0.35	89	10.48	129	7.53
10	5.46	50	5.32	90	1.61	130	0.27
11	1.65	51	0.58	91	19.46	131	1.52
12	33.05	52	0.84	92	0.50	132	0.78
13	1.89	53	1.67	93	7.62	133	10.01
14	1.29	54	23.39	94	2.14	134	4.43
15	0.38	55	27.58	95	8.12	135	2.63
16	0.41	56	81.74	96	26.62	136	0.37
17	2.84	57	0.85	97	20.40	137	0.79
18	1.94	58	2.74	98	30.85	138	4.92
19	0.52	59	1.17	99	1.02	139	2.23
20	4.32	60	6.49	100	0.92	140	5.30
21	0.37	61	0.55	101	0.15	141	34.04
22	0.44	62	1.96	102	0.59	142	1.44
23	0.34	63	2.80	103	2.64	143	7.70
24	0.46	64	7.25	104	13.12	144	1.69
25	0.37	65	104.60	105	1.90	145	0.98
26	1.10	66	76.55	106	3.24	146	25
27	0.56	67	0.40	107	2.48	147	11
28	0.23	68	0.41	108	32.96	148	49
29	0.21	69	3.91	109	51.25	149	65
30	0.36	70	0.50	110	0.86	150	24
31	0.41	71	0.59	111	4.00	151	16
32	27.55	72	12.44	112	2.22	152	42
33	0.60	73	6.79	113	9.72	153	0.39
34	1.00	74	2.91	114	15.39		
35	1.36	75	3.92	115	2.99		
36	0.35	76	1.06	116	0.24		
37	0.43	77	17.12	117	0.56		
38	0.58	78	13.28	118	0.66		
39	1.09	79	1.72	119	4.29		
40	1.18	80	40.38	120	0.05		

[0343] Test Example 2: CSF1R phosphorylation assay in human CSF1R overexpressing cell
 Example Compounds were tested in H4 cells stably transfected with human CSF1R

(H4/hCSF1R). H4/hCSF1R cells were cultured in DMEM medium supplemented with 10% FBS, 0.5 mg/mL Geneticin (G418), 100 units/mL penicillin and 100 µg/mL streptomycin in T150 flask and split twice a week. For the experiment, the cells were trypsinized, counted and diluted with culture medium to 1.11×10^5 cell/mL. The cells were seeded into 96-well culture plate with 180 µL for each well (20,000 cells/well). Compounds were serially diluted with DMSO to make an 8-point half-log fold concentration series, and then diluted with culture medium to 10 fold of final concentration. Each compound concentration was added to cells at 20 µL/well. The plates were mixed briefly using an orbital shake and incubated for 1 hour at 37°C, 5% CO₂, and 95% humidified atmosphere. And then 22 µL of hCSF1 (300 ng/mL, #300-25, Peprotech) were added to each well. On every plate, 100% response control, treated with hCSF1 without compounds, and 0% response control, no hCSF1 treatment, were prepared to calculate percent inhibition of test compounds and Z prime value. The plates were mixed briefly again and incubated for 15 min at 37°C, 5% CO₂, and 95% humidified atmosphere. CSF1R phosphorylation was detected by ELISA kit (PathScan(R) Phospho-CSF1R/M-CSF-R (panTyr) Sandwich ELISA Kit, 13491C, CST) following the instruction. Medium in each well was aspirated off and cell were washed with 200 µL of ice-cold PBS. After adding 50 µL of lysis buffer with phosphatase and protease inhibitors, the plates were incubated for 20 minutes at 4°C. One hundred µL of sample diluent was added and mixed by an orbital shaker. 80 µL of cell lysate was transferred to ELISA plate. The plates were sealed and stored overnight at 4°C sealed. The next day lysates were removed and plates were washed with 200 µL of wash buffer 4 times. The remaining wash buffer was tapped out before 100 µL of detection antibody solution was added and plates were incubated for one hour at 37°C. The antibody solution was removed and plates were washed with 200 µL of wash buffer 4 times. One hundred µL of HRP linked secondary antibody solution was added and plates were incubated for 30 minutes at 37°C. The antibody solution was removed and plates were washed with 200 µL of wash buffer 4 times. One hundred µL/well of TMB substrate was added and plates were incubated for 10 minutes at room temperature. One hundred µL of stop solution was added to the plates and the absorbance at 450 nm was measured by Infinite M1000 (Tecan). The average background was subtracted and result normalized to 100% response control. The IC₅₀ value was calculated by plotting the percentage of inhibition for CSF1R phosphorylation against the concentration of a compound in curve fitting of a non-linear regression using GraphPad Prism 7 software.

[0344] Results are shown in the following table.

