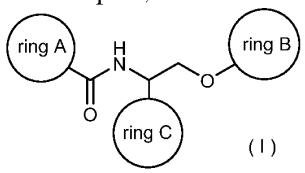
HETEROCYCLIC DERIVATIVES HAVING S1P3 RECEPTOR ANTAGONISTIC ACTIVITY

TECHNICAL FIELD

[001] The present disclosure, in one aspect, relates to a compound of formula (I):



(I)

[002] (wherein, all the symbols have the same meanings as described below), which has $S1P_3$ receptor antagonistic activity, or a pharmaceutically acceptable salt thereof (hereinafter occasionally abbreviated as the compound of the present disclosure).

BACKGROUND ART

[003] Sphingosine-1-phosphate [(2S,3R,4E)-2-amino-3-hydroxyoctadec-4-enyl-1-phosphate; hereinafter occasionally abbreviated as S1P] is a lipid which is synthesized by metabolic turnover of sphingolipids in cells and by the extracellular action of a secreted sphingosine kinase. It is proposed that sphingosine-1-phosphate acts as an intercellular communication mediator as well as an intracellular second messenger.

[004] It is known that S1P receptor has 5 subtypes ($S1P_1$, $S1P_2$, $S1P_3$, $S1P_4$, and $S1P_5$ receptor), among S1P receptors, $S1P_3$ receptor (also known as S1PR3, S1P3, or EDG-3) is express in a wide variety of cell and contribute metabolic regulation, proliferation, survival, and cell motility.

[005] $S1P_3$ receptor plays an essential role in the pathophysiological processes related to neurodegenerative disease, brain injuries, astrocytoma, cancer, lung adenocarcinoma, ovarian cancer, breast cancer, cerebrovascular disease, neoplasms, endometriosis, fibrosis, liver injury, liver cirrhosis, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, diabetes, hyperglycemia, obesity, brain ischemia, cardiomegaly, atherosclerosis, asthma, chronic obstructive pulmonary disease, acute lung injury and sepsis.

[006] Astrocyte is a kind of glial cell which plays a crucial role in the central nervous systems by regulating blood-brain/tumor barrier permeability and participating in the inflammatory response.

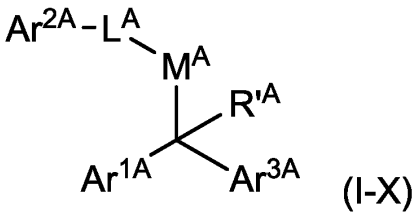
[007] Neuroinflammation is known to be an exacerbating factor in neurodegenerative diseases. Furthermore, Neuroinflammatory astrogliosis is a common pathology in human Amyotrophic Lateral Sclerosis (see Non patent Literatures 1).

[008] Reactive astrocytes that help to drive death of neurons and oligodendrocytes are highly present in human neurodegenerative diseases including Amyotrophic Lateral Sclerosis, Alzheimer's Disease, Huntington's Disease, Parkinson's Disease, and Multiple Sclerosis (see Non patent Literatures 2).

[009] Especially $S1P_3$ receptor is highly expressed in reactive astrocytes and its expression is enhanced by inflammatory stimuli. $S1P_3$ receptor mediates activation of Ras homolog family member A (RhoA) and induction of Cyclooxygenase-2 (COX-2), Interleukin-6 (IL-6) and Vascular Endothelial Growth Factor A (VEGFa) mRNA and enhances the inflammatory response of astrocyte (see Non patent Literatures 3).

[010] On the other hand, Patent Literature 1 states that the compound of the following formula (I-X) is a compound having $S1P_3$ receptor antagonistic activity.

[011] Formula (I-X) is as follows:



(I-X)

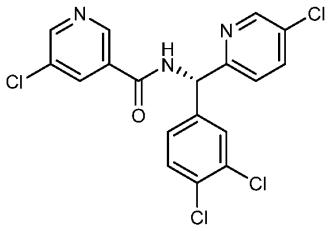
[012] wherein each of Ar^{1A}, Ar^{2A}, and Ar^{3A} is independently selected (C6-C10) aryl ring system or a (5- to 10-membered) heteroaryl ring system;

[013] R'^{A} is independently H, or (Cl-C4)alkyl;

[014] M^A is a bond, $(CH_2)_{1-2}$;

[015] L^A is a bond, NR, C(=O), SO_2, C(=NR), or $C(=O)CR_2$, and the definition of groups was partially excerpted.

[016] Patent Literature 1 discloses the following compound (Compound ID : CYM 52467).



[017] However, none of prior arts disclose nor suggest that the compound of the

present disclosure.

CITATIONS LIST

[018] Patent Literature

[019] Patent Literature 1: WO 2016/053855 A

[020] Non Patent Literatures

[021] Non Patent Literature 1: Nature communications, Vol. 11, No. 3753, 2020

[022] Non Patent Literature 2: Nature, Vol. 541, No. 7638, pages 481 - 487, 2017

[023] Non Patent Literature 3: Journal of neuroinflammation, Vol.14, No. 111, 2017

SUMMARY OF INVENTION

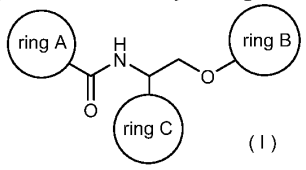
PROBLEMS TO BE SOLVED BY THE INVENTION

[024] An object of the present disclosure is to provide a compound which has $S1P_3$ receptor antagonistic activity.

MEAN FOR SOLVING THE PROBLEM

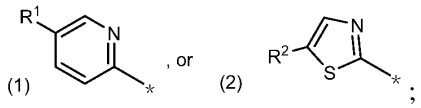
[025] The present inventors conducted intensive studies for achieving the above object, and as a result, they found that the object can be achieved by a compound of formula (I) or a pharmaceutically acceptable salt thereof.

[026] That is, the present disclosure provides, for example, embodiments of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

[027] wherein ring A is



;

[028] the * mark represents a bonding position with a carbonyl group;

[029] ring B is 5-6 membered heterocyclic ring which may be substituted by 1 to 4 R^3 or 5-6 membered carbocyclic ring which may be substituted by 1 to 5 R^4;

[030] when two or more R^3s are substituted, a plurality of R^3s may be the same or different;

[031] when two or more R^4s are substituted, a plurality of R^4s may be the same or different;

[032] ring C is 5-6 membered heterocyclic ring which may be substituted by 1 to 4 R^5 or 5-6 membered carbocyclic ring which may be substituted by 1 to 5 R^6;

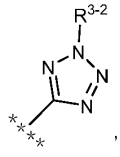
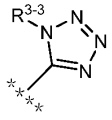
[033] when two or more R^5s are substituted, a plurality of R^5s may be the same or different;

[034] when two or more R^6s are substituted, a plurality of R^6s may be the same or different;

[035] R^1 is selected from the group consisting of (1) a halogen atom, (2) C1-4 alkyl group and (3) C1-4 haloalkyl group;

[036] R^2 is selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) C1-4 alkyl group and (4) C1-4 haloalkyl group ;

[037] R^3 is selected from the group consisting of (1) a halogen atom, (2) C1-4 alkyl group, (3) C1-4 haloalkyl group, (4) C1-4 alkoxy group, (5) C1-4 haloalkoxy group, (6) cyano, (7) $S(=O)_2$-R^{3-1},

(8)  , and (9)  ;

[038] R^{3-1} is a hydrogen atom or C1-4 alkyl group;

[039] when two or more R^3s are substituted, a plurality of R^{3-1}s may be the same or different;

[040] R^{3-2} is a hydrogen atom or C1-4 alkyl group;

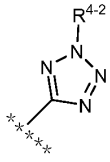
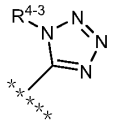
[041] when two or more R^3s are substituted, a plurality of R^{3-2}s may be the same or different;

[042] R^{3-3} is a hydrogen atom or C1-4 alkyl group;

[043] when two or more R^3s are substituted, a plurality of R^{3-3}s may be the same or different;

[044] the **** mark represents a bonding position with ring B;

[045] R^4 is selected from the group consisting of (1) a halogen atom, (2) C1-4 alkyl group, (3) C1-4 haloalkyl group, (4) C1-4 alkoxy group, (5) C1-4 haloalkoxy group, (6) cyano, (7) $S(=O)_2$-R^{4-1},

(8)  , and (9)  ;

[046] R^{4-1} is a hydrogen atom or C1-4 alkyl group;

[047] when two or more R^4s are substituted, a plurality of R^{4-1}s may be the same or different;

[048] R^{4-2} is a hydrogen atom or C1-4 alkyl group;

[049] when two or more R^4s are substituted, a plurality of R^{4-2}s may be the same or different;

[050] R^{4-3} is a hydrogen atom or C1-4 alkyl group;

[051] when two or more R^4s are substituted, a plurality of R^{4-3}s may be the same or different;

[052] the ***** mark represents a bonding position with ring B;

[053] R^5 is selected from the group consisting of (1) a halogen atom, (2) C1-4 alkyl group, (3) C1-4 haloalkyl group, (4) C1-4 alkoxy group and (5) C1-4 haloalkoxy group;

[054] R^6 is selected from the group consisting of (1) a halogen atom, (2) C1-4 alkyl group, (3) C1-4 haloalkyl group, (4) C1-4 alkoxy group and (5) C1-4 haloalkoxy group, and

[055] a pharmaceutical composition comprising the above compound of formula (I) or a pharmaceutically acceptable salt thereof.

EFFECTS OF THE INVENTION

[056] The compound of the present disclosure has $S1P_3$ receptor antagonistic activity. Therefore, the compound of the present disclosure is useful for treating an $S1P_3$-mediated disease.

BRIEF DESCRIPTION OF DRAWINGS

[057] Fig. 1; Shows that the effect of Example 23 on plasma Neurofilament Light Chain (NfL) levels in the amyotrophic lateral sclerosis model mouse (SOD1 mice). The vertical axis shows the concentration of plasma NfL and the horizontal axis shows the group to which vehicle, the test compound or Riluzole was administered. $p<0.05 compared to WT group (Mann-Whitney U-test). *p<0.05 compared to vehicle-treated group (Steel's test), #p<0.05compared to riluzole-treated group (Mann-Whitney U-test).

[058] Fig. 2; Shows that the effect of Example 40 on notch bar test in the Multiple system atrophy model mouse (PLP-SYN mice). The vertical axis shows the hind limb errors (%) and the horizontal axis shows group to which vehicle or the test compound was administered. ###p<0.0001 compared to WT group (Welch's t -test). *p<0.05 and **p<0.01 compared to vehicle-treated group (Dunnett's test).

[059] Fig. 3; Shows that the effect of Example 23 and 40 on Relative expression level of CXCL8 in the astrocyte derived from ALS patient iPS cell. ##p<0.005 compared to DMSO and MeOH treated group (Welch's t -test). **p<0.005 compared to DMSO and S1P treated group (Welch's t -test).

[060] Fig. 4; Shows that the effect of Example 23 and Example 40 on Relative expression level of CXCL8 in the astrocytoma cell line.

[061] Fig. 5; Shows that the effect of Example 23 and Example 40 on Relative expression level of IL6 in the astrocytoma cell line.

MODE FOR CARRYING OUT THE INVENTION

[062] Hereinafter, the present disclosure will be described in detail with reference to specific embodiments. However, the present disclosure is not limited to the following embodiments, and can be carried out in an arbitrary form without departing from the gist of the invention.

[063] Unless defined otherwise, all technical, scientific terms, and abbreviations used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[064] In addition, in the present disclosure, all contents of all patent documents and non-patent documents or references explicitly cited may be cited herein as part of the present specification.

[065] In the present disclosure, “antagonistic activity” refers to the action of interacting with a receptor to attenuate intracellular signaling caused by the ligand's interaction with a receptor.

[066] In the present disclosure, "inverse agonistic activity" refers to the action of interacting with a constitutively active receptor to attenuate intracellular signaling without a influence of a ligand.

[067] In the present disclosure, "liver microsome" refers to a fragment of endoplasmic reticulum and attached ribosomes obtained by the centrifugation of homogenized liver cells.

[068] In the present disclosure, "electron transport system" as used herein refers to a series of protein complexes that transfer electrons via redox reactions on mitochondrial inner membrane which is a part of respiratory reactions. This electron transport and formation of proton concentration gradient across the membrane occur simultaneously, and the proton gradient is used for ATP synthesis.

[069] In the present disclosure, examples of halogen include fluorine, chlorine, bromine and iodine atoms.

[070] In the present disclosure, examples of C1-4 alkyl group include methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, isobutyl, and isomers thereof.

[071] In the present disclosure, examples of C1-4 haloalkyl group include fluoromethyl, chloromethyl, bromomethyl, iodomethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 2-fluoroethyl, 2-chloroethyl, pentafluoroethyl, 1-fluoropropyl, 2-chloropropyl, 3-fluoropropyl, 3-chloropropyl, 4,4,4-trifluorobutyl, 1,1-difluoroethyl, 2-fluoro-2-propanyl, 4-bromobutyl, and isomers thereof.

[072] In the present disclosure, examples of C1-4 alkoxy group include ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, tert-butoxy, and isomers thereof.

[073] In the present specification, examples of C1-4 haloalkoxy group include trifluoromethoxy, trichloromethoxy, chloromethoxy, bromomethoxy, fluoromethoxy, iodomethoxy, difluoromethoxy, dibromomethoxy, 2-chloroethoxy, 2,2,2-trifluoroethoxy, 2,2,2-trichloroethoxy, 3-bromopropoxy, 3-chloropropoxy, 2,3-dichloropropoxy, and isomers thereof.

[074] In the present disclosure, examples of 5-6 membered heterocyclic ring include pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, furan, pyran, thiophene, thiopyran, oxazole, isoxazole, thiazole, isothiazole, furazan, oxadiazole, oxazine, oxadiazine, thiadiazole, thiazine, thiadiazine, pyrroline, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazoline, tetrazolidine, pyrazoline, pyrazolidine, dihydropyridine, tetrahydropyridine, piperidine, dihydropyrazine, tetrahydropyrazine, piperazine, dihydropyrimidine, tetrahydropyrimidine, perhydropyrimidine, dihydropyridazine, tetrahydropyridazine, perhydropyridazine, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran,

dihydrothiophene, tetrahydrothiophene, dihydrothiopyran, tetrahydrothiopyran, dihydrooxazole, tetrahydrooxazole (oxazolidine), dihydroisoxazole, tetrahydroisoxazole (isoxazolidine), dihydrothiazole, tetrahydrothiazole (thiazolidine), dihydroisothiazole, tetrahydroisothiazole (isothiazolidine), dihydrofurazan, tetrahydrofurazan, dihydrooxadiazole, tetrahydrooxadiazole (oxadiazolidine), dihydrooxazine, tetrahydrooxadiazine, dihydrooxadiazine, tetrahydrooxadiazine, dihydrothiadiazole, tetrahydrothiadiazole (thiadiazolidine), dihydrothiazine, tetrahydrothiazine, dihydrothiadiazine, tetrahydrothiadiazine, morpholine, thiomorpholine, oxathiane, dioxolane, dioxane, dithiolane, and dithiane rings.

[075] In the present disclosure, 5-6 membered heterocyclic ring is preferably 5-6 membered aromatic heterocyclic ring, and more preferably 5-6 membered nitrogen-containing aromatic heterocyclic ring.

[076] In the present disclosure, examples of 5-6 membered aromatic heterocyclic ring include pyrrole, imidazole, triazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, oxazole, isoxazole, thiazole, and isothiazole.

[077] In the present disclosure, examples of 5-6 membered nitrogen-containing aromatic heterocyclic ring include pyrrole, imidazole, triazole, pyrazole, pyridine, pyrazine, pyrimidine, and pyridazine.

[078] In the present disclosure, examples of 5-6 membered carbocyclic ring include cyclopentane, cyclohexane, cyclopentene, cyclohexene, cyclopentadiene, cyclohexadiene, and benzene.

[079] The singular forms “a”, “an”, and “the” include plural referents unless the context clearly dictates otherwise.