[Table 5]

EX	IC ₅₀ (nM)	EX	IC ₅₀ (nM)	EX	IC ₅₀ (nM)	EX	IC ₅₀ (nM)
47	2.8	64	58.2	85	0.5	110	28.5
49	1.9	67	11	92	4	112	62.4
51	12.4	68	5.6	93	82.5	116	20.6
52	3.8	69	48.2	94	26	117	11.2
57	10.9	76	5.3	100	12.5	118	17.2
58	28.4	78	100	101	0.4	138	169.7
60	81	79	15.9	102	3		
62	13.5	82	63.8	103	23.5		

[0345] Test Example 3. Kinase assay for selectivity within receptor type tyrosine kinases (RTKs)

Five kinds of commercially available RTKs (as shown in the following table) were subjected to the tests using a LabChip EZReader II and ProfilerPro kinase selectivity assay kits (PerkinElmer). Compounds were serially diluted (half log scale; 10 concentrations) in DMSO. Two hundred nL of serially diluted compounds were mixed with 10 μ L of kinase buffer (50 mM HEPES pH7.5, 10 mM MgCl₂, 1 mM EGTA, 0.01% Brij-35) containing substrate (10 μ M) and ATP (198 μ M (CSF1R), 86 μ M (FLT3, cKit, PDGFR β , or TrkC)) to reach 2 times concentration. The fluorescently-labelled peptide substrates were shown in the following table. Each enzyme diluted solution (200 ng/mL) was added at 10 μ L in all wells. 0% inhibition controls contained no inhibitor and 100% inhibition controls contained no ATP. The plates were mixed on a plate shaker for a few seconds and incubated for 60 min at room temperature. The termination buffer (100 mM HEPES pH7.5, 40 mM EDTA, 1 mM DTT, 0.015% Brij-35, 0.13% LabChip Sipper Chip Coating Reagent 3 (760050, PerkinElmer)) was added at 60 μ L in all wells. Phosphorylated and unphosphorylated peptides were separated by electrophoresis and detected by those fluorescence. Percent conversion from substrate to product was determined using the peak heights. The IC₅₀ value was calculated by plotting the percentage of inhibition against the concentration of compound in curve fitting of a non-linear regression using GraphPad Prism 7 software. Compounds were confirmed to show selective inhibitory activity against CSF1R compared to at least one of the tested kinases.

[0346] [Table 6]

Enzyme			Substrate: ProfilerPro Kinase Peptide (PerkinElmer)	
Name	Supplier	Cat#	Substrate#	Cat#
CSF1R	Life Technologies	PV3610	30	760430
FLT3	Life Technologies	PV4108	2	760346
cKit	Carna Biosciences	08-156	30	760430
PDGFR β	Carna Biosciences	08-158	30	760430
TrkC	Life Technologies	PV3617	27	760424

[0347] Test Example 4. Pharmacokinetics/Pharmacodynamics

Male Mice (C57BL/6J, The Jackson Laboratory Japan, eight weeks old) were orally administered with test compounds in 5% gum arabic in water as vehicle. Mice administered with vehicle only were used as a negative control. In each study, one control group and one or more test compound administered group(s) were prepared, but each group was only administered with one test compound at one concentration. Blood was collected via retro orbital puncture into heparin capillary at 30 minutes, 1 hour, 2 hours and 6 hours after dosing. After anesthetization, blood was collected through posterior vena cava into heparin tubes and brain was harvested at 24 hours after dosing. The blood was centrifuged at 1,710 g for 10 minutes at 4°C to obtain plasma. The half hemisphere of the brain was homogenized in 3-fold weight of saline by PHYSCOTRON homogenizer (NS-360D, Microtec) and subjected to pharmacokinetic study. The other half hemisphere was soaked in RNAlater (AM7021, Life Technologies) for gene expression assay.

[0348] Determination of Compound in Mouse Plasma and Brain Homogenates

The compound in mouse plasma and brain homogenates was quantified with the high-performance liquid chromatographic-electrospray ionization tandem mass spectrometry method. The compound was dissolved in DMSO and was diluted with methanol to prepare the standard solutions. The concentrations of calibration curve samples were 0.01 to 10 µg/mL, and those of quality control samples were 0.03, 5, and 8 µg/mL. To each sample, the internal standard solution (spiperone: 500 ng/mL) and methanol were added and mixed. The mixture was centrifuged at 6130 g for 10 minutes at 10°C or below to obtain the supernatant. The supernatant was mixed with water/acetonitrile (1:1, v/v). Liquid chromatography and tandem mass spectrometry analysis were carried out with the Prominence UFLC system (Shimadzu Corp.) and the switching valve (Valco Instruments Co. Inc.). Chromatographic separation was achieved on an XBridge C18 (3.5 µm, 2.1 mmID x 50 mm, Waters Corp.). A binary gradient was formed with 10 mmol/L ammonium acetate aqueous solution and acetonitrile at a flow rate of 0.55 mL/min. The ionization method was electrospray ionization with a positive mode. Multiple reaction monitoring mode utilizing the precursor and product ions of the analyte and internal standard was employed. The peak-area ratios of the analyte to the IS in the calibration curve samples were obtained. The quadratic regression equation ($Y = aX^2 + bX + c$, weight: $1/X^2$) was calculated by the least square method using the peak-area ratios (Y) and the spiked concentrations (X). The concentrations of the analyte in the samples were determined by substituting the obtained peak-area ratios into the above equations. Analyst version 1.5.1 (AB Sciex Pte. Ltd.) was used for the construction of the calibration curve, and the determination of peak areas and concentrations. The mean of concentration at each time