[080] As used herein, the term “or” is a disjunction (that is, and/or) and does not indicate an exclusive disjunction unless explicitly indicated by the terms “either”, “otherwise”, “alternatively”, and words of similar effect.

[081] In the present disclosure, R^1 is preferably a halogen atom, or C1-4 alkyl group, and more preferably a halogen atom. Furthermore preferable R^1 is a chlorine atom, a fluorine atom, or a bromine atom. Most preferable R^1 is a chlorine atom.

[082] In the present disclosure, R^2 is preferably a hydrogen atom, or a halogen atom, and more preferably a hydrogen atom, or a chlorine atom.

[083] In the present disclosure, R^3 is preferably C1-4 alkyl group, or C1-4 haloalkyl group, and more preferably C1-4 haloalkyl group. Most preferable R^3 is trifluoromethyl.

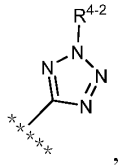
[084] In the present disclosure, R^{3-1} is preferably C1-4 alkyl group, and more preferably methyl.

[085] In the present disclosure, R^{3-2} is preferably C1-4 alkyl group, and more

preferably methyl.

[086] In the present disclosure, R^{3-3} is preferably C1-4 alkyl group, and more preferably methyl.

[087] In the present disclosure, R^4 is preferably a halogen atom, C1-4 haloalkyl group, cyano, $S(=O)_2$-R^{4-1}, or



,

[088] and more preferably a halogen atom, C1-4 haloalkyl group, or cyano. Most preferable R^4 is chlorine atom, fluorine atom, trifluoromethyl, or cyano.

[089] In the present disclosure, R^{4-1} is preferably C1-4 alkyl group, and more preferably methyl.

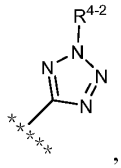
[090] In the present disclosure, R^{4-2} is preferably C1-4 alkyl group, and more preferably methyl.

[091] In the present disclosure, R^{4-3} is preferably C1-4 alkyl group, and more preferably methyl.

[092] In the present disclosure, R^5 is preferably C1-4 haloalkyl group, and more preferably trifluoromethyl.

[093] In the present disclosure, R^6 is preferably a halogen atom, and more preferably a fluorine atom.

[094] In the present disclosure, R^{4A} is preferably a hydrogen atom, a halogen atom, C1-4 haloalkyl group, $S(=O)_2$-R^{4-1}, or



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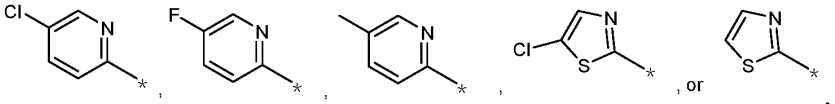
[095] and more preferably a hydrogen atom, a halogen atom, or C1-4 haloalkyl group. Furthermore preferable ring R^{4A} is a fluorine atom.

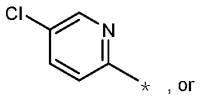
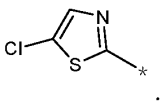
[096] In the present disclosure, R^{4B} is preferably a hydrogen atom, a halogen atom, or cyano. Furthermore preferable ring R^{4B} is a hydrogen atom.

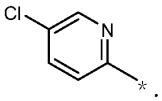
[097] In the present disclosure, R^{6A} is preferably a halogen atom. Furthermore preferable ring R^{6A} is a fluorine atom.

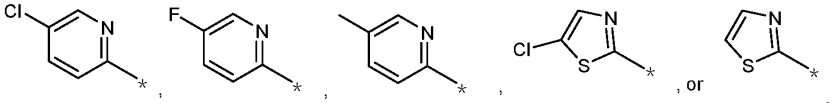
[098] In the present disclosure, R^{6B} is preferably a halogen atom. Furthermore

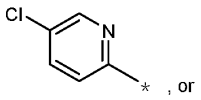
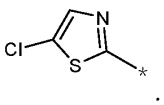
preferable ring R^{6B} is a fluorine atom.

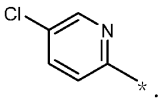
[099] In the present disclosure, ring A is preferably , , , , or ,

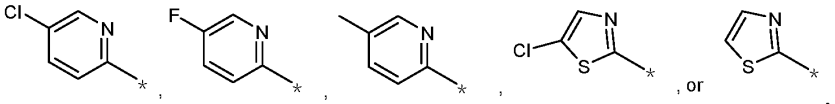
[0100] and more preferably , or .

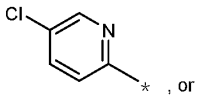
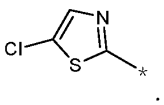
[0101] Furthermore preferable ring A is .

[0102] In the present disclosure, ring A-1 is preferably , , , , or ,

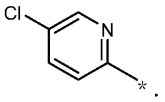
[0103] and more preferably , or .

[0104] Furthermore preferable ring A-1 is .

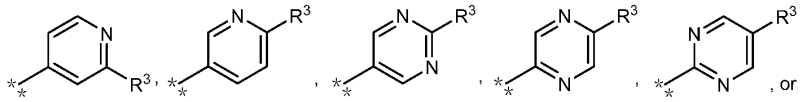
[0105] In the present disclosure, ring A-2 is preferably , , , , or ,

[0106] and more preferably , or .

[0107] Furthermore preferable ring A-2 is

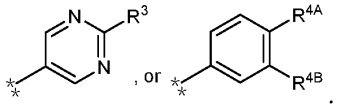


[0108] In the present disclosure, ring B is preferably 5-6 membered nitrogen-containing aromatic heterocyclic ring which may be substituted by 1 to 4 R^3 or a benzene which may be substituted by 1 to 5 R^4, and more preferably (1) a pyridine, (2) a pyrimidine, (3) a pyrazine, (1) to (3) in ring B may be substituted by 1 to 4 R^3, or (4) a benzene which may be substituted by 1 to 5 R^4. Furthermore preferable ring B is

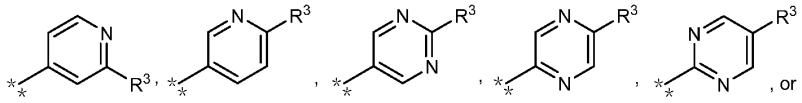


[0109] benzene substituted by 1 or 2 R^4.

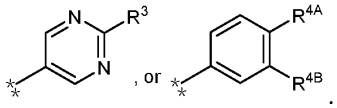
[0110] Most preferable ring B is



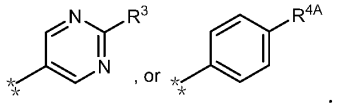
[0111] In the present disclosure, ring B-1 is preferably



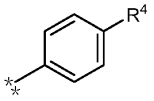
[0112] benzene substituted by 1 or 2 R^4, and more preferably



[0113] In the present disclosure, ring B-2 is preferably

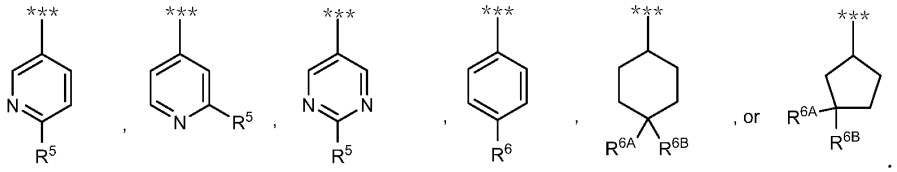


[0114] In the present disclosure, ring B-3 is preferably

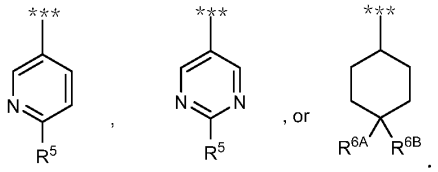


[0115] In the present disclosure, ring C is preferably 5-6 membered nitrogen-containing aromatic heterocyclic ring which may be substituted by 1 to 4 R^5 or a 5-6 membered carbocyclic ring which may be substituted by 1 to 5 R^6, and more preferably (1) a pyridine, (2) a pyrimidine, (1) or (2) in ring C may be substituted by 1 to 4 R^5, (3)

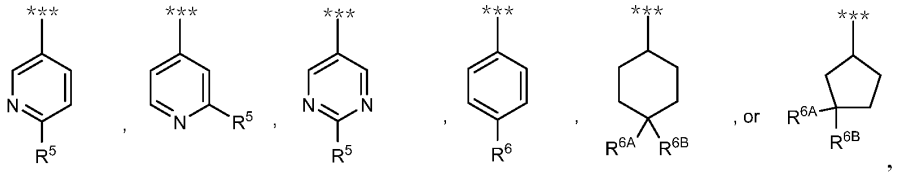
a benzene, (4) a cyclopentane, or (5) a cyclohexane, (3) to (5) in ring C may be substituted by 1 to 5 R^6. Furthermore preferable ring C is



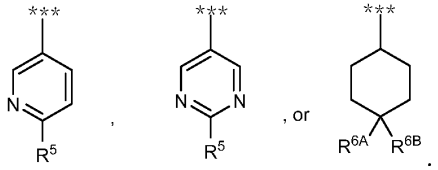
[0116] Most preferable ring C is



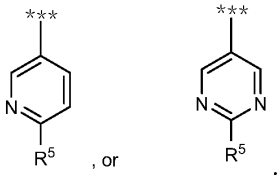
[0117] In the present disclosure, ring C-1 is



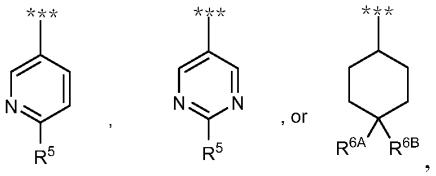
[0118] and more preferably



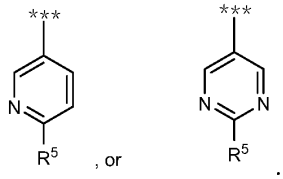
[0119] Most preferable ring C-1 is



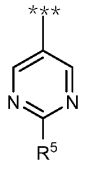
[0120] In the present disclosure, ring C-2 is



[0121] and more preferably



[0122] In the present disclosure, ring C-3 is



[0123] All symbols are as defined below.

[0124] In the present disclosure, preferably, ring B and ring C do not represent 5-6 membered carbocyclic ring at the same time.

[0125] In the present disclosure, preferably, R^{4A} and R^{4B} do not represent a hydrogen atom at the same time.

[0126] In the present disclosure, preferably, R^{6A} and R^{6B} do not represent a hydrogen atom at the same time.

[0127] The number of R^3 substituted in ring B is preferably an integer of 1 or 2, and more preferably an integer of 1.

[0128] The number of R^4 substituted in ring B is preferably an integer of 1 or 2, and more preferably an integer of 1.

[0129] The number of R^5 substituted in ring C is preferably an integer of 1 or 2, and more preferably an integer of 1.

[0130] The number of R^6 substituted in ring C is preferably an integer of 1 or 2, and more preferably an integer of 1.

[0131] The number of R^3 substituted in ring B-1 is preferably an integer of 1 or 2, and more preferably an integer of 1.

[0132] The number of R^4 substituted in ring B-1 is preferably an integer of 1 or 2, and more preferably an integer of 1.

[0133] The number of R^5 substituted in ring C-1 is preferably an integer of 1 or 2, and more preferably an integer of 1.

[0134] The number of R^6 substituted in ring C-1 is preferably an integer of 1 or 2, and more preferably an integer of 1.

[0135] In the present disclosure, the compound of formula (I) is preferably a combination of the preferred definitions of ring A, ring B, ring C, R^1, R^2, R^3, R^4, R^5, R^6, R^{3-1}, R^{3-2}, R^{3-3}, R^{4-1}, R^{4-2}, and R^{4-3}.

[0136] In the present disclosure, the compound of formula (I-1) is preferably a combination of the preferred definitions of ring A-1, ring B-1, ring C-1, R^1, R^2, R^3, R^4, R^5, R^6, R^{3-1}, R^{3-2}, R^{3-3}, R^{4-1}, R^{4-2}, and R^{4-3}.

[0137] In the present disclosure, the compound of formula (I-2) is preferably a combination of the preferred definitions of ring A-2, ring B-2, ring C-2, R^1, R^2, R^3, R^{4A}, R^{4B}, R^5, R^{6A}, R^{6B}, R^{3-1}, R^{3-2}, R^{3-3}, R^{4-1}, R^{4-2}, and R^{4-3}.

[0138] In the present disclosure, the compound of formula (I-3) is preferably a combination of the preferred definitions of ring B-3, ring C-3, R^3, R^4, R^5, R^{3-1}, R^{3-2}, R^{3-3}, R^{4-1}, R^{4-2}, and R^{4-3}.

[0139] In the present disclosure, another embodiment of the compound of formula (I), formula (I-1), formula (I-2) or formula (I-3) is most preferably an example compound described in Examples described later or a pharmaceutically acceptable salt thereof.

[0140] All isomers are included in the present disclosure unless otherwise indicated. For example, the alkyl group, the alkoxy group, and the like include linear groups and branched groups thereof. In addition, isomers (E-, Z-, cis-, and trans-forms) in a double bond, a ring, and a fused ring, isomers (R-, S-forms, α-, β-forms, enantiomer, and diastereomer) due to the presence of an asymmetric carbon, optically active substances (D-, L-, d-, and l-forms) having optical rotation, polar substances obtained through chromatographic separation (high-polarity substances and low-polarity substances), equilibrium compounds, rotational isomers, mixtures of these at an appropriate ratio, and racemic mixtures are all included in the present disclosure. In addition, all isomers by tautomerism are also included in the present disclosure.

[0141] Further, optical isomers in the present disclosure may include, not only 100%-pure isomers, but also isomers contain less than 50%-other optical isomers.

[0142] In the present disclosure, unless otherwise specified, the symbol:



[0143] represents that a substituent is bonded to the back side of the paper surface (that is, α-configuration), the symbol:



[0144] represents that a substituent is bonded to the front side of the paper surface (that is, β-configuration), the symbol:



[0145] represents α-configuration or β-configuration, and the symbol:



[0146] represents a mixture of α- and β-configurations at an appropriate ratio, as would be apparent to those skilled in the art.

[0147] In the present specification, the symbol "ξ" in the compound name indicates that the steric configuration of a substituent attached to the chiral atom is either α-configuration or β-configuration (IUPAC. Compendium of Chemical Terminology, 2nd ed. (the "Gold Book") compiled by A. D. McNaught and A.Wilkinson. Blackwell Scientific Publications, Oxford (1997). Online version (2019-) created by S. J. Chalk. ISBN 0-9678550-9-8. https://doi.org/10.1351/goldbook.).

[0148] In the present disclosure, all references with respect to the compound of the present disclosure include the compound of formula (I), a salt thereof, a solvate thereof, an N-oxide thereof, or a cocrystal thereof, or a solvate of a salt of the compound of formula (I) or a cocrystal thereof.

[Salt]

[0149] The compound of formula (I) is converted into a salt by a known method.

[0150] The salt is a pharmaceutically acceptable salt.

[0151] The salt is preferably water-soluble.

[0152] Examples of the pharmaceutically acceptable salt include, acid addition salts, alkali metal salts, alkaline earth metal salts, ammonium salts, and amine salts.

[0153] Examples of the acid addition salt include inorganic acid salts such as hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, and nitrate, or organic acid salts such as acetate, lactate, tartrate, benzoate, citrate, methanesulfonate, ethanesulfonate, trifluoroacetate, benzenesulfonate, toluenesulfonate, isethionate, glucuronate, and gluconate.

[0154] Examples of the alkali metal salt include a potassium salt and a sodium salt.

[0155] Examples of the alkaline earth metal salt include a calcium salt and a magnesium salt.

[0156] Examples of the ammonium salt include a tetramethylammonium salt.

[0157] Examples of the amine salt include a triethylamine salt, a methylamine salt, a dimethylamine salt, a cyclopentylamine salt, a benzylamine salt, a phenethylamine salt, a piperidine salt, a monoethanolamine salt, a diethanolamine salt, a tris(hydroxymethyl)aminomethane salt, a lysine salt, an arginine salt, and an N-methyl-D-glucamine salt.

[0158] In addition, the compound of the present disclosure can be converted into an N-oxide by any method. The N-oxide represents a compound obtained by oxidizing a nitrogen atom of the compound of formula (I).