point, and the concentration ratio of brain to plasma (K_p) were calculated with Microsoft Excel 2013 (Microsoft Corp). Brain concentrations were corrected with dilution factor (4-time dilution) of brain homogenates. The pharmacokinetic parameters

(C_{max} , t_{max} , $t_{1/2,z}$, AUC_t , and AUC_{∞})

were calculated with the aid of non-compartmental model, Phoenix(R) WinNonlin(R) 8.0 (Certara LP).

[0349] Quantification of microglia related gene expression

RNA was extracted from each brain using Maxwell(R) RSC simplyRNA Tissue Kit (AS1340, Promega), RNAdvance Tissue kit (A32646, Beckman Coulter), or RNeasy Mini Kit (74106, Qiagen). RNA concentration and purity was assessed using spectrophotometer (DropSense96, Trinean or Nanodrop, Thermo Scientific). Equal amount of RNA was reverse transcribed to cDNA using High-Capacity RNA-to-cDNA Kit (4388950, Life Technologies) or High-Capacity cDNA Reverse Transcription Kit (4368813, Life Technologies). Quantitative PCR was performed on LightCycler 480 (Roche) or ViiA7 (Thermo Scientific) using a TaqMan Fast Universal PCR Master Mix (#4352042, Life Technologies) or TaqMan Fast Advanced Master Mix (4444964, Life Technologies). Data was analyzed using $\Delta\Delta C_t$ method or fold change which was relatively calculated by standard curve that was made from 5-points 1:2 dilution of vehicle treated animals. GAPDH gene was used as an internal control for normalization. Percentage inhibition of CD11b gene was calculated by taking the rate of decrease in the absence of drug as 0%. The primers used in this study were the followings: GAPDH gene (Mm99999915_g1, Life Technologies), CD11b gene (Mm00434455_m1, Life Technologies). All calculation were performed with Microsoft Excel 2013 (Microsoft Corp).

[0350] Results of administration of the 30 mg/kg dose of test compounds are shown in the following table, unless otherwise noted.

[Table 7]

EX	CD11b inhibition (%)	EX	CD11b inhibition (%)	EX	CD11b inhibition (%)
47	++++	76	+++	102	++++
49	++++	85	++++	110	++++
51	++++	92	+++	112	++++
57	+++	93	++++	116	++
67	++++	94	++++	117	+++
68	++++	100	++++	118	++
69	++	101	++++	138	+++*

More than 20 to 40%: ++, 40 to 60%: +++, 60 to 100%: ++++

*: a result of the 100 mg/kg dose

Industrial Applicability

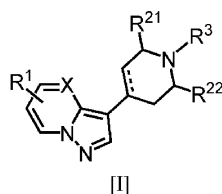
[0351] A compound of Formula [I], or a salt thereof, may have CSF1R inhibitory activity and is expected to be useful for treating, preventing, and/or diagnosing diseases associated with CSF1R.

Claims

[Claim 1]

A compound represented by Formula [I], or a salt thereof:

[Chem.1]



wherein

R¹ is hydrogen, halogen, -CN, -L¹¹-R¹¹ optionally substituted with one or more R¹², or -R¹¹ optionally substituted with one or more R¹²;

L¹¹ is -C₁₋₃ alkylene-, -C₁₋₃ alkylene-C(=O)-, -O-, -O-C₁₋₃ alkylene-, -O-C₁₋₃ alkylene-O-, -OCH₂C(=O)O-, -C(=O)-, -C(=O)NH-, or -NH-C(=O)-;

R¹¹ is

- a) C₁₋₆ alkyl,
- b) C₁₋₆ haloalkyl,
- c) C₃₋₈ cycloalkyl, or
- d) a saturated or unsaturated 4- to 10-membered monocyclic, bicyclic, or spiro heterocyclyl;

R¹² is each independently halogen, -OH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl-O-C₁₋₆ alkyl, C₃₋₈ cycloalkyl, a saturated or unsaturated 4- to 10-membered monocyclic, bicyclic, or spiro heterocyclyl optionally substituted with one or more C₁₋₆ alkyl;