[0159] The compound of formula (I) and a pharmaceutically acceptable salt thereof may exist in a non-solvated form or in a solvated form with a pharmaceutically acceptable solvent such as water or ethanol. The solvate is preferably a hydrate. The compound of formula (I) and a pharmaceutically acceptable salt thereof can be converted into a solvate.

[0160] The compound of formula (I) can form a cocrystal with an appropriate cocrystal former. The cocrystal is preferably a pharmaceutically acceptable cocrystal that is formed with a pharmaceutically acceptable cocrystal former. The cocrystal is typically defined as a crystal in which two or more different molecules are formed by intermolecular interaction that is different from ionic bonds. The cocrystal may be a complex of a neutral molecule and a salt. The cocrystal can be prepared by a known method, for example, by melting crystallization, recrystallization from a solvent, or physically pulverizing the components together. Suitable cocrystal formers include those described in WO 2006/007448.

[0161] In the present disclosure, all references to the compound of the present disclosure include a compound of formula (I), a pharmaceutically acceptable salt thereof, an N-oxide thereof, a solvate thereof (for example, a hydrate), or a cocrystal thereof, or an N-oxide of a pharmaceutically acceptable salt of the compound of formula (I), a solvate thereof (for example, a hydrate), or a cocrystal thereof.

[Prodrug]

[0162] The prodrug of the compound of formula (I) refers to a compound that is converted into the compound of formula (I) through a reaction with an enzyme, gastric acid, or the like in vivo. Examples of the prodrug of the compound of formula (I) include: compounds in which an amino group is acylated, alkylated, or phosphorylated (for example, compounds in which the amino group of the compound of formula (I) is eicosanoylated, alanylated, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidyl methylated,

pivaloyloxymethylated, acetoxymethylated, tert-butylated, or the like) in the case where the compound of formula (I) has an amino group; compounds in which a hydroxyl group is acylated, alkylated, phosphorylated, or borated (for example, compounds in which the hydroxyl group of the compound of formula (I) is acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarylated, alanylated, dimethylaminomethylcarbonylated, or the like) in the case where the compound of formula (I) has a hydroxyl group; and compounds in which a carboxy group is esterified or amidated (for example, compounds in which the carboxy group of the compound of formula (I) is ethyl esterified, phenyl esterified, carboxymethyl esterified, dimethylaminomethyl esterified, pivaloyloxymethyl esterified, 1-{(ethoxycarbonyl)oxy}ethyl esterified, phthalidyl esterified, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterified, 1-{[(cyclohexyloxy)carbonyl]oxy}ethyl esterified, methylamidated, or the like) in the case where the compound of formula (I) has a carboxy group. These compounds can be produced by a method known per se. The prodrug of the compound of formula (I) may be either a hydrate or a non-hydrate. In addition, the prodrug of the compound of formula (I) may be a compound that is converted into the compound of general formula (I) under a physiological condition as described in "Development of Pharmaceuticals", Vol. 7, "Molecular Design", pp. 163 to 198, published by Hirokawa Shoten, 1990.

[0163] Furthermore, each atom constituting the compound of formula (I) may be substituted with an isotope thereof (for example, ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{16}N, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{77}Br, and ^{125}I) or the like.

[Processes for the preparation of the compound of the present disclosure]

[0164] A compound of the present disclosure can be produced by appropriately improving known methods, for example, methods shown below, methods equivalents thereto, the method described in Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 3rd Edition (Richard C. Larock, John Wiley & Sons Inc, 2018), the methods described in Examples or the like, and using a combination thereof. A salt may be used as the starting material thereof. The order of carrying out each reaction can be appropriately changed depending on the protecting group introduced and reaction conditions.

[0165] In addition, a compound having an amino group, a tetrazolyl group, a carboxyl group, or a hydroxyl group can be produced, if necessary, by performing a known deprotection reaction after an appropriate reaction step, by using a compound protected with a protecting group commonly used for these groups. The protecting group is, for

example, the protecting groups described in T. W. Greene, Protective Groups in Organic Synthesis, Wiley, New York, 5th Edition, 2014.

[0166] Examples of the protecting group of a carboxyl group include methyl, ethyl, tert-butyl, trichloroethyl, benzyl (Bn), phenacyl, p-methoxybenzyl, trityl, and 2-chlorotrityl.

[0167] Examples of the protecting group of an amino group or a tetrazolyl group include a benzyloxycarbonyl group, a tert-butoxycarbonyl group, an allyloxycarbonyl (Alloc) group, a 1-methyl-1(4-biphenyl)ethoxycarbonyl (Bpoc) group, a trifluoroacetyl group, a 9-fluorenylmethoxycarbonyl group, a benzyl (Bn) group, a p-methoxybenzyl group, a benzyloxymethyl (BOM) group, and a 2-(trimethylsilyl)ethoxymethyl (SEM) group.

[0168] Examples of the protecting group of a hydroxyl group or hydroxamic acid include methyl, trityl, methoxymethyl (MOM), 1-ethoxyethyl (EE), methoxyethoxymethyl (MEM), 2-tetrahydropyranyl (THP), trimethylsilyl (TMS), triethylsilyl (TES), tert-butyldimethylsilyl (TBDMS), tert-butyldiphenylsilyl (TBDPS), acetyl (Ac), pivaloyl, benzoyl, benzyl (Bn), p-methoxybenzyl, allyloxycarbonyl (Alloc), and 2,2,2-trichloroethoxycarbonyl (Troc).

[0169] The deprotection reaction is known, and can be performed by, for example, the following methods:

(1) a deprotection reaction by alkaline hydrolysis;

(2) a deprotection reaction under an acidic condition;

(3) a deprotection reaction by hydrogenolysis;

(4) a deprotection reaction of a silyl group;

(5) a deprotection reaction by using a metal; and

(6) a deprotection reaction by using a metal complex.

[0170] These methods are specifically described as follows.

(1) The deprotection reaction by alkaline hydrolysis is performed, for example, at 0 to 40°C, in an organic solvent (for example, methanol, tetrahydrofuran (hereinafter, THF), and dioxane), by using a hydroxide of an alkali metal (for example, sodium hydroxide, potassium hydroxide, and lithium hydroxide), a hydroxide of an alkaline earth metal (for example, barium hydroxide and calcium hydroxide), a carbonate (for example, sodium carbonate and potassium carbonate), or an aqueous solution or mixture thereof.

(2) The deprotection reaction under an acidic condition is performed, for example, at 0 to 100°C, in an organic solvent (for example, dichloromethane, chloroform, dioxane, ethyl acetate, methanol, isopropyl alcohol, THF, and anisole), in an organic

acid (for example, acetic acid, trifluoroacetic acid, methanesulfonic acid, and p-tosylic acid) or an inorganic acid (for example, hydrochloric acid and sulfuric acid), or a mixture thereof (for example, hydrogen bromide/acetic acid), in the presence or absence of 2,2,2-trifluoroethanol.

(3) The deprotection reaction by hydrogenolysis is performed, for example, at 0 to 200°C, in a solvent (for example, an ether-based solvent such as THF, dioxane, dimethoxyethane, and diethyl ether; an alcohol-based solvent such as methanol and ethanol; a benzene-based solvent such as benzene and toluene; a ketone-based solvent such as acetone and methyl ethyl ketone; a nitrile-based solvent such as acetonitrile; an amide-based solvent such as N,N-dimethylformamide (hereinafter, DMF); water, ethyl acetate, acetic acid, or a mixed solvent of two or more thereof), in the presence of a catalyst (for example, palladium-carbon, palladium black, palladium hydroxide-carbon, platinum oxide, and Raney nickel), under a hydrogen atmosphere under normal pressure or pressure, or in the presence of ammonium formate.

(4) The deprotection reaction of a silyl group is performed, for example, at 0 to 40°C, in an organic solvent (for example, THF and acetonitrile) miscible with water, by using tetrabutylammonium fluoride. In addition, the deprotection reaction is performed, for example, at -10 to 100°C, in an organic acid (for example, acetic acid, trifluoroacetic acid, methanesulfonic acid, and p-tosylic acid) or an inorganic acid (for example, hydrochloric acid and sulfuric acid), or a mixture thereof (for example, hydrogen bromide/acetic acid).

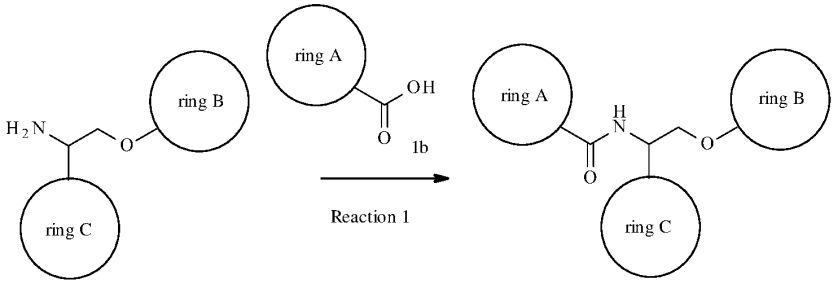
(5) The deprotection reaction using a metal is performed, for example, at 0 to 40°C, in an acidic solvent (for example, a mixed solution of acetic acid, a buffer solution having a pH of 4.2 to 7.2, or a solution thereof with an organic solvent such as THF), in the presence of powdery zinc while applying ultrasonic waves if necessary.

(6) The deprotection reaction using a metal complex is performed, for example, at 0 to 40°C, in an organic solvent (for example, dichloromethane, DMF, THF, ethyl acetate, acetonitrile, dioxane, and ethanol), water, or a mixed solvent thereof, in the presence of a trapping reagent (for example, tributyltin hydride, triethylsilane, dimedone, morpholine, diethylamine, and pyrrolidine), an organic acid (for example, acetic acid, formic acid, and 2-ethylhexanoic acid), and/or an organic acid salt (for example, sodium 2-ethylhexanoate and potassium 2-ethylhexanoate), in the presence or absence of a phosphine-based reagent (for example, triphenylphosphine), by using a metal complex (for example, tetrakistriphenylphosphine palladium(0), bis(triphenylphosphine)palladium(II) dichloride, palladium(II) acetate, and tris(triphenylphosphine)rhodium(I) chloride).

[0171] The reaction disclosed in the present disclosure may be performed by a batch process (also referred to as batch production or batch manufacturing) performed by a procedure of charging a reactant into container, performing a reaction and a post-treatment, and collecting a product, or may be performed by a flow process (also referred to as continuous flow production or continuous flow manufacturing) that is a method of continuously charging a reactant from one side of a reactor and continuously collecting a product from the other side.

[0172] The compound of formula (I) can be produced by Reaction Scheme 1.

Reaction Scheme 1



1a (I)

[0173] wherein ring A, ring B, and ring C have the same meanings as described above.

[0174] In the Reaction Scheme 1, Reaction 1 can be carried out by using a compound of formula 1a and a compound of formula 1b and subjection the compounds to an amidation reaction.

[0175] The amidation is known. For example, it includes the method

(1) via an acyl halide,

(2) via a mixed acid anhydride,

(3) using a condensing agent.

[0176] These methods are explained as follows.

(1) The method via an acyl halide may be carried out, for example, by reacting a carboxylic acid with an acyl halide (for example, oxalyl chloride or thionyl chloride) in an organic solvent (for example, chloroform, dichloromethane, diethyl ether or tetrahydrofuran) or without a solvent at -20°C to reflux temperature. And then, the obtained acyl halide derivative may be reacted with an amine in an organic solvent (for example, chloroform, dichloromethane, diethyl ether or tetrahydrofuran) in the presence of a base (for example, pyridine, triethylamine, dimethylaniline, dimethylaminopyridine or diisopropylethylamine) at 0 to 40°C. As an alternative, the obtained acyl halide derivative may be reacted with an amine in an organic solvent (for example, dioxane,

tetrahydrofuran) using an alkaline aqueous solution (for example, sodium hydrogen carbonate, sodium hydroxide) at -78 to 40°C.

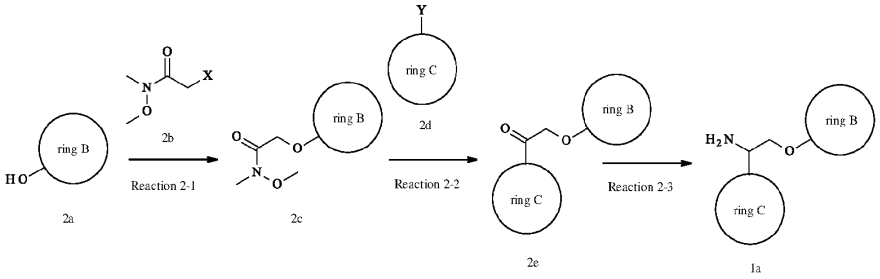
(2) The method via a mixed acid anhydride may be carried out, for example, by reacting a carboxylic acid with an acyl halide (for example, pivaloyl chloride, p-toluenesulfonyl chloride or methanesulfonyl chloride) or an acid derivative (for example, ethyl chloroformate or isobutyl chloroformate) in an organic solvent (for example, chloroform, dichloromethane, diethyl ether, tetrahydrofuran) or without a solvent, in the presence of a base (for example, pyridine, triethylamine, dimethylaniline, dimethylaminopyridine or diisopropylethylamine) at 0 to 40°C. And then the obtained mixed acid anhydride derivative may be reacted with an amine in an organic solvent (for example, chloroform, dichloromethane, diethyl ether or tetrahydrofuran), at 0 to 40°C.

(3) The method using a condensing agent may be carried out, for example, by reacting a carboxylic acid with amine in an organic solvent (for example, chloroform, dichloromethane, N,N-dimethylformamide, diethyl ether or tetrahydrofuran) or without a solvent, in the presence or absence of a base (for example, pyridine, triethylamine, dimethylaniline or dimethylaminopyridine), using a condensing agent (for example, 1,3-dicyclohexyl carbodiimide (DCC), 1-ethyl-3-[3-(dimethylamino)propyl] carbodiimide (EDC), 1,1'-carbodiimidazole (CDI), 2-chloro-1-methylpyridinium iodide, or 1-propanephosphonic acid cyclic anhydride (PPA)), in the presence or absence of 1-hydroxybenzotiazole (HOBt), or using 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (hereinafter, HATU) at 0 to 40°C.

[0177] The reaction described in (1), (2) and (3) may be carried out under an inert gas (for example, argon or nitrogen) to avoid water in order to obtain a preferable result.

[0178] The compound of formula 1a can be produced by Reaction Scheme 2, 3, 4, or 5.

Reaction Scheme 2



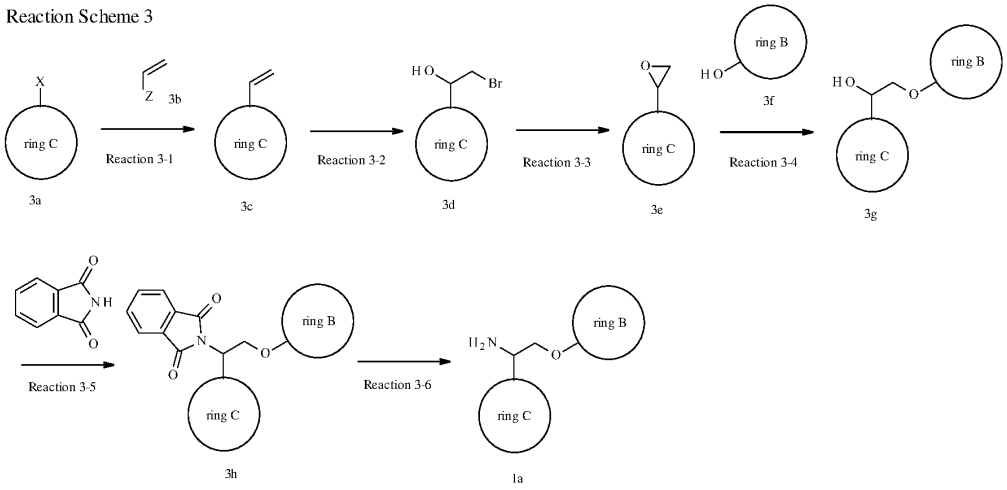
[0179] wherein X represents a halogen atom, a trifluoromethanesulfonyloxy group (hereinafter, OTf group), a methanesulfonyloxy group (hereinafter, OMs group), or a toluenesulfonyloxy group (hereinafter, OTs), Y represents a halogen atom and the other symbols have the same meanings as described above.

[0180] In the Reaction Scheme 2, Reaction 2-1 can be carried out by subjecting a compound of formula 2a and a compound of formula 2b to an etherification reaction. The etherification reaction is known and is carried out, for example, in an organic solvent (for example, N,N-dimethylformamide, dimethyl sulfoxide, chloroform, dichloromethane, diethyl ether, tetrahydrofuran, or methyl t-butyl ether) in the presence of an alkali metal hydroxide (for example, sodium hydroxide, potassium hydroxide, or lithium hydroxide), an alkaline earth metal hydroxide (for example, barium hydroxide or calcium hydroxide), or a carbonate (for example, sodium carbonate or potassium carbonate), or an aqueous solution thereof or a mixture thereof at 0 to 100°C.

[0181] In the Reaction Scheme 2, Reaction 2-2 can be carried out by subjecting a compound of formula 2c and a compound of formula 2d to an anion reaction. The anion reaction is known and is carried out, for example, in an organic solvent (for example, tetrahydrofuran or diethyl ether) in the presence of a metal reagent (for example, Grignard reagent or butyl lithium) at a temperature of -78 to 40°C.

[0182] In the Reaction Scheme 2, Reaction 2-3 can be carried out by subjecting a compound of formula 2e and amine source (for example, ammonium acetate or ammonium formate) to a reductive amination reaction. The reductive amination reaction is known and is carried out, for example, in an organic solvent (for example, dichloroethane, dichloromethane, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, acetic acid, tetrahydrofuran, methanol, or a mixture thereof) in the presence of a reducing agent (for example, sodium triacetoxyborohydride, sodium cyanoborohydride, or sodium borohydride) at a temperature of 0 to 40°C.

Reaction Scheme 3



[0183] wherein Z represents a borane derivative such as boronic acid ($B(OH)_2$) or its ester derivative and the other symbols have the same meanings as described above.

[0184] In the Reaction Scheme 3, Reaction 3-1 can be carried out by subjecting a compound of formula 3a and a compound of formula 3b to a Suzuki coupling reaction. The Suzuki coupling reaction is known and is carried out, for example, in an organic solvent (for example, benzene, toluene, N,N-dimethylformamide, dioxane, tetrahydrofuran, methanol, acetonitrile, dimethoxyethane, or acetone) in the presence of a base (for example, sodium ethylate, sodium hydroxide, potassium hydroxide, triethylamine, sodium carbonate, sodium hydrogen carbonate, potassium carbonate, cesium carbonate, thallium carbonate, tripotassium phosphate, cesium fluoride, barium hydroxide, or tetrabutylammonium fluoride), or an aqueous solution thereof or a mixture thereof and a catalyst (for example, tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$), bis(triphenylphosphine)palladium dichloride ($PdCl_2(PPh_3)_2$), palladium acetate ($Pd(OAc)_2$), palladium black, 1,1'-bis(diphenylphosphinoferrocene)dichloropalladium ($PdCl_2(dppf)_2$), diallyl palladium dichloride ($PdCl_2(allyl)_2$), phenylbis(triphenylphosphine)palladium iodide ($PhPdI(PPh_3)_2$), or tris(dibenzylideneacetone)dipalladium (hereinafter, $Pd_2(dba)_3$)) at room temperature to 120°C.

[0185] In the Reaction Scheme 3, Reaction 3-2 can be carried out by subjecting a compound of formula 3c to a bromohydrin formation. The bromohydrin formation is known and is carried out, for example, in an organic solvent (for example, acetone, acetonitrile or dimethyl sulfoxide) in the presence of water and bromo reagent (for example, N-bromosuccinimide or hydrogen bromide) at 0 to 80°C.

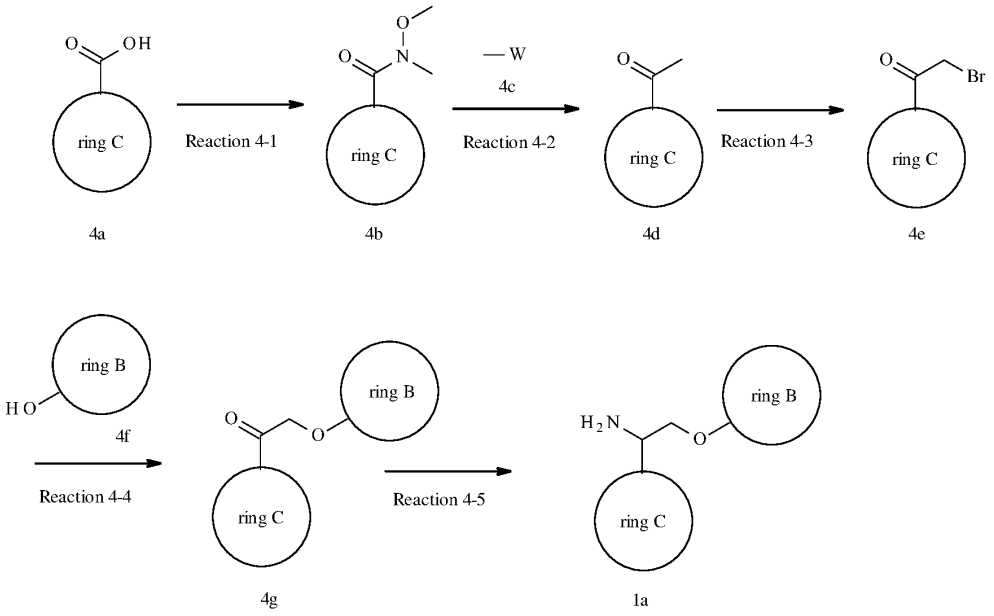
[0186] In the Reaction Scheme 3, Reaction 3-3 can be carried out by subjecting a compound of formula 3d to an etherification reaction. An etherification can be carried out by the same method described above for the preparation of the compound of formula 2c in Reaction Scheme 2.

[0187] In the Reaction Scheme 3, Reaction 3-4 can be carried out by subjecting a compound of formula 3e and a compound of formula 3f to an epoxide ring-opening reaction. The epoxide ring-opening reaction is known and is carried out, for example, in an organic solvent (for example, dimethyl sulfoxide, N,N-dimethyl formamide, toluene or tetrahydrofuran) in the presence of an alkali metal hydroxide (for example, sodium hydroxide, potassium hydroxide, or lithium hydroxide), an alkaline earth metal hydroxide (for example, barium hydroxide or calcium hydroxide), or a carbonate (for example, sodium carbonate or potassium carbonate) at 0 to 100°C.

[0188] In the Reaction Scheme 3, Reaction 3-5 can be carried out by subjecting a compound of formula 3g and phthalimide to a Mitsunobu reaction. The Mitsunobu reaction is known and is carried out, for example, in an organic solvent (for example, dichloromethane, diethyl ether, tetrahydrofuran, acetonitrile or toluene) in the presence of an azo compound (for example, diethyl azodicarboxylate (hereinafter, DEAD), diisopropyl azodicarboxylate, 1,1'-(azodicarbonyl)dipiperidine, or 1,1'-azobis(N,N-dimethylformamide)), or a phosphine compound (for example, triphenylphosphine, tributylphosphine, trimethylphosphine, or polymer-supported triphenylphosphine) at 0 to 60°C.

[0189] In the Reaction Scheme 3, Reaction 3-6 can be carried out by subjecting a compound of formula 3h to a phthalimide deprotection reaction. The phthalimide deprotection reaction is known and is carried out, for example, in an organic solvent (for example, methanol, ethanol, dichloromethane or tetrahydrofuran) in the presence of hydrazine hydrate at room temperature to 100°C.

Reaction Scheme 4



[0190] wherein W represents magnesium bromide (MgBr), magnesium chloride (hereinafter, MgCl), magnesium iodide (MgI) or lithium and the other symbols have the same meanings as described above.

[0191] In the Reaction Scheme 4, Reaction 4-1 can be carried out by subjecting a compound of formula 4a and N,O-dimethylhydroxyamine or the salt thereof to an amidation reaction. An amidation reaction can be carried out by the same method described above for the preparation of the compound of formula (I) in Reaction Scheme 1.

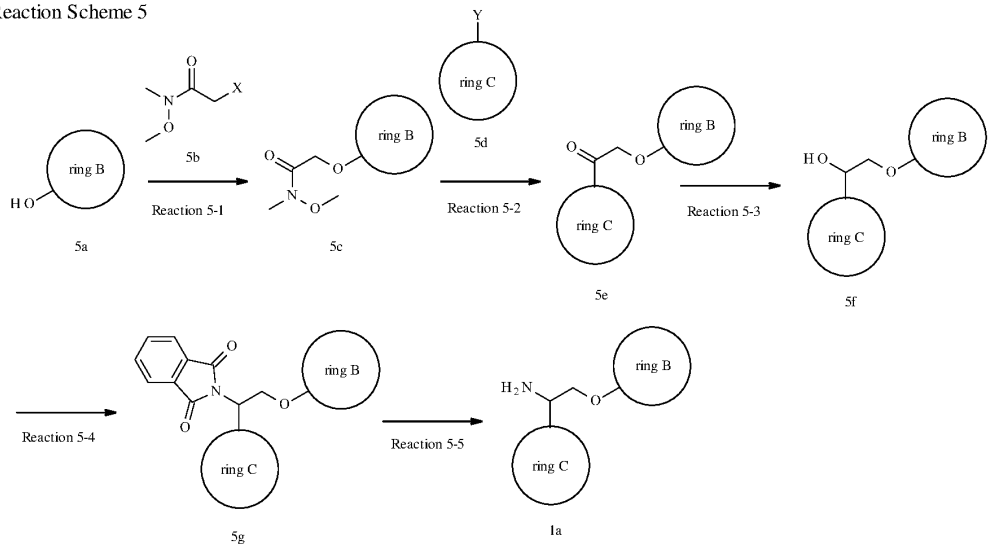
[0192] In the Reaction Scheme 4, Reaction 4-2 can be carried out by subjecting a compound of formula 4b and a compound of formula 4c to an anion reaction. An anion reaction can be carried out by the same method described above for the preparation of the compound of formula 2e in Reaction Scheme 2.

[0193] In the Reaction Scheme 4, Reaction 4-3 can be carried out by subjecting a compound of formula 4d to a bromination reaction. The bromination reaction is known and is carried out for example, in an organic solvent (for example, N,N-dimethyl formamide, tetrahydrofuran or methanol) in the presence of a bromination reagent (for example, N-bromosuccinimide, bromine or phenyltrimethylammonium tribromide) at -20 ºC to 40 ºC.

[0194] In the Reaction Scheme 4, Reaction 4-4 can be carried out by subjecting a compound of formula 4e and a compound of formula 4f to an etherification reaction. An etherification can be carried out by the same method described above for the preparation of the compound of formula 2c in Reaction Scheme 2.

[0195] In the Reaction Scheme 4, Reaction 4-5 can be carried out by subjecting a compound of formula 4g and amine source (for example, ammonium acetate or ammonium formate) to a reductive amination reaction. A reductive amination can be carried out by the same method described above for the preparation of the compound of formula 1a in Reaction Scheme 2.

Reaction Scheme 5



[0196] wherein all symbols have the same meanings as described above.

[0197] In the Reaction Scheme 5, Reaction 5-1 can be carried out by subjecting a compound of formula 5a and a compound of formula 5b to an etherification reaction. An etherification reaction can be carried out by the same method described above for the preparation of the general formula 2c in Reaction Scheme 2.

[0198] In the Reaction Scheme 5, Reaction 5-2 can be carried out by subjecting a compound of formula 5c and a compound of formula 5d to an anion reaction. An anion reaction can be carried out by the same method described above for the preparation of the compound of formula 2e in Reaction Scheme 2.

[0199] In the Reaction Scheme 5, Reaction 5-3 can be carried out by subjecting a compound of formula 5e to a reduction reaction of carbonyl group. The reduction reaction of carbonyl group is known and is carried out, for example, in an organic solvent (for example, tetrahydrofuran, methanol, ethanol or dichloromethane) in the

presence of a reducing agent (for example, sodium tetrahydroborate, lithium aluminum tetrahydride or sodium cyanoborohydride) at 0 to 80°C.

[0200] In the Reaction Scheme 5, Reaction 5-4 can be carried out by subjecting a compound of formula 5f and phthalimide to a Mitsunobu reaction. A Mitsunobu reaction can be carried out by the same method described above for the preparation of the compound of formula 3h in Reaction Scheme 3.

[0201] In the Reaction Scheme 5, Reaction 5-5 can be carried out by subjecting a compound of formula 5g to a phthalimide deprotection reaction. A phthalimide deprotection reaction can be carried out by the same method described above for the preparation of the compound of formula 1a in Reaction Scheme 3.

[0202] In the present disclosure, the compound of formula 1b, formula 2a, formula 2b, formula 2d, formula 3a, formula 3b, formula 3f, formula 4a, formula 4c, formula 4f, formula 5a, formula 5b or formula 5d used as starting materials and/or intermediates are known, or can be easily produced by combining known methods, for example, the methods described in Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 3rd Edition (Richard C. Larock, John Wiley & Sons Inc, 2018) and the like, or methods obtained by partially modifying known methods or the like.

[0203] Among the compound of the present disclosure, a compound having optical activity can be produced by using a starting material or reagent having optical activity, or by optically separating a racemic intermediate and then converting to the present disclosure compound therefrom, or optically separating a racemic form of the compound of the present disclosure.

[0204] This optical separation is known, and examples thereof include a method in which a salt, a complex, or the like is formed with another optically active compound, and then a target compound is isolated after recrystallization or directly separated using a chiral column or the like.

[0205] In the reactions in the present specification, a reaction involving heating can be performed using a water bath, an oil bath, a sand bath, or a microwave, as would be apparent to those skilled in the art.

[0206] In the reactions in the present specification, a solid-phase supported reagent that is supported on a polymer (for example, polystyrene, polyacrylamide, polypropylene, polyethylene glycol, and the like) may be appropriately used.

[0207] In the reactions in the present specification, the reaction product can be purified by ordinary purification means, for example, distillation under normal pressure or reduced pressure, high-performance liquid chromatography using silica gel or magnesium silicate, thin-layer chromatography, methods using an ion-exchange resin or

a scavenger resin, column chromatography, washing, and recrystallization. The purification may be performed for each reaction or may be performed after completion of some reactions.

[Toxicity]

[0208] The toxicity of the compound of the present disclosure is low, and therefore can be used as a medicament safely.

[Application to pharmaceuticals]

[0209] The compound of the present disclosure has an $S1P_3$ receptor antagonistic activity, and therefore, is useful as an agent for preventing and/or treating an $S1P_3$-mediated disease.

[0210] In the present disclosure, examples of the $S1P_3$-mediated disease include, neurodegenerative diseases, pain, cancer, liver diseases, diseases of endocrine and metabolic system, cardiac diseases, or respiratory disorders.