R²¹ and R²² are hydrogen, or R²¹ and R²² together with the adjacent heterocyclic form a bridged bicyclic ring;

R³ is -L³¹-R³¹ optionally substituted with one or more R³², or R³¹ optionally substituted with one or more R³²; provided that R³ is not -C(=O)O-tert-butyl;

L³¹ is -C(=O)-, -C(=O)O-, -C(=O)O-C₁₋₃ alkylene-, -C(=O)-C₁₋₃ alkylene-O-, -C(=O)-C₁₋₃ alkylene-O-C₁₋₃ alkylene-, or -C(=O)NH-C₁₋₃ alkylene-;

R³¹ is

- a) C₁₋₆ alkyl,
- b) C₁₋₆ haloalkyl,
- c) C₃₋₈ cycloalkyl,
- d) phenyl, or

e) a saturated or unsaturated 4- to 10-membered monocyclic, bicyclic, or spiro heterocyclyl;

R^{32} is each independently halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_{3-8} cycloalkyl;

X is CR^1 or N;

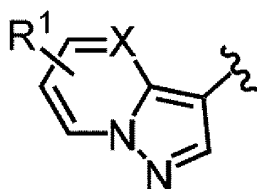
a bond:

[Chem.2]

is single or double bond; and

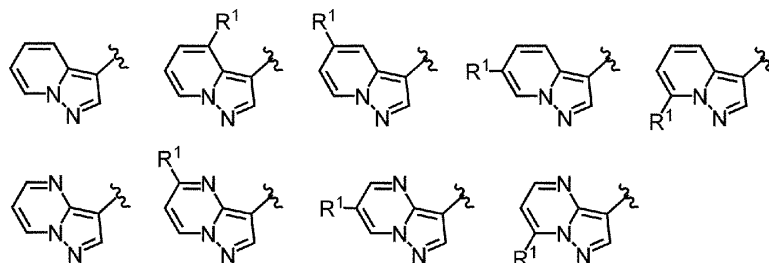
a moiety represented by the formula:

[Chem.3]



is any one of the following structures:

[Chem.4]



provided that R^1 is halogen, -CN, $-L^{11}-R^{11}$ optionally substituted with one or more R^{12} , or $-R^{11}$ optionally substituted with one or more R^{12} .

[Claim 2]

The compound according to claim 1, or a salt thereof, wherein R^{11} is

a) C_{1-6} alkyl,

b) C_{1-6} haloalkyl,

c) C_{3-8} cycloalkyl,

d1) a saturated or unsaturated 4- to 6-membered monocyclic heterocyclyl containing 1 to 2 nitrogen atoms as ring-constituting

heteroatom,

d2) a saturated 4- to 6-membered monocyclic heterocyclyl containing 1 oxygen atom as ring-constituting heteroatom,

d3) a saturated or unsaturated 5- to 6-membered monocyclic heterocyclyl containing 1 to 2 nitrogen atoms and 1 oxygen atom as ring-constituting heteroatom,

d4) an unsaturated 5-membered monocyclic heterocyclyl containing 1 to 2 nitrogen atoms and 1 sulfur atom as ring-constituting heteroatom,

d5) a saturated or unsaturated 7- to 9-membered bicyclic heterocyclyl containing 2 to 3 nitrogen atoms as ring-constituting heteroatom,

d6) a saturated or unsaturated 7- to 9-membered bicyclic heterocyclyl containing 1 to 2 nitrogen atoms and 1 oxygen atom as ring-constituting heteroatom,

d7) a saturated or unsaturated 9-membered bicyclic heterocyclyl containing 1 nitrogen atom, 1 oxygen atom and 1 sulfur atom as ring-constituting heteroatom,

d8) a saturated or unsaturated 6- to 10-membered bicyclic heterocyclyl containing 1 oxygen atom as ring-constituting heteroatom,

d9) a saturated 7-membered spiro heterocyclyl containing 1 to 2 nitrogen atoms as ring-constituting heteroatom, or

d10) a saturated 7- to 8-membered spiro heterocyclyl containing 1 nitrogen atom and 1 oxygen atom as ring-constituting heteroatom.

[Claim 3]

The compound according to claim 1 or 2, or a salt thereof, wherein R¹² is each independently halogen, -OH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl-O-C₁₋₆ alkyl, C₃₋₈ cycloalkyl, a saturated 4- to 6-membered monocyclic heterocyclyl containing 1 oxygen atom as ring-constituting heteroatom, or a saturated 6- to 10-membered spiro heterocyclyl containing 2 nitrogen atoms as ring-constituting heteroatom optionally substituted with C₁₋₆ alkyl.