[0211] In the present disclosure, examples of neurodegenerative diseases include Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Amyotrophic Lateral Sclerosis (hereinafter, ALS), Frontotemporal Dementia, Friedreich's Ataxia, Multiple System Atrophy (hereinafter, MSA), Lewy Body Dementia, Progressive Supranuclear Palsy (hereinafter, PSP), Pick's Disease, Creutzfeldt-Jakob Disease, Spinocerebellar Ataxia (hereinafter, SCA), Duchenne Muscular Dystrophy, Charcot-Marie-Tooth Disease, Fabry's Disease, Mitochondrial Diseases, Prader-Willi Syndrome, Rett Syndrome, Krabbe Disease, Batten Disease, Sandhoff Disease, Tay-Sachs Disease, Gaucher's Disease, Mucopolysaccharidosis type I, Mucopolysaccharidosis type II, Mucopolysaccharidosis type III (for example, Mucopolysaccharidosis type IIIA), Mucopolysaccharidosis type IV, Mucopolysaccharidosis type VI, Mucopolysaccharidosis type VII, Mucopolysaccharidosis type IX, Klippel-Feil Syndrome, Niemann-Pick Disease, Wilson's Disease, Alexander Disease, Canavan Disease, Lesch-Nyhan Syndrome, Adrenoleukodystrophy, Sturge-Weber Syndrome, Machado-Joseph Disease, Refsum's Disease, Dilated Virchow-Robin Spaces, Wernicke-Korsakoff Syndrome, Idiopathic Normal Pressure Hydrocephalus, CADASIL, Creatine Deficiency Syndrome, Shy-Drager Syndrome, SMON, Spondylosis Deformans, Encephalomalacia, Pontocerebellar Hypoplasia, Möbius Syndrome, Left Hemisphere Syndrome, Cerebellar Atrophy, Meniere's Disease, Merkel Cell Carcinoma, Corticobasal Degeneration, Oculopharyngeal Muscular Dystrophy, Cerebrovascular disease (for example, cerebral infarction, stroke, subarachnoid hemorrhage, cerebral

hemorrhage, transient ischemic attack, ischemia/reperfusion injury), epilepsy and the like.

[0212] In the present disclosure, Mucopolysaccharidosis type III is preferably Mucopolysaccharidosis type IIIA.

[0213] In the present disclosure, Cerebrovascular disease is preferably cerebral infarction.

[0214] In the present disclosure, examples of cancer include cancer associated with cerebral nerve (for example, pediatric brain tumors (for example, neuroblastoma, medulloblastoma, astrocytoma (for example, juvenile pilocytic astrocytoma), ependymoma, craniopharyngioma, germ cell tumors, optic nerve glioma, choroid plexus papilloma and pontine glioma), adult brain tumors (for example, adult astrocytoma, adult malignant astrocytoma, adult glioblastoma, adult ependymoma, adult malignant ependymoma, adult malignant oligodendroglioma, adult medulloblastoma, adult meningioma and adult malignant meningioma), glioma (for example, astrocytoma, oligodendroglioma, ependymoma and brain stem glioma), pituitary adenoma, acoustic schwannoma, retinoblastoma and uveal malignant melanoma), respiratory tract cancer (for example, pharyngeal cancer (for example, nasopharyngeal cancer, oropharyngeal cancer and hypopharyngeal cancer), laryngeal cancer, nasal sinus cancer, lung cancer (for example, small cell cancer and non-small-cell cancer), thymoma and mesothelioma), gastrointestinal cancer (for example, esophageal cancer, gastric cancer, duodenal cancer and large bowel cancer (for example, colon cancer, rectal cancer and anal cancer)), oral cancer (for example, gingival cancer, tongue cancer and salivary gland cancer), urinary system cancer (for example, penile cancer, renal pelvis · ureter cancer, renal cell cancer, testicular tumor, prostate cancer and bladder cancer), cancers that affect women (for example, vulvar cancer, uterine cancer (for example, cervical cancer and endometrial cancer), uterine sarcoma, trophoblastic disease (for example, hydatidiform mole, choriocarcinoma, placental-site trophoblastic tumor and persistent trophoblastic disease), vaginal cancer, breast cancer, breast sarcoma, ovarian cancer and ovarian germ cell tumor), skin cancer (for example, melanoma (also known as malignant melanoma) (for example, malignant lentiginous melanoma, superficial spreading melanoma, nodular melanoma, acral lentiginous melanoma and erosive melanoma), mycosis fungoides, squamous cell carcinoma, basal cell carcinoma, premonitory signs of skin cancer · intraepidermal carcinoma (for example, actinic keratosis, Bowen's disease and Paget's disease), lymphomatoid papulosis, cutaneous CD30 positive anaplastic large cell lymphoma, Sezary syndrome and cutaneous B-cell lymphoma), bone and muscle cancer (for example, osteosarcoma, soft tissue sarcoma,

rhabdomyosarcoma, synovial sarcoma and liposarcoma), thyroid cancer, carcinoid, liver cancer (also known as hepatoma), hepatoblastoma, bile duct cancer, gallbladder cancer, pancreatic cancer, pancreatic endocrine tumors (for example, insulinoma, gastrinoma and VIPoma), carcinoma of unknown primary, hereditary tumors · familial tumors (for example, hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis, hereditary breast and ovarian cancer syndrome, Li-Fraumeni syndrome, hereditary melanoma, Wilms' tumor, hereditary papillary renal cell carcinoma, von Hippel-Lindau syndrome and multiple endocrine neoplasia), leukemia (for example, acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, chronic myeloid leukemia, chronic myeloproliferative disorder, adult T-cell leukemia-lymphoma, chronic lymphocytic leukemia and small lymphocytic lymphoma), multiple myeloma, primary macroglobulinemia, malignant lymphoma (for example, Hodgkin's lymphoma, non-Hodgkin's lymphoma (intermediate- and high-grade lymphomas, Burkitt's lymphoma, lymphoblastic lymphoma, follicular lymphoma, mantle-cell lymphoma, MALT (Mucosa-Associated Lymphoid Tissue) lymphoma and NK (natural killer) cell lymphoma)) and the like.

[0215] In the present disclosure, examples of liver diseases include Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E, Alcoholic liver disease, Non-alcoholic fatty liver disease, Non-alcoholic steatohepatitis, Cirrhosis, Liver cancer, Hemochromatosis, Wilson's disease, Primary biliary cirrhosis, Primary sclerosing cholangitis, Autoimmune hepatitis, Gilbert's syndrome, Liver abscess, Liver fibrosis, Hepatic encephalopathy, Liver failure, Portal hypertension, Ascites, Hepatorenal syndrome, Budd-Chiari syndrome, Glycogen storage disease, Alpha-1 antitrypsin deficiency, Liver adenoma, Hepatocellular carcinoma, Cholangiocarcinoma, Liver cysts, Hepatic steatosis, Hepatomegaly, Liver fluke infection, Hepatic vein thrombosis, Hepatic artery thrombosis, Hepatitis X (unknown etiology hepatitis), Drug-induced liver disease, Toxic hepatitis, Liver granuloma, Liver necrosis, Liver hemangioma, Liver sarcoma, Biliary atresia, Caroli disease, Alagille syndrome, Crigler-Najjar syndrome, Dubin-Johnson syndrome, Rotor syndrome, Tyrosinemia, Von Gierke disease and the like.

[0216] In the present disclosure, examples of diseases of endocrine and metabolic system include Diabetes Mellitus, Hypothyroidism, Hyperthyroidism, Addison's disease, Cushing's syndrome, Hashimoto's thyroiditis, Graves' disease, Acromegaly, Gigantism, Dwarfism, Hypopituitarism, Hyperpituitarism, Polycystic ovary syndrome (hereinafter, PCOS), Osteoporosis, Hyperparathyroidism, Hypoparathyroidism, Adrenal insufficiency, Adrenal hyperplasia, Pheochromocytoma, Hyperaldosteronism,

Hypoaldosteronism, Hypercortisolism, Hypocortisolism, Hyperinsulinism, Hypoinsulinism, Hyperprolactinemia, Hypoprolactinemia, Hypergonadism, Hypogonadism, Hyperandrogenism, Hypoandrogenism, Hyperestrogenism, Hypoestrogenism, Hyperlipidemia, Hypolipidemia, Hypercalcemia, Hypocalcemia, Hyperkalemia, Hypokalemia, Hypernatremia, Hypoatremia, Hyperglycemia, Hypoglycemia, Hyperuricemia, Hypouricemia, Hyperphosphatemia, Hypophosphatemia, Hyperthyroxinemia, Hypothyroxinemia, Hypertriiodothyroninemia, Hypotriiodothyroninemia.and the like.

[0217] In the present disclosure, examples of cardiac diseases include Ischemic Heart Disease, Coronary Artery Disease, Heart Failure, Arrhythmia, Atrial Fibrillation, Ventricular Fibrillation, Hypertrophic Cardiomyopathy, Dilated Cardiomyopathy, Restrictive Cardiomyopathy, Myocardial Infarction, Angina Pectoris, Heart Valve Disease, Rheumatic Heart Disease, Congenital Heart Disease, Pulmonary Heart Disease, Cardiogenic Shock, Endocarditis, Myocarditis, Pericarditis, Cardiac Tamponade, Aortic Aneurysm, Aortic Dissection, Aortic Stenosis, Mitral Valve Prolapse, Mitral Valve Stenosis, Mitral Regurgitation, Aortic Regurgitation, Tricuspid Stenosis, Tricuspid Regurgitation, Pulmonary Stenosis, Pulmonary Regurgitation, Infective Endocarditis, Cardiac Asthma, Cardiac Cachexia, Cardiac Ischemia, Cardiac Syncope, Sudden Cardiac Death, Cardiac Arrest, Ventricular Tachycardia, Supraventricular Tachycardia, Sick Sinus Syndrome, Heart Block, Long QT Syndrome, Short QT Syndrome, Wolff-Parkinson-White Syndrome, Brugada Syndrome, Takotsubo Cardiomyopathy, Hypertension, Hypertensive Heart Disease, Stroke and the like.

[0218] In the present disclosure, examples of respiratory disorders include Asthma, Chronic Obstructive Pulmonary Disease, Pneumonia, Tuberculosis, Lung Cancer, Cystic Fibrosis, Bronchitis, Emphysema, Pulmonary Hypertension, Occupational Lung Diseases, Pulmonary Edema, Pleural Effusion, Pneumothorax, Hemothorax, Pulmonary Embolism, Acute Respiratory Distress Syndrome (hereinafter, ARDS), Interstitial Lung Disease, Mesothelioma, Sarcoidosis, Asbestosis, Bronchiectasis, Hypoxia, Hypercapnia, Pulmonary Fibrosis, Chronic Bronchitis, Silicosis, Pulmonary Abscess, Sleep Apnea, Legionnaires' Disease, Lung Abscess, Pulmonary Alveolar Proteinosis, Respiratory Syncytial Virus, Influenza, CoronaVirus Infectious Disease, emerged in 2019, Severe Acute Respiratory Syndrome, Middle East Respiratory Syndrome, Bird Flu, Hantavirus Pulmonary Syndrome, Anthrax, Bronchiolitis, Croup, Epiglottitis, Pertussis, Tuberculosis, Lung Nodule, Pulmonary Sequestration, Hypersensitivity Pneumonitis, Pulmonary Actinomycosis, Pulmonary Eosinophilia, Pulmonary Alveolar Microlithiasis, Pulmonary Atelectasis, Lymphangioleiomyomatosis, Pulmonary Arterial Hypertension,

Lobar Pneumonia, Aspiration Pneumonia, Walking Pneumonia, Community-Acquired Pneumonia, Hospital-Acquired Pneumonia, Ventilator-Associated Pneumonia, Pneumocystis Pneumonia, Chlamydophila Pneumonia, Mycoplasma Pneumonia, Legionella Pneumonia, Bronchopneumonia, Lipoid Pneumonia, Eosinophilic Pneumonia, Swine Flu, Metastatic Lung Cancer, Non-Small Cell Lung Cancer, Small Cell Lung Cancer, Bronchial Asthma, Allergic Asthma, Non-Allergic Asthma, Exercise-Induced Asthma, Cough-Variant Asthma, Occupational Asthma, Nocturnal Asthma, Status Asthmaticus, Restrictive Lung Disease, Idiopathic Pulmonary Fibrosis, Nontuberculous Mycobacterial Infection, Laryngotracheobronchitis, Middle East Respiratory Syndrome, Severe Acute Respiratory Syndrome, Obstructive Sleep Apnea, Central Sleep Apnea, Mixed Sleep Apnea, Cheyne-Stokes Respiration, Lung Transplant Rejection, Tracheal Stenosis, Tracheobronchomalacia, Tracheoesophageal Fistula, Tracheal Neoplasms, Pulmonary Lymphangioleiomyomatosis, Pulmonary Nocardiosis, Pulmonary Sarcoidosis, Pulmonary Blastomycosis, Pulmonary Histoplasmosis, Pulmonary Sporotrichosis, Pulmonary Aspergillosis, Pulmonary Cryptococcosis, Pulmonary Candidiasis, Pulmonary Mucormycosis, Pulmonary Coccidioidomycosis, Pulmonary Paracoccidioidomycosis and the like.

[0219] In the use of the compound of the present disclosure for the purpose of preventing and/or treating the above-mentioned diseases, the substance that acts as an active ingredient, is usually formulated together with a pharmaceutically acceptable carrier such as various additives or solvents, and then administered systemically or topically, orally or parenterally. Here, the pharmaceutically acceptable carrier means a substance other than the active ingredient, which is generally used for pharmaceutical preparation. The pharmaceutically acceptable carrier preferably does not exhibit a pharmacological action at the dosage of the preparation, is harmless, and does not interfere with the therapeutic effect of the active ingredient. The pharmaceutically acceptable carrier can also be used for the purpose of, for example, enhancing the usefulness of the active ingredient and the preparation, facilitating the formulation, stabilizing the quality, or improving the usability. Specifically, substances described in "Japanese Pharmaceutical Excipients Directory" published in 2000 by Yakuji Nippo Limited (edited by International Pharmaceutical Excipients Council Japan) and the like may be appropriately selected according to the purpose.

[0220] The compound of the present disclosure can be administered to a mammal (preferably human, more preferably a human patient) in a pharmaceutically effective amount.

[0221] Since the dosage of the compound of the present disclosure depends on age, body weight, symptom, desired therapeutic effect, route of administration, period of treatment, and the like, the dosage inevitably varies. The compound of the present disclosure is generally administered orally in the range of 0.1 ng to 1,000 mg per patient per administration, or parenterally administered or continuously administered intravenously in the range of 0.01 ng to 100 mg per patient per administration.
[0222] Needless to say, the dosage varies depending on various conditions as described above. Therefore, a dosage smaller than the above dosage may be sufficient, or a dosage beyond the above range may be required.
[0223] Examples of the dosage form thereof include preparations for oral administration (for example, tablets, capsules, granules, powders, oral solutions, syrups, and oral jellies), preparations for oral cavity (for example, oral tablets, oral sprays, oral semisolids, and oral rinses), preparations for injection (for example, injectables), preparations for dialysis (for example, dialysis agents), preparations for inhalation (for example, inhalants), preparations for ophthalmic application (for example, eye drops and ophthalmic ointments), preparations for otologic application (for example, ear drops), preparations for nasal application (for example, nose drops), preparations for rectum (for example, suppositories, semisolids for rectum, and enemas for rectal application), preparations for vagina (for example, vaginal tablets and vaginal suppositories), and preparations for skin (for example, external solid agents, external liquid agents, sprays, ointments, creams, gels, and patches).

[Preparation for oral administration]
[0224] Examples of the preparation for oral administration include tablets, capsules, granules, powders, oral solutions, syrups, and oral jellies. The preparation for oral administration includes rapidly disintegrating preparations in which the releasability of the active ingredient from the preparation is not particularly adjusted; and controlled-release preparations such as enteric-coated preparations and sustained-release preparations in which the releasability is adjusted according to the purpose by unique formulation design and formulation method. The enteric-coated preparation refers to a preparation designed to release the active ingredient mainly in the small intestine without releasing the active ingredient in the stomach, for the purpose of preventing the degradation of the active ingredient in the stomach or reducing the irritation of the active ingredient to the stomach. The enteric-coated preparation can be usually produced by coating with an acid-insoluble enteric-coated base. The sustained-release preparation refers to a preparation in which the release rate, release time, and release

site of the active ingredient from the preparation are adjusted for the purpose of reducing the number of administrations or attenuating side effects. The sustained-release preparation can be usually produced by using an appropriate sustained-release agent. Among preparations for oral administration, capsules, granules, tablets, and the like can be coated with an appropriate coating agent such as a saccharide, a sugar alcohol, or a polymer compound, for the purpose of, for example, facilitating ingestion or preventing degradation of the active ingredient.

(1) Tablet

[0225] The tablet is a solid preparation that is administered orally and has a certain shape. The tablet includes those generally referred to as tablets, such as uncoated tablets, film-coated tablets, sugar-coated tablets, multilayer tablets, and dry-coated tablets, as well as orally rapidly disintegrating tablets, chewable tablets, effervescent tablets, dispersible tablets, and soluble tablets. In the production of the uncoated tablet, the following method (a), (b), or (c) is usually used:

(a) Additives such as an excipient, a binder, and a disintegrant are added to the active ingredient and mixed to prepare a homogeneous mixture, the mixture is granulated by an appropriate method using water or a solution containing a binder, then a lubricant or the like is added to the granulated product and mixed, and the resulting mixture was compression-molded;

(b) Additives such as an excipient, a binder, and a disintegrant are added to the active ingredient and mixed to prepare a homogeneous mixture, and the mixture is directly compression-molded; or the active ingredient, a lubricant, and the like are added to granules prepared in advance with additives to prepare a homogeneous mixture, and then the mixture is compression-molded; and

(c) Additives such as an excipient and a binder are added to the active ingredient and mixed to prepare a homogeneous mixture, a kneaded product obtained by wetting the mixture with a solvent is poured into a predetermined mold and molded, and then the molded product is dried by an appropriate method.

[0226] The film-coated tablet can be usually produced by thinly coating an uncoated tablet with an appropriate coating agent such as a polymer compound. The sugar-coated tablet can be usually produced by coating an uncoated tablet with a coating agent containing a saccharide or a sugar alcohol. The multilayer tablet can be produced by forming layers of powder particles having different compositions and compression-molding the layered powder particles by an appropriate method. The dry-coated tablet can be produced by covering an inner core tablet with an outer layer having a

composition different from that of the inner core tablet. The tablet can also be an enteric-coated tablet or a sustained-release tablet by a known appropriate method. The orally rapidly disintegrating tablet, the chewable tablet, the effervescent tablet, the dispersible tablet, and the soluble tablet are those in which unique functions are imparted to the tablets by appropriate selection of additives, and can be produced according to the above-described methods for producing the tablet. Incidentally, the orally rapidly disintegrating tablet refers to a tablet that can be taken by being rapidly dissolved or disintegrated in the oral cavity; the chewable tablet refers to a tablet that is chewed and taken; the effervescent tablet refers to a tablet that dissolves or disperses while rapidly foaming in water; the dispersible tablet refers to a tablet that is taken by being dispersed in water; and the soluble tablet refers to a tablet that is taken by being dissolved in water. The effervescent tablet can be produced by using an appropriate acidic substance, a carbonate, a bicarbonate, or the like as an additive.

(2) Capsule

[0227] The capsule is a preparation in which ingredients are filled in a capsule or encapsulated with a capsule base, and includes hard capsules, soft capsules, and the like. The hard capsule can be produced by adding an additive such as an excipient to the active ingredient and mixing them to prepare a homogeneous mixture, or forming the mixture into particles or a molded product by an appropriate method, and filling, in a capsule, the mixture, the particles, or the molded product as it is or after each content is slightly molded. The soft capsule can be produced by encapsulating a mixture of the active ingredient and an additive in a certain shape with an appropriate capsule base such as gelatin having increased plasticity by adding glycerin, D-sorbitol, or the like. The capsule may be an enteric-coated capsule or a sustained-release capsule prepared by a known appropriate method, and a colorant, a preservative, or the like may be added to the capsule base.

(3) Granule

[0228] The granule is a preparation granulated in a granular form, and includes effervescent granules and the like in addition to those generally referred to as granules. In the production of the granule, the following method (a), (b), or (c) is usually used:

(a) An excipient, a binder, a disintegrant, or other additives are added to a powdery active ingredient and mixed to prepare a homogeneous mixture, and then the mixture is granulated by an appropriate method;

(b) An additive such as an excipient is added to the active ingredient prepared in a granular form in advance, and mixed to prepare a homogeneous mixture; and
(c) An additive such as an excipient is added to the active ingredient prepared in a granular form in advance and mixed, and the mixture is then formed into granules by an appropriate method.
[0229] The granule may be coated as necessary, and may be an enteric-coated granule or a sustained-release granule prepared by a known appropriate method. The effervescent granule can be produced by using an appropriate acidic substance, a carbonate, a bicarbonate, or the like as an additive. The effervescent granule refers to a granule that dissolves or disperses while rapidly foaming in water. The granule can also be made into a fine granule by adjusting the size of the particle.

(4) Powder
[0230] The powder is a powdery preparation, and can be usually produced by adding an excipient or other additives to the active ingredient and mixing them to prepare a homogeneous mixture.

(5) Oral solution
[0231] The oral solution is a liquid or flowable viscous gel preparation, and includes, in addition to those generally referred to as oral solutions, an elixir, a suspension, an emulsion, a lemonade, and the like. The oral solution can be usually produced by adding an additive and purified water to the active ingredient, followed by mixing, uniformly dissolving or emulsifying or suspending, and filtering as necessary. The elixir refers to a clear liquid oral solution containing sweet and aromatic ethanol. The elixir can be usually produced by adding ethanol, purified water, a flavoring agent, and white sugar, other saccharides or a sweetener to a solid active ingredient or a leachate thereof, dissolving components, and preparing a clear liquid by filtration or other methods. The suspension refers to an oral solution in which the active ingredient is finely and homogeneously suspended. The suspension can be usually produced by adding a suspending agent or other additives and purified water or oil to a solid active ingredient, and performing suspension by an appropriate method to homogenize the entire active ingredient. The emulsion refers to an oral solution in which the active ingredient is finely and homogeneously emulsified. The emulsion can be usually produced by adding an emulsifier and purified water to a liquid active ingredient, and performing emulsification by an appropriate method to homogenize the mixture. The lemonade refers to a clear liquid oral solution having a sweet taste and a sour taste.

(6) Syrup

[0232] The syrup is a viscous liquid preparation or solid preparation containing a saccharide or sweetener, and includes preparations for syrup and the like. The syrup can be usually produced by adding the active ingredient to a solution of white sugar, other saccharides or a sweetener, or a single syrup, followed by dissolving, mixing, suspending, or emulsifying, and if necessary, boiling the mixed liquid, followed by hot filtration. The preparation for syrup refers to a granular or powdery preparation that becomes a syrup when water is added, and may also be referred to as a dry syrup. The preparation for syrup can be usually produced using a saccharide or a sweetener as an additive in accordance with the method for producing the granule or powder.

(7) Oral jelly

[0233] The oral jelly is a formed gel preparation having no fluidity, and can be usually produced by adding an additive and a polymer gel base to the active ingredient and mixing them, gelatinizing the mixture by an appropriate method, and forming the resulting gel into a certain shape.

[Preparation for injection]

(1) Injectable

[0234] The injectable is a solution, a suspension or an emulsion, or a solid sterile preparation to be dissolved or suspended when used, which is administered subcutaneously, intramuscularly, or directly administered to a body tissue such as blood vessel or an organ. The injectable includes a lyophilized injectable, a powder injectable, a filled syringe, a cartridge, an infusion, an embedded injectable, a long acting injectable, and the like, in addition to those generally referred to as injectables. In the production of the injectable, the following method (a), or (b) is usually used:

(a) A homogeneous solution is prepared by dissolving, suspending, or emulsifying the active ingredient as it is or a mixture obtained by adding an additive to the active ingredient, in water for injection, another aqueous solvent, a non-aqueous solvent or the like. Then, the prepared solution is filled in a container for injection, and then the container is sealed, followed by sterilization; and

(b) A homogeneous solution is prepared by dissolving, suspending, or emulsifying the active ingredient as it is or a mixture obtained by adding an additive to the active ingredient, in water for injection, another aqueous solvent, a non-aqueous solvent or the

like. Then, the prepared solution is aseptically filtrated or aseptically prepared, the resulting solution is filled in a container for injection, and the container is sealed.

[0235] The lyophilized injectable can be usually produced by dissolving the active ingredient as it is or a mixture of the active ingredient and an additive such as an excipient, in water for injection, aseptically filtering the solution, filling the solution in a container for injection, and then lyophilizing the solution, or directly filling the solution in a container after lyophilizing the solution in a dedicated container. The powder injectable can be usually produced by crystallizing a powder subjected to aseptic filtration to prepare a powder, and if necessary, adding a sterilized additive to the prepared powder, and filling the powder in a container for injection. A filled syringe can be usually produced by preparing a solution, a suspension, or an emulsion with the active ingredient as it is or with the active ingredient and an additive, and then filling the prepared solution, suspension, or emulsion in a glass syringe. The cartridge refers to an injectable used by inserting a cartridge filled with a drug solution into a dedicated syringe. The cartridge filled with the drug solution can be usually produced by preparing a solution, a suspension, or an emulsion with the active ingredient as it is or with the active ingredient and an additive, and filling the prepared solution, suspension, or emulsion into the cartridge. The infusion refers to 100 mL or more of injectable usually administered intravenously. The embedded injectable refers to a solid or gel-like injection which is applied subcutaneously, intramuscularly or the like by using an implantation tool or by surgery, for the purpose of releasing the active ingredient over a long period of time. The embedded injectable can be usually produced by using a biodegradable polymer compound and forming the compound into a pellet, microsphere, or gel. The long acting injectable refers to an injectable which is applied intramuscularly or the like for the purpose of releasing the active ingredient over a long period of time. The sustained injectable can be usually produced by dissolving or suspending the active ingredient in a vegetable oil or the like, or preparing a microsphere suspension containing a biodegradable polymer compound.

[0236] The compound of the present disclosure may also be administered as a concomitant drug in combination with another drug for:

1) complementation and/or enhancement of the prophylactic and/or therapeutic effects of the compound;

2) improvement of kinetics and absorption, and reduction in dosage; and/or

3) attenuation of side effects of the compound.

[0237] With respect to a combination drug comprising the compound of the present disclosure and other drug, may be administered in the form of a blending drug in which

both ingredients are blended in one preparation, or may be administered in the form of separate preparations. Administration in this separate preparations includes simultaneous administration and administration by time difference. In addition, administration by time difference may be performed by administering the compound of the present disclosure first and then administering another drug later, or by administering another drug first and then administering the compound of the present disclosure later. The administration methods of the drugs may be the same or different.

[0238] The disease for which the above combination drug has a prophylactic and/or therapeutic effect is not particularly limited as long as it is a disease for which the prophylactic and/or therapeutic effect of the compound of the present disclosure are complemented and/or enhanced.

[0239] Examples of the other drug(s) for complementation and/or enhancement of the prophylactic and/or therapeutic effect of the compound of the present disclosure on neurodegenerative disease include Donepezil, Rivastigmine, Galantamine, Memantine, Aducanumab, Lecanemab, Levodopa, Carbidopa, Entacapone, Pramipexole, Ropinirole, Rotigotine, Selegiline, Rasagiline, Amantadine, Tetrabenazine, Deutetrabenazine, Riluzole, Edaravone, Tofersen, Sodium phenylbutyrate/taurursodiol, Idebenone, Coenzyme Q10, L-DOPA, Trihexyphenidyl, Benzatropine, Prednisone, Deflazacort, Pimozide, Tacrolimus, Miglustat, Acetazolamide, Baclofen, Tizanidine, Dantrolene, Diazepam, Clonazepam, Gabapentin, Thiamine, Folinic Acid, Betaine, Creatine, Alteplase, Aspirin, Clopidogrel, Warfarin, Rivaroxaban, Apixaban, Idursulfase, Baclofen, Metoprolol, Pregabalin, Amitriptyline and the like.

[0240] Examples of the other drug(s) for complementation and/or enhancement of the prophylactic and/or therapeutic effect of the compound of the present disclosure on cancer include Cisplatin, Carboplatin, Oxaliplatin, Gemcitabine, Paclitaxel, Docetaxel, Doxorubicin, Epirubicin, Irinotecan, Topotecan, Fluorouracil, Capecitabine, Methotrexate, Vincristine, Vinblastine, Vinorelbine, Etoposide, Ifosfamide, Cyclophosphamide, Chlorambucil, Melphalan, Busulfan, Temozolomide, Imatinib, Dasatinib, Nilotinib, Erlotinib, Gefitinib, Sunitinib, Sorafenib, Lapatinib, Trastuzumab, Rituximab, Bevacizumab, Cetuximab, Panitumumab, Pembrolizumab, Nivolumab, Ipilimumab, Atezolizumab, Durvalumab, Tamoxifen, Letrozole, Anastrozole, Exemestane, Leuprolide, Goserelin, Bicalutamide, Flutamide, Prednisone, Dexamethasone, Hydroxyurea, Thalidomide, Lenalidomide, Bortezomib, Carfilzomib, Ixazomib, Daratumumab, Elotuzuma and the like.

[0241] Examples of the other drug(s) for complementation and/or enhancement of the prophylactic and/or therapeutic effect of the compound of the present disclosure on liver diseases include an Interferon, Ribavirin, Sofosbuvir, Daclatasvir, Ledipasvir, Velpatasvir, Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir, Elbasvir, Grazoprevir, Glecaprevir, Pibrentasvir, Lamivudine, Adefovir, Entecavir, Telbivudine, Tenofovir, Peginterferon alfa-2a, Peginterferon alfa-2b, Simeprevir, Boceprevir, Telaprevir, Prednisone, Azathioprine, Mycophenolate mofetil, Cyclosporine, Tacrolimus, Ursodeoxycholic acid, Obeticholic acid, Fenofibrate, Bezafibrate, Pravastatin, Simvastatin, Atorvastatin, Rosuvastatin, Ezetimibe, Metformin, Pioglitazone, Vitamin E, N-acetylcysteine, Pentoxifylline, Orlistat, Liraglutide, Betaine, Cholestyramine, Rifampin, Naltrexone, Acamprosate, Disulfiram, Metadoxine, Furosemide, Spironolactone, Propranolol, Nadolol, Isosorbide mononitrate, Lactulose, Rifaximin, Neomycin, Metronidazole, Vancomycin, Albumin, Terlipressin, Midodrine, Octreotide, Vasopressin, Tolvaptan, Satavaptan, Zinc, Copper, Penicillamine, Trientine, Deferoxamine, Deferasirox, Deferiprone, Phlebotomy, Iron chelation therapy, Liver transplantation and the like.

[0242] Examples of the other drug(s) for complementation and/or enhancement of the prophylactic and/or therapeutic effect of the compound of the present disclosure on diseases of endocrine and metabolic system include Insulin, Metformin, Glipizide, Levothyroxine, Methimazole, Hydrocortisone, Prednisone, Fludrocortisone, Spironolactone, Octreotide, Somatropin, Bromocriptine, Cabergoline, Clomiphene, Raloxifene, Alendronate, Calcitriol, Cinacalcet, Mifepristone, Ketoconazole, Phenoxybenzamine, Doxazosin, Eplerenone, Glucagon, Sitagliptin, Exenatide, Liraglutide, Testosterone, Estradiol, Progesterone, Spironolactone, Finasteride, Dutasteride, Atorvastatin, Simvastatin, Rosuvastatin, Ezetimibe, Fenofibrate, Gemfibrozil, Calcium Carbonate, Calcium Gluconate, Sodium Polystyrene Sulfonate, Sodium Bicarbonate, Sodium Chloride, Dextrose, Allopurinol, Febuxostat, Sevelamer, Calcium Acetate, Levothyroxine, Liothyronine and the like.

[0243] Examples of the other drug(s) for complementation and/or enhancement of the prophylactic and/or therapeutic effect of the compound of the present disclosure on cardiac diseases include Aspirin, Clopidogrel, Warfarin, Heparin, Enoxaparin, Dabigatran, Rivaroxaban, Apixaban, Beta blockers (for example, Metoprolol, Atenolol), Angiotensin-converting enzyme inhibitors (ACE inhibitors, for example, Ramipril), angiotensin receptor blockers (ARBs, for example, Valsartan), Calcium channel blockers (for example, Amlodipine, Diltiazem), Diuretics (for example, Furosemide, Hydrochlorothiazide), Nitrates (for example, Isosorbide Mononitrate, Nitroglycerin),

Statins (for example, Atorvastatin, Simvastatin), Digoxin, Amiodarone, Dronedarone, Sotalol, Ranolazine, Ivabradine, Hydralazine, Isosorbide dinitrate, Sacubitril/Valsartan, Eplerenone, Spironolactone and the like.