[Claim 4]

The compound according to any one of claims 1 to 3, or a salt thereof, wherein

L¹¹ is methylene, ethylene, methylene-C(=O)-, -O-, -O-methylene, -O-ethylene, -O-ethylene-O-, -OCH₂C(=O)O-, -C(=O)-, -C(=O)NH-, or -NH-C(=O)-,

R¹¹ is methyl, methyl-d₃, ethyl, propyl, isopropyl, isobutyl, difluoromethyl, trifluoromethyl, difluoroethyl, difluoropropyl, trifluoropropyl, cyclopropyl, cyclobutyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidiny, piperidiny, morpholino, pyrazolyl, thiazolyl,

thiadiazolyl, tetrahydroimidazo[1,2-a]pyridinyl, dihydroimidazo[2,1-c][1,4]oxazinyl, dihydropyrazolo[5,1-c][1,4]oxazinyl, dihydropyrano[4,3-d]thiazolyl, hexahydropyrrolo[3,4-c]pyrrolyl, tetrahydrofuro[3,4-c]pyrrolyl, 2-oxabicyclo[2.1.1]hexanyl, 2-azaspiro[3.3]heptanyl, or 2-oxa-6-azaspiro[3.3]heptanyl, and R^{12} is each independently fluoro, methyl, methyl- d_3 , difluoromethyl, trifluoromethyl, methoxyethyl, cyclopropyl, -OH, oxetanyl, or 2,6-diazaspiro[3.3]heptanyl optionally substituted with methyl.

[Claim 5]

The compound according to any one of claims 1 to 4, or a salt thereof, wherein R^1 is hydrogen, halogen, cyano, C_{1-6} alkyl, C_{1-6} alkyl-O- optionally substituted with one or more deuteriums, OH or C_{1-6} alkyl-O-, C_{1-6} alkyl-OC(=O)CH₂O-, C_{1-6} haloalkyl-O-, C_{1-6} haloalkyl-O- C_{1-6} alkylene-, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl-O-, C_{3-8} cycloalkyl- C_{1-6} alkylene-O- optionally substituted with halogen, C_{1-6} alkyl or C_{1-6} haloalkyl, C_{3-8} cycloalkyl-C(=O)-, C_{3-8} cycloalkyl-NH-C(=O)-, azetidiny optionally substituted with halogen, azetidiny- C_{1-6} alkylene-O- optionally substituted with oxetanyl, azetidiny-O- optionally substituted with oxetanyl, piperidinyl optionally substituted with oxetanyl, morpholino, morpholino- C_{1-6} alkylene, morpholino- C_{1-6} alkylene-O-, morpholino-C(=O)- C_{1-6} alkylene, pyrazolyl optionally substituted with C_{1-6} alkyl, C_{1-6} alkyl substituted with one or more deuteriums, C_{1-6} alkyl-O- C_{1-6} alkylene, thiazolyl optionally substituted with C_{1-6} haloalkyl or diazaspiroheptyl optionally substituted with C_{1-6} alkyl, thiadiazolyl optionally substituted with C_{1-6} alkyl, oxetanyl- C_{1-6} alkylene-O- optionally substituted with halogen or C_{1-6} alkyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydroimidazo[1,2-a]pyrazinyl, dihydroimidazo[2,1-c][1,4]oxazinyl, dihydropyrano[4,3-d]thiazolyl, dihydropyrazolo[5,1-c][1,4]oxazinyl, hexahydropyrrolo[3,4-c]pyrrolyl, tetrahydrofuro[3,4-c]pyrrolyl, 2-oxabicyclo[2.1.1]hexanyl- C_{1-6} alkylene-O-, 2-azaspiro[3.3]heptanyl optionally substituted with halogen, 2-oxa-6-azaspiro[3.3]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl-C(=O)-, or 2-azaspiro[3.3]heptanyl- C_{1-6} alkylene-O- optionally substituted with halogen.

[Claim 6]

The compound according to any one of claims 1 to 5, or a salt thereof, wherein R^1 is hydrogen, fluoro, chloro, cyano, isopropyl, methoxy, methoxy- d_3 , difluoromethoxy, ethoxy, 2-methoxyethoxy, 2-methoxy-2-oxoethoxy, 2,2-difluoroethoxy, 2-(difluoromethoxy)ethoxy, 2-(trifluoromethoxy)ethoxy,

2-hydroxy-2-methylpropoxy, 2-methoxy-2-methylpropoxy, 2,2-difluoropropoxy, 3,3-difluoropropoxy, 3,3,3-trifluoropropoxy, cyclopropyl, cyclopropoxy, cyclopropylmethoxy, cyclopropanecarbonyl, cyclopropylcarbonyl, (1-fluorocyclopropyl)methoxy, (2,2-difluorocyclopropyl)methoxy, 2-(3,3-difluorocyclobutyl)ethoxy, (2,2-difluoro-1-methylcyclopropyl)methoxy, (1-(difluoromethyl)cyclopropyl)methoxy, (1-(trifluoromethyl)cyclopropyl)methoxy, azetidin-1-yl, 3,3-difluoroazetidin-1-yl, (1-(oxetan-3-yl)azetidin-3-yl)oxy, (1-(oxetan-3-yl)azetidin-3-yl)methoxy, 1-methyl-1H-pyrazol-4-yl, 1-(methyl-d₃)-1H-pyrazol-4-yl, 1-(2-methoxyethyl)-1H-pyrazol-4-yl, 1,3,5-trimethyl-1H-pyrazol-4-yl, 1-cyclopropyl-1H-pyrazol-4-yl, 1-cyclopropyl-3,5-dimethyl-1H-pyrazol-4-yl, 3,5-dimethyl-1-(methyl-d₃)-1H-pyrazol-4-yl, 1-(oxetan-3-yl)piperidin-4-yl, (1-methylpiperidin-4-yl)oxy, (oxetan-3-yl)methoxy, (3-fluorooxetan-3-yl)methoxy, (3-methyloxetan-3-yl)methoxy, morpholino, morpholinomethyl, 2-morpholino-2-oxoethyl, 2-morpholinoethoxy, 2-morpholinoethyl, thiazol-4-yl, thiazol-5-yl, (trifluoromethyl)thiazol-4-yl, 1,2,4-thiadiazol-5-yl, 3-methyl-1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-2-yl, tetrahydro-2H-pyran-4-yl, tetrahydrofuran-3-yl, 7-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-2-yl, 5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl, 6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-3-yl, 5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-2-yl, 6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-yl, ((1s,4s)-2-oxabicyclo[2.1.1]hexan-1-yl)methoxy, tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl, 2-oxa-6-azaspiro[3.3]heptan-6-yl, 2-oxa-6-azaspiro[3.3]heptane-6-carbonyl, 6,6-difluoro-2-azaspiro[3.3]heptan-2-yl, 2-(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)ethoxy, or 2-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)thiazol-5-yl.

[Claim 7] The compound according to any one of claims 1 to 6, or a salt thereof, wherein R²¹ and R²² are hydrogen.

[Claim 8] The compound according to any one of claims 1 to 7, or a salt thereof, wherein R³¹ is

- a) C₁₋₆ alkyl,
- b) C₁₋₆ haloalkyl,

- c) C₃₋₈ cycloalkyl,
- d) phenyl,
- e1) a saturated or unsaturated 4- to 6-membered monocyclic heterocyclyl containing 1 to 2 nitrogen atoms as ring-constituting heteroatom,
- e2) a saturated 4- to 6-membered monocyclic heterocyclyl containing 1 oxygen atom as ring-constituting heteroatom,
- e3) a saturated or unsaturated 5- to 6-membered monocyclic heterocyclyl containing 1 to 2 nitrogen atoms and 1 oxygen atom as ring-constituting heteroatom,
- e4) an unsaturated 5-membered monocyclic heterocyclyl containing 1 to 2 nitrogen atoms and 1 sulfur atom as ring-constituting heteroatom,
- e5) a saturated or unsaturated 7- to 9-membered bicyclic heterocyclyl containing 1 to 2 nitrogen atoms and 1 oxygen atom as ring-constituting heteroatom, or
- e6) a saturated 7- to 8-membered spiro heterocyclyl containing 1 nitrogen atom and 1 oxygen atom as ring-constituting heteroatom.

[Claim 9]

The compound according to any one of claims 1 to 8, or a salt thereof, wherein

L³¹ is -C(=O)-, -C(=O)O-, -C(=O)O-methylene-, -C(=O)O-ethylene-, -C(=O)-ethylene-O-, -C(=O)-methylene-O-methylene-, or -C(=O)NH-ethylene-,

R³¹ is methyl, tert-butyl, cyclopropyl, cyclobutyl, cyclohexyl, phenyl, oxazolyl, thiazolyl, oxadiazolyl, pyrimidinyl, tetrahydrofuranyl, azetidiny, or 6-oxa-1-azaspiro[3.4]octanyl, and

R³² is each independently fluoro, methyl, ethyl, cyclopropyl, difluoromethyl, or trifluoromethyl.