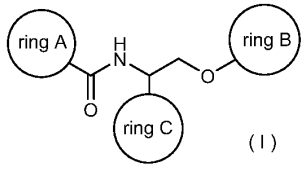
[0244] Examples of the other drug(s) for complementation and/or enhancement of the prophylactic and/or therapeutic effect of the compound of the present disclosure on respiratory disorders include Albuterol, Prednisone, Budesonide/Formoterol, Fluticasone/Salmeterol, Tiotropium, Levalbuterol, Fluticasone, Albuterol, Azithromycin, Amoxicillin, Doxycycline, Levofloxacin, Ciprofloxacin, Isoniazid, Rifampin, Ethambutol, Pyrazinamide, Ipratropium, Tiotropium, Aclidinium, Olodaterol, Formoterol, Salmeterol, Mometasone, Fluticasone, Budesonide, Beclomethasone, Ciclesonide, Theophylline, Roflumilast, Zafirlukast, Montelukast, Zileuton, Omalizumab, Mepolizumab, Reslizumab, Benralizumab, Dupilumab, Cromolyn sodium, Nedocromil, Hydrocortisone, Dexamethasone, Methylprednisolone, Prednisolone, Metformin, Guaifenesin, Codeine, Hydrocodone, Dextromethorphan, Oseltamivir, Zanamivir, Peramivir, Baloxavir, Ivermectin, Ribavirin, Amantadine, Rimantadine, Zanamivir, Remdesivir, Lopinavir/ritonavir, Umifenovir, Favipiravir, Tocilizumab, Sarilumab, Anakinra, Baricitinib, Ruxolitinib, Fedratinib, Eculizumab, Ravulizumab, Interferon beta-1a, Interferon beta-1b, Interferon alfa-2a, Interferon alfa-2b, Interferon alfa-n3, Peginterferon alfa-2a, Peginterferon alfa-2b, Interferon alfa-2b, Peginterferon alfa-2b, Interferon alfa-2a, Interferon alfa-n3 and the like.

[0245] The disease against which the above-described combined medicine exhibits the prophylactic and/or therapeutic effect is not particularly limited as long as the disease is that against which the prophylactic and/or therapeutic effect of the compound of the present disclosure is complemented and/or enhanced.

[0246] Any two or more of the other drugs may be administered in combination.

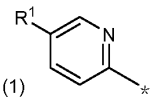
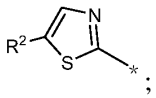
[0247] In addition, other drugs that complement and/or enhance the prophylactic and/or therapeutic effect of the compound of the present disclosure include not only those that have been found to date but also those that will be found in the future based on the mechanism described above.

[0248] [1] A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

[0249] wherein ring A is

(1)  , or (2)  ;

[0250] the * mark represents a bonding position with a carbonyl group;

[0251] ring B is 5-6 membered heterocyclic ring which may be substituted by 1 to 4 R^3 or 5-6 membered carbocyclic ring which may be substituted by 1 to 5 R^4;

[0252] when two or more R^3s are substituted, a plurality of R^3s may be the same or different;

[0253] when two or more R^4s are substituted, a plurality of R^4s may be the same or different;

[0254] ring C is 5-6 membered heterocyclic ring which may be substituted by 1 to 4 R^5 or 5-6 membered carbocyclic ring which may be substituted by 1 to 5 R^6;

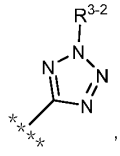
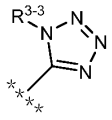
[0255] when two or more R^5s are substituted, a plurality of R^5s may be the same or different;

[0256] when two or more R^6s are substituted, a plurality of R^6s may be the same or different;

[0257] R^1 is selected from the group consisting of (1) a halogen atom, (2) C1-4 alkyl group and (3) C1-4 haloalkyl group;

[0258] R^2 is selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) C1-4 alkyl group and (4) C1-4 haloalkyl group;

[0259] R^3 is selected from the group consisting of (1) a halogen atom, (2) C1-4 alkyl group, (3) C1-4 haloalkyl group, (4) C1-4 alkoxy group, (5) C1-4 haloalkoxy group, (6) cyano, (7) $S(=O)_2$-R^{3-1},

(8)  , and (9)  ;

[0260] R^{3-1} is a hydrogen atom or C1-4 alkyl group;

[0261] when two or more R^3s are substituted, a plurality of R^{3-1}s may be the same or different;

[0262] R^{3-2} is a hydrogen atom or C1-4 alkyl group;

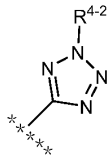
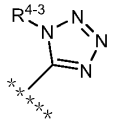
[0263] when two or more R^3s are substituted, a plurality of R^{3-2}s may be the same or different;

[0264] R^{3-3} is a hydrogen atom or C1-4 alkyl group;

[0265] when two or more R^3s are substituted, a plurality of R^{3-3}s may be the same or different;

[0266] the **** mark represents a bonding position with ring B;

[0267] R^4 is selected from the group consisting of (1) a halogen atom, (2) C1-4 alkyl group, (3) C1-4 haloalkyl group, (4) C1-4 alkoxy group, (5) C1-4 haloalkoxy group, (6) cyano, (7) $S(=O)_2$-R^{4-1},

(8)  , and (9)  ;

[0268] R^{4-1} is a hydrogen atom or C1-4 alkyl group;

[0269] when two or more R^4s are substituted, a plurality of R^{4-1}s may be the same or different;

[0270] R^{4-2} is a hydrogen atom or C1-4 alkyl group;

[0271] when two or more R^4s are substituted, a plurality of R^{4-2}s may be the same or different;

[0272] R^{4-3} is a hydrogen atom or C1-4 alkyl group;

[0273] when two or more R^4s are substituted, a plurality of R^{4-3}s may be the same or different;

[0274] the ***** mark represents a bonding position with ring B;

[0275] R^5 is selected from the group consisting of (1) a halogen atom, (2) C1-4 alkyl group, (3) C1-4 haloalkyl group, (4) C1-4 alkoxy group and (5) C1-4 haloalkoxy group;

[0276] R^6 is selected from the group consisting of (1) a halogen atom, (2) C1-4 alkyl group, (3) C1-4 haloalkyl group, (4) C1-4 alkoxy group and (5) C1-4 haloalkoxy group.

[0277] [2] The compound or a pharmaceutically acceptable salt thereof according to [1],

[0278] wherein ring B is selected from the group consisting of (1) a pyridine, (2) a pyrimidine, (3) a pyrazine, and (4) a benzene;

[0279] (1) to (3) in ring B may be substituted by 1 to 4 R^3;

[0280] when two or more R^3s are substituted, a plurality of R^3s may be the same or different;

[0281] (4) in ring B may be substituted by 1 to 5 R^4;

[0282] when two or more R^4s are substituted, a plurality of R^4s may be the same or different;

[0283] and the other symbols are as defined in [1].

[0284] [3] The compound or a pharmaceutically acceptable salt thereof according to [1] or [2],

[0285] wherein ring C is selected from the group consisting of (1) a pyridine, (2) a pyrimidine, (3) a benzene, (4) a cyclopentane, and (5) a cyclohexane;

[0286] (1) or (2) in ring C may be substituted by 1 to 4 R^5;

[0287] when two or more R^5s are substituted, a plurality of R^5s may be the same or different;

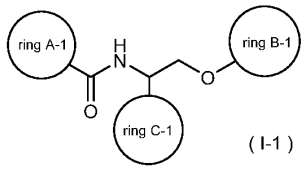
[0288] (3) to (5) in ring C may be substituted by 1 to 5 R^6;

[0289] when two or more R^6s are substituted, a plurality of R^6s may be the same or different;

[0290] and the other symbols are as defined in [1].

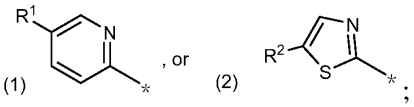
[0291] [4] The compound or a pharmaceutically acceptable salt thereof according to any one of [1] to [3],

[0292] wherein the compound is formula (I-1):



(I-1)

[0293] wherein ring A-1 is



;

[0294] ring B-1 is selected from the group consisting of (1) a pyridine, (2) a pyrimidine, (3) a pyrazine, and (4) a benzene;

[0295] (1) to (3) in ring B-1 may be substituted by 1 to 4 R^3;

[0296] when two or more R^3s are substituted, a plurality of R^3s may be the same or different;

[0297] (4) in ring B-1 may be substituted by 1 to 5 R^4;

[0298] when two or more R^4s are substituted, a plurality of R^4s may be the same or different;

[0299] ring C-1 is selected from the group consisting of (1) a pyridine, (2) a pyrimidine, (3) a benzene, (4) a cyclopentane, and (5) a cyclohexane;

[0300] (1) or (2) in ring C-1 may be substituted by 1 to 4 R^5;

[0301] when two or more R^5s are substituted, a plurality of R^5s may be the same or different;

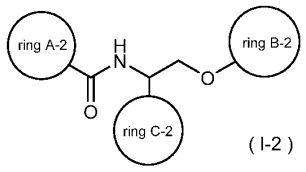
[0302] (3) to (5) in ring C-1 may be substituted by 1 to 5 R^6;

[0303] when two or more R^6s are substituted, a plurality of R^6s may be the same or different;

[0304] and the other symbols are as defined in [1].

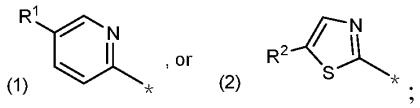
[0305] [5] The compound or a pharmaceutically acceptable salt thereof according to any one of [1] to [4],

[0306] wherein the compound is formula (I-2);



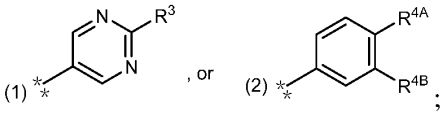
(I-2)

[0307] wherein ring A-2 is



;

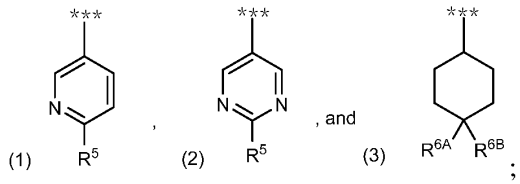
[0308] ring B-2 is



;

[0309] the ** mark represents a bonding position with an oxygen atom;

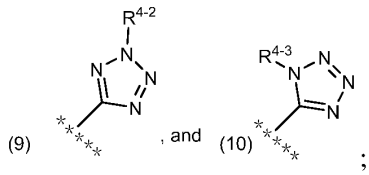
[0310] ring C-2 is selected from the group consisting of



;

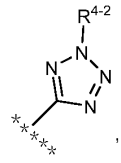
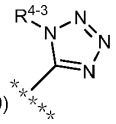
[0311] the *** mark represents a bonding position with a carbon atom;

[0312] R^{4A} is selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) C1-4 alkyl group, (4) C1-4 haloalkyl group, (5) C1-4 alkoxy group, (6) C1-4 haloalkoxy group, (7) cyano, (8) $S(=O)_2$-R^{4-1},



;

[0313] R^{4B} is selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) C1-4 alkyl group, (4) C1-4 haloalkyl group, (5) C1-4 alkoxy group, (6) C1-4 haloalkoxy group, (7) cyano, (8) $S(=O)_2$-R^{4-1},

(9)  , and (10) 

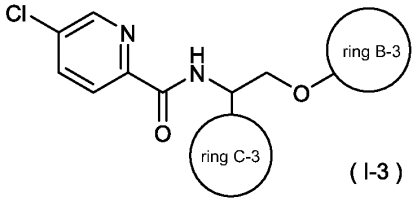
[0314] R^{6A} is selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) C1-4 alkyl group, (4) C1-4 haloalkyl group, (5) C1-4 alkoxy group and (6) C1-4 haloalkoxy group;

[0315] R^{6B} is selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) C1-4 alkyl group, (4) C1-4 haloalkyl group, (5) C1-4 alkoxy group and (6) C1-4 haloalkoxy group;

[0316] and the other symbols are as defined in [1].

[0317] [6] The compound or a pharmaceutically acceptable salt thereof according to any one of [1] to [5],

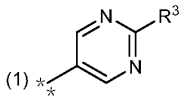
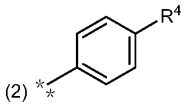
[0318] wherein the compound is formula (I-3):



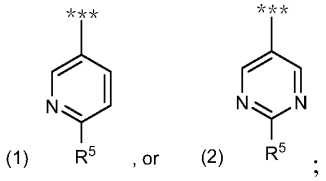
(I-3) ;

[0319] wherein

[0320] ring B-3 is

(1)  , or (2)  ;

[0321] ring C-3 is



;

[0322] the ** mark represents a bonding position with an oxygen atom;

[0323] the *** mark represents a bonding position with a carbon atom;

[0324] and the other symbols are as defined in [1].

[0325] [7] The compound or a pharmaceutically acceptable salt thereof according to any one of [1] to [6], wherein the compound is

[0326] (1) 5-chloro-N-{2-[4-(trifluoromethyl)phenoxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide;
[0327] (2) 5-chloro-N-(1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl)-2-pyridinecarboxamide;
[0328] (3) 5-chloro-N-[(1S)-1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-2-pyridinecarboxamide;
[0329] (4) 5-chloro-N-(1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl)-1,3-thiazole-2-carboxamide;
[0330] (5) 5-chloro-N-[(1ξ)-1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-1,3-thiazole-2-carboxamide;
[0331] (6) 5-chloro-N-{2-(4-chloro-3-fluorophenoxy)-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide;
[0332] (7) 5-chloro-N-{(1S)-2-(4-chloro-3-fluorophenoxy)-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide;
[0333] (8) 5-chloro-N-[1-(4,4-difluorocyclohexyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-2-pyridinecarboxamide;
[0334] (9) 5-chloro-N-[(1S)-1-(4,4-difluorocyclohexyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-2-pyridinecarboxamide;
[0335] (10) 5-chloro-N-[1-(4,4-difluorocyclohexyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-1,3-thiazole-2-carboxamide;
[0336] (11) 5-chloro-N-[(1ξ)-1-(4,4-difluorocyclohexyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-1,3-thiazole-2-carboxamide;
[0337] (12) 5-chloro-N-{2-(3-cyanophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide;
[0338] (13) 5-chloro-N-{(1ξ)-2-(3-cyanophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide;
[0339] (14) 5-chloro-N-{(1ξ)-2-(4-chloro-3-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide;
[0340] (15) 5-chloro-N-{2-(4-chlorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide, or
[0341] (16) 5-chloro-N-{(1S)-2-(4-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide.
[0342] [8] A pharmaceutical composition comprising the compound or a pharmaceutically acceptable salt thereof according to any one of [1] to [7].

[0343] [8-1] A pharmaceutical composition comprising the compound or a pharmaceutically acceptable salt thereof according to any one of [1] to [7] and a pharmaceutically acceptable carrier.
[0344] [9] The pharmaceutical composition according to [8] or [8-1], which is a prophylactic and/or therapeutic agent for an $S1P_3$-mediated disease.
[0345] [10] The pharmaceutical composition according to [9], wherein the $S1P_3$-mediated disease is neurodegenerative disease, cancer, liver disease, disease of endocrine and metabolic system, cardiac disease, or respiratory disorder.
[0346] [11] The pharmaceutical composition according to [10], wherein the neurodegenerative disease is Alzheimer's Disease, dementia, Amyotrophic Lateral Sclerosis, Multiple System Atrophy, spinal cord injury, Cerebrovascular disease, Alexander disease, Sandhoff disease or Mucopolysaccharidosis type III.
[0347] [11-1] The pharmaceutical composition according to [10], wherein the neurodegenerative disease is Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Multiple System Atrophy, spinal cord injury, Cerebrovascular disease, Alexander disease, Sandhoff disease or Mucopolysaccharidosis type III.
[0348]
[0349] [12] A method for preventing and/or treating an $S1P_3$-mediated disease comprising administering an effective amount of the compound or a pharmaceutically acceptable salt thereof according to any one of [1] to [7] to a mammal.
[0350] [13] The compound or a pharmaceutically acceptable salt thereof according to any one of [1] to [7] for use in preventing and/or treating an $S1P_3$-mediated disease.
[0351] [14] Use of the compound or a pharmaceutically acceptable salt thereof according to any one of [1] to [7] for manufacturing a prophylactic and/or therapeutic agent for an $S1P_3$-mediated disease.