[Claim 10]

The compound according to any one of claims 1 to 9, or a salt thereof, wherein R³ is C₁₋₆ haloalkyl-O-C(=O)-, C₃₋₈ cycloalkyl-O-C(=O)- optionally substituted with halogen or C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl-C₁₋₆ alkylene-O-C(=O)- optionally substituted with C₁₋₆ alkyl, phenyl-CH₂OCH₂-C(=O)- optionally substituted with C₁₋₆ alkyl, phenoxy-C₁₋₆ alkylene-C(=O)- optionally substituted with C₁₋₆ alkyl, phenyl-C₁₋₃ alkylene-NH-C(=O)-, azetidiny-C(=O)- optionally substituted with halogen or C₁₋₆ haloalkyl, oxazolyl-C₁₋₆ alkylene-O-C(=O)- optionally substituted with C₁₋₆ alkyl, oxadiazolyl optionally substituted with C₁₋₆ alkyl or C₃₋₈ cycloalkyl, thiazolyl-C₁₋₆ alkylene-O-C(=O)- optionally substituted with C₁₋₆ haloalkyl, pyrimidinyl optionally substituted with

[Claim 11]

C₁₋₆ alkyl, tetrahydrofuranyl-C₁₋₆ alkylene-O-C(=O)-,

3-oxa-6-azabicyclo[3.1.1]heptanyl-C(=O)-, or

6-oxa-1-azaspiro[3.4]octanyl-C(=O)-.

The compound according to any one of claims 1 to 10, or a salt thereof,

wherein R³ is 5-ethylpyrimidin-2-yl, 5-methyl-1,2,4-oxadiazol-3-yl,

3-cyclopropyl-1,2,4-oxadiazol-5-yl,

(2-(difluoromethyl)azetidin-1-yl)carbonyl,

(3,3-difluoroazetidin-1-yl)carbonyl,

(3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)carbonyl,

6-oxa-1-azaspiro[3.4]octan-1-ylcarbonyl, azetidin-1-ylcarbonyl,

2-(p-tolyloxy)ethylcarbonyl, 2-phenoxyethylcarbonyl,

((2-methylbenzyl)oxy)methylcarbonyl, phenylethylcarbonyl,

1,1,1-trifluoro-2-methylpropan-2-yloxy carbonyl,

1-fluoro-2-methylpropan-2-yloxy carbonyl, cyclopropoxycarbonyl, cy-

clopopylmethoxycarbonyl, (1-methylcyclopropyl)methoxycarbonyl,

3,3-difluorocyclobutoxycarbonyl,

(1R,3R)-3-(trifluoromethyl)cyclobutoxycarbonyl,

(1S,3S)-3-(trifluoromethyl)cyclobutoxycarbonyl,

4,4-difluorocyclohexyloxy carbonyl, benzyloxy carbonyl, oxazol-

4-ylmethoxycarbonyl, 1-(oxazol-4-yl)ethoxycarbonyl,

(2-methyloxazol-4-yl)methoxycarbonyl,

2-(thiazol-4-yl)ethoxycarbonyl, thiazol-4-ylmethoxycarbonyl,

(2-(trifluoromethyl)thiazol-4-yl)methoxycarbonyl, or

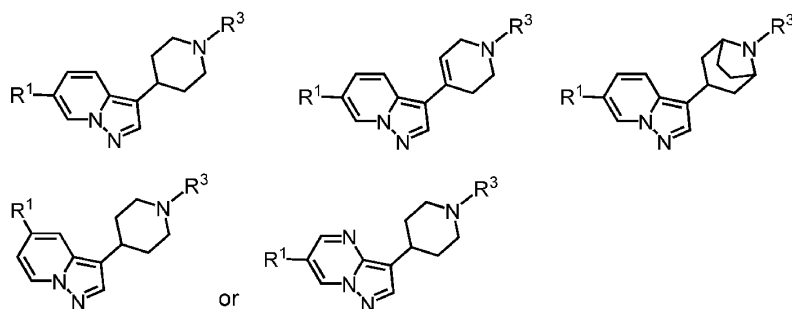
(tetrahydrofuran-2-yl)methoxycarbonyl.

[Claim 12]

The compound according to any one of claims 1 to 6 and 8 to 11, or a

salt thereof, wherein the compound of Formula [I] is

[Chem.5]

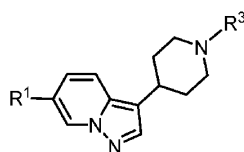


[Claim 13]

The compound according to any one of claims 1 to 12, or a salt thereof,

wherein the compound of Formula [I] is

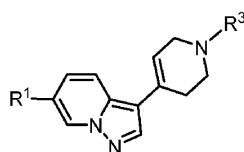
[Chem.6]



[Claim 14]

The compound according to any one of claims 1 to 12, or a salt thereof, wherein the compound of Formula [I] is

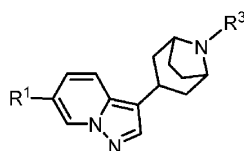
[Chem.7]



[Claim 15]

The compound according to any one of claims 1 to 6 and 8 to 12, or a salt thereof, wherein the compound of Formula [I] is

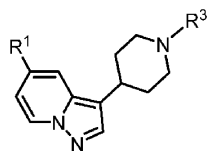
[Chem.8]



[Claim 16]

The compound according to any one of claims 1 to 12, or a salt thereof, wherein the compound of Formula [I] is

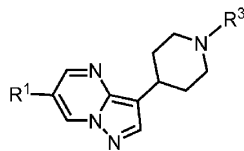
[Chem.9]



[Claim 17]

The compound according to any one of claims 1 to 12, or a salt thereof, wherein the compound of Formula [I] is

[Chem.10]



[Claim 18]

The compound according to any one of claims 1 to 11, or a salt thereof, wherein X is CH.

[Claim 19]

The compound according to any one of claims 1 to 11, or a salt thereof,

- wherein X is N.
- [Claim 20] The compound according to any one of claims 1 to 11, or a salt thereof, wherein the bond:
[Chem.11]

- is single bond.
- [Claim 21] The compound according to any one of claims 1 to 11, or a salt thereof, wherein the bond:
[Chem.12]

- is double bond.
- [Claim 22] The compound according to any one of claims 1 to 21, or a salt thereof, wherein R¹ is 2-methoxyethoxy, cyclopropoxy, (1-methylpiperidin-4-yl)oxy, 2,2-difluoroethoxy, 1-cyclopropyl-3,5-dimethyl-1H-pyrazol-4-yl, 1-cyclopropyl-1H-pyrazol-4-yl, tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl, 6,6-difluoro-2-azaspiro[3.3]heptan-2-yl, 2-oxa-6-azaspiro[3.3]heptan-6-yl, thiazol-5-yl, or 1-methyl-1H-pyrazol-4-yl.
- [Claim 23] The compound according to any one of claims 1 to 22, or a salt thereof, wherein R³ is cyclopropoxycarbonyl, (1-fluoromethyl-2-methylpropan-2-yl)oxycarbonyl, oxazol-4-ylmethoxycarbonyl, thiazol-4-ylmethoxycarbonyl, or 3,3-difluoroazetidin-1-ylcarbonyl.
- [Claim 24] The compound according to claim 1, or a salt thereof, wherein the compound is selected from the group consisting of the following compounds.

- [Claim 26] A pharmaceutical composition comprising a compound according to any one of claims 1-25, or a salt thereof, as an active ingredient and a pharmaceutically acceptable carrier or excipient.
- [Claim 27] A therapeutic, preventative, and/or diagnostic agent for a disease caused by CSF1R comprising a compound according to any one of claims 1-25, or a salt thereof, as an active ingredient.
- [Claim 28] The agent according to claim 27, wherein the disease caused by CSF1R is selected from Alzheimer's disease (AD), tauopathies, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), HIV-associated neurocognitive disorders (HAND), prion disease, trauma brain injury (TBI), Parkinson's disease, pain, spinal cord injury, Crohn's disease, radiation-induced lung fibrosis, glaucoma, infections, cardiovascular diseases such as inflammation post myocardial infarction, bone diseases, muscular dystrophy, or asthma.
- [Claim 29] A method for treating, preventing, and/or diagnosing a disease caused by CSF1R, which comprises administering to a human in need thereof an effective amount of a compound according to any one of claims 1-25, or a salt thereof.
- [Claim 30] The method according to claim 29, wherein the disease caused by CSF1R is selected from Alzheimer's disease (AD), tauopathies, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), HIV-associated neurocognitive disorders (HAND), prion disease, trauma brain injury (TBI), Parkinson's disease, pain, spinal cord injury, Crohn's disease, radiation-induced lung fibrosis, glaucoma, infections, cardiovascular diseases such as inflammation post myocardial infarction, bone diseases, muscular dystrophy, or asthma.
- [Claim 31] A compound according to any one of claims 1-25, or a salt thereof, for use in the treatment, prevention, and/or diagnosis of a disease caused by CSF1R.
- [Claim 32] The compound, or a salt thereof, for use according to claim 31, wherein the disease caused by CSF1R is selected from Alzheimer's disease (AD), tauopathies, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), HIV-associated neurocognitive disorders (HAND), prion disease, trauma brain injury (TBI), Parkinson's disease, pain, spinal cord injury, Crohn's disease, radiation-induced lung fibrosis, glaucoma, infections, cardiovascular diseases such as inflammation post myocardial infarction, bone diseases, muscular dystrophy, or asthma.

- [Claim 33] Use of a compound according to any one of claims 1-25, or a salt thereof, in the manufacture of a medicament for treating, preventing, and/or diagnosing a disease caused by CSF1R.
- [Claim 34] The use according to claim 33, wherein the disease caused by CSF1R is selected from Alzheimer's disease (AD), tauopathies, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), HIV-associated neurocognitive disorders (HAND), prion disease, trauma brain injury (TBI), Parkinson's disease, pain, spinal cord injury, Crohn's disease, radiation-induced lung fibrosis, glaucoma, infections, cardiovascular diseases such as inflammation post myocardial infarction, bone diseases, muscular dystrophy, or asthma.