EXAMPLES

[Synthesis Examples]
[0352] The solvent in parentheses shown in the description of the separation by chromatography and TLC indicates an eluting solvent or developing solvent used therefor, and the ratio represents the volume ratio.
[0353] The solvent in parentheses shown in the description of NMR indicates the solvent used for the measurement.
[0354] The present compounds and compounds described in Example are denominated according to the IUPAC nomenclature.

[0355] Naming according to the IUPAC nomenclature can be done using, for example, ACD/Name (Registered Trademark, version 2019.2.0, available from Advanced Chemistry Development Inc.), ACD/Name Batch (Registered Trademark, version 12.02.45356, available from Advanced Chemistry Development Inc.) or ChemDraw Professional (Registered Trademark, version 17.1.0.105 or 18.0.0.231, available from PerkinElmer Inc.).

[0356] In each of the following Examples, the name of the objective compound of the Example is described subsequently to the number of the Example, and the compound is sometimes referred to as the "title compound".

[0357] LCMS analysis conditions are as below. The MS data in Examples were measured by Reversed-phase LCMS method.

[0358] **Reversed-phase LCMS (A):**

[0359] Reversed-phase LCMS analysis was obtained on a SHIMADZU LC20-MS2010 with ESI source. MS parameters were as follows: Mobile Phase: 1.5 mL/4 L TFA in water (solvent A) and 0.75 mL/4 L TFA in acetonitrile (solvent B), using the elution gradient 5%-95% (solvent B) over 0.7 minutes, and holding at 95% for 0.4 minutes, at a flow rate of 1.5 ml/min; Column: Chromolith. Flash RP-18e 25-3mm; Wavelength: UV 220nm and 254nm; Column temperature: 50°C; MS ionization: ESI.

[0360] **Reversed-phase LCMS (B):**

[0361] Reversed-phase LCMS analysis was obtained on a SHIMADZU LCMS-2020 with ESI source. MS parameters were as follows: Mobile Phase: 0.1% TFA in water (solvent A) and 0.1% TFA in acetonitrile (solvent B), using the elution holding at 5% (solvent B) for 0.1 minutes, gradient 5%-95% (solvent B) over 1.1 minutes and holding at 95% for 0.4 minutes at a flow rate of 1.0 ml/min; Column: YMC Triart C18 Φ2.0 mm* L30mm; Wavelength: UV 220nm, 254nm; Column temperature: 30°C; detector MS, ELSD; MS ionization: ESI.

[0362] **Reversed-phase LCMS (C):**

[0363] Reversed-phase LCMS analysis was obtained on a SHIMADZU LC20-MS2010 with ESI source. MS parameters were as follows: Mobile Phase: 1.5 mL/4 L TFA in water (solvent A) and 0.75 mL/4 L TFA in acetonitrile (solvent B), using the elution gradient 5%-95% (solvent B) over 0.7 minutes, and holding at 95% for 0.4 minutes, at a flow rate of 1.5 ml/min; Column: MERCK, RP-18e 25-2mm; Wavelength: UV 220nm and 254nm; Column temperature: 50°C; MS ionization: ESI.

[0364] **Reversed-phase LCMS (D):**

[0365] Reversed-phase LCMS analysis was obtained on a SHIMADZU LC20-MS2010 with ESI source. MS parameters were as follows: Mobile Phase: 0.8 mL/4 L

$NH_3 \cdot H_2O$ in water (solvent A) and acetonitrile (solvent B), using the elution gradient 10%-80% (solvent B) over 2 minutes, and holding at 80% for 0.48 minutes, at a flow rate of 1.2 ml/min; Column: Xbridge Shield RP-18,5um,2.1x50mm; Wavelength: UV 220nm and 254nm; Column temperature: 50°C; MS ionization: ESI.

[0366] **Reversed-phase LCMS (E):**

[0367] Reversed-phase LCMS analysis was obtained on a SHIMADZU LCMS-2020 with ESI source. MS parameters were as follows: Mobile Phase: 0.1% formic acid in water (solvent A) and 0.1% formic acid in acetonitrile (solvent B), using the elution holding at 5% (solvent B) for 0.1 minutes, gradient 5%-95% (solvent B) over 1.1 minutes and holding at 95% for 0.4 minutes at a flow rate of 1.0 ml/min; Column: YMC Triart C18 Φ2.0 mm* L30mm; Wavelength: UV 220nm, 254nm; Column temperature: 30°C; detector MS, ELSD; MS ionization: ESI.

[0368] Reference Example 1

[0369] N-methoxy-N-methyl-2-[4-(trifluoromethyl)phenoxy]acetamide

[0370] To a solution of 2-chloro-N-methoxy-N-methylacetamide (382 mg) (CAS No.: 67442-07-3) and 4-hydroxybenzotrifluoride (300 mg) (CAS No.: 402-45-9) in N, N-dimethylformamide (DMF) (5 mL) was added potassium carbonate (512 mg). The reaction mixture was stirred at 20°C for 16 h to give a yellow solution. LCMS showed desired MS. The mixture was poured into water (10 mL) and extracted with ethyl acetate (30 mL x 2), the organic layer was washed by water (10 mL x3), brine (10 mL), dried with sodium sulfate and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 78 : 22) to give the title compound (481 mg).

[0371] LCMS (C) Retention time (min) : 0.839 ;

[0372] MS (ESI, Pos.) 264 $(M + H)^+$.

[0373] Reference Example 2

[0374] 2-[4-(trifluoromethyl)phenoxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethanone

[0375] To a solution of 5-bromo-2-(trifluoromethyl)pyridine (100 mg) (CAS No.: 436799-32-5) in tert-butyl methyl ether (MTBE) (2.5 mL) was added n-butyllithium (0.25 mL, 2.5M) drop-wise at -78°C. The reaction was stirred at -78°C for 20 min. The reaction was treated with a solution of the compound (120 mg) prepared in Reference Example 1 in MTBE (1 mL) dropwise at -78°C. The reaction was stirred at -78°C for 2 h. LCMS showed desired MS. The reaction was quenched with water (5 mL), diluted with ethyl acetate (8 mL). The organic layer was washed with water (5 mL) and brine (5 ml), then, dried over sodium sulfate, concentrated under reduced

pressure. The residue was purified by prep-TLC (petroleum ether: ethyl acetate = 6 : 1) to give the title compound (40 mg).

[0376] LCMS (C) Retention time (min) : 0.992 ;

[0377] MS (ESI, Pos.) 350 $(M + H)^+$.

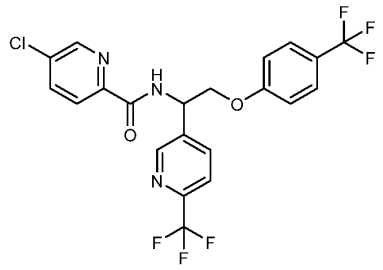
[0378] Reference Example 3

[0379] 2-[4-(trifluoromethyl)phenoxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethanamine

[0380] To a solution of the compound (40 mg) prepared in Reference Example 2 and ammonium acetate (88 mg) in methanol (2 mL) was added sodium cyanoborohydride (16 mg) at 25°C. The mixture was stirred at 65°C. LCMS showed desired MS. Water (5 mL) was poured into and extracted with ethyl acetate (10 mL x3), washed with water (5 mL), brine (5 mL), dried by sodium sulfate and concentrated under reduced pressure to give the title compound (30 mg).

[0381] Example 1

[0382] 5-chloro-N-{2-[4-(trifluoromethyl)phenoxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide



[0383] To a solution of the compound (30 mg) prepared in Reference Example 3, 5-chloro-2-pyridinecarboxylic acid (10 mg) (CAS No.: 86873-60-1) and N,N-diisopropylethylamine (DIEA) (0.03 mL) in DMF (1 mL) was added 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) (33 mg). The mixture was stirred at 20°C for 1 h to give a brown solution. LCMS showed desired MS. Water (5 mL) was poured into and extracted with ethyl acetate (10 mL x2). The organic layer was washed with water (5 mL x2), brine (5 mL), dried with sodium sulfate and concentrated under reduced pressure. The crude was purified by TLC (petroleum ether: ethyl acetate = 4 : 1) to give the title compound (3.9 mg) .

[0384] LCMS (C) Retention time (min) : 1.066 ;

[0385] MS (ESI, Pos.) 490 $(M + H)^+$;

[0386] ^{1}H-NMR(DMSO-d_6) : δ 9.70, 8.95, 8.74, 8.24, 8.14, 8.03, 7.94, 7.64, 7.16, 5.65, 4.65, 4.48.

[0387] Reference Example 4

[0388] 2-(3,5-difluorophenoxy)-N-methoxy-N-methylacetamide

[0389] To a solution of 3,5-difluorophenol (300 mg) (CAS No.: 2713-34-0) and in DMF (5 mL) was added potassium carbonate (510 mg), 2-chloro-N-methoxy-N-methylacetamide (270 mg). The reaction mixture was stirred at 25 °C for 16 h to give a yellow solution. The reaction was quenched with water (10 mL), extracted with ethyl acetate (20 mL x3). The organic layer was washed water (20 mL x4), brine (30 mL x2) and dried over sodium sulfate, concentrated. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 91 : 9) to give the title compound (530 mg).

[0390] ^{1}H-NMR($CDCl_3$) : δ 6.42-6.66, 4.80, 3.78, 3.25.

[0391] Reference Example 5

[0392] 2-(3,5-difluorophenoxy)-1-[6-(trifluoromethyl)-3-pyridinyl]ethanone

[0393] To a solution of 5-bromo-2-(trifluoromethyl)pyridine (100 mg) and N,N,N',N'-tetramethylethylenediamine (TMEDA) (0.07 mL) in MTBE (2 mL) was added n-butyllithium (0.23 mL, 2.5M in hexane) drop-wise at -78°C. The reaction was stirred at -78°C for 10 min. The reaction was treated with a solution of the compound (108 mg) prepared in Reference Example 4 in MTBE (1 mL) drop-wise at -78°C. The reaction was stirred at -78°C for 2 h to give a brown solution. The reaction was quenched with water (5 mL), extracted with ethyl acetate (5 mL x2). The organic layer was washed with water (5 mL) and brine (5 mL), then, dried over sodium sulfate, concentrated in vacuum to give crude residue. The residue was purified by prep-TLC (petroleum ether: ethyl acetate = 4 : 1) to give the title compound (30 mg).

[0394] LCMS (A) Retention time (min) : 0.859 ;

[0395] MS (ESI, Pos.) 318 $(M + H)^+$.

[0396] Reference Example 6

[0397] 2-(3,5-difluorophenoxy)-1-[6-(trifluoromethyl)-3-pyridinyl]ethanamine

[0398] To a solution of the compound (50 mg) prepared in Reference Example 5 in methanol (1 mL) was added ammonium acetate (133 mg) and sodium cyanoborohydride (26 mg), the mixture stirred at 70 °C for 2 h to give a yellow solution. LCMS showed the reaction was completed. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (5 mL x3). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to give the title compound (50 mg).

[0399] LCMS (A) Retention time (min) : 0.674 ;

[0400] MS (ESI, Pos.) *m/z* 360 $(M + CH_3CN + H)^+$.

[0401] Example 2

[0402] 5-chloro-N-{2-(3,5-difluorophenoxy)-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide

[0403] To a solution of 5-chloro-2-pyridinecarboxylic acid (18 mg) in DMF (1 mL) was added DIEA (0.06 mL), HATU (60 mL) and the compound (50 mg) prepared in Reference Example 6. The mixture was stirred at 20 °C for 1 h to give a brown solution. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (5 mL x3). The combined organic layers were washed with water (5 mL x4) and brine (5 mL x2), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (petroleum ether: ethyl acetate = 1 : 1) and then lyophilized to give the title compound (10.3 mg).

[0404] LCMS (D) Retention time (min) : 2.185 ;

[0405] MS (ESI, Pos.) 458 $(M + H)^+$;

[0406] ^{1}H-NMR($CDCl_3$) : δ 8.86, 8.71, 8.54, 8.13, 7.99, 7.86, 7.70, 6.42 - 6.52, 5.65, 4.31 - 4.45.

[0407] Reference Example 7

[0408] N-methoxy-N-methyl-2-[(2-methyl-5-pyrimidinyl)oxy]acetamide

[0409] To a solution of 2-methylpyrimidine-5-ol (1 g) (CAS No.: 35231-56-2) and in acetonitrile (10 mL) was added potassium carbonate (2.5 g), 2-chloro-N-methoxy-N-methylacetamide (1.5 g). The reaction mixture was stirred at 50°C for 16 h to give a white mixture. The reaction mixture was diluted with dichloromethane (5 mL) and filtered. The filtrate was concentrated. The residue was triturated with ethyl acetate/petroleum ether/dichloromethane (10 mL/10 mL/10 mL) and dried in air to give the title compound (500 mg). The mother liquor was concentrated and purified by silica gel column chromatography (dichloromethane : ethyl acetate = 20 : 80) to give the title compound (1.3 g, impure).

[0410] ^{1}H-NMR(DMSO-d_6) : δ 8.39, 5.08, 3.75, 3.12, 2.54.

[0411] Reference Example 8

[0412] 2-[(2-methyl-5-pyrimidinyl)oxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethanone

[0413] To a solution of 5-bromo-2-(trifluoromethyl)pyridine (600 mg) in tetrahydrofuran (THF) (3.3 mL) was added isopropylmagnesiumchloride lithiumchloride complex (iPrMgCl·LiCl) (2.0 mL, 1.3M in THF) at 0°C. The mixture was stirred at 0°C for 2 h to give a mixture. The compound (280 mg) prepared in Reference Example 7 in THF (3 mL) was added to the above mixture. The reaction mixture was stirred at 0°C for 1 h to give a yellow solution. The reaction was quenched with water (5 mL), extracted with ethyl acetate (10 mL x3). The organic

layer was washed with brine (10 mL), then, dried over sodium sulfate, concentrated in vacuum to give crude residue. The residue was purified by silica gel column chromatography (40~60% ethyl acetate in dichloromethane) to give the title compound (210 mg).

[0414] LCMS (C) Retention time (min) : 0.795 ;

[0415] MS (ESI, Pos.) 298 $(M + H)^+$.

[0416] Reference Example 9

[0417] 2-[(2-methyl-5-pyrimidinyl)oxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethanamine

[0418] To a solution of the compound (500 mg) prepared in Reference Example 8 in methanol (6 mL) was added ammonium acetate (1.3 g) and the mixture was stirred at 40°C for 1 h. Then sodium cyanoborohydride (212 mg) was added. The mixture stirred at 40°C for 1 h to give a yellow solution. The reaction was concentrated in vacuum. The residue was diluted with water (10 mL) and extracted with ethyl acetate (10 mL x3). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (dichloromethane : ethyl acetate = 30 : 70 → dichloromethane : methanol = 90 : 10) to give the title compound (250 mg).

[0419] ^{1}H-NMR(DMSO-d_6) : δ 8.85, 8.42, 8.16 - 8.18, 7.89, 4.39-4.42, 4.19 - 4.25, 2.53.

[0420] Reference Example 10

[0421] 5-chloro-N-{2-[(2-methyl-5-pyrimidinyl)oxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide

[0422] To a solution of the compound (250 mg) prepared in Reference Example 9 and 5-chloro-2-pyridinecarboxylic acid (159 mg) in DMF (4 mL) was added DIEA (0.27 mL) at 0°C for 10 min. Then, the solution was treated with HATU (383 mg) at 0°C. The mixture was stirred at 0°C for 1 h to give a brown solution. The reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (15 mL x3). The combined organic layers were washed with water (15 mL x4) and brine (20 mL x2), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : ethyl acetate = 50 : 50) to give the title compound (280 mg).

[0423] LCMS (C) Retention time (min) : 0.870 ;

[0424] MS (ESI, Pos.) 438 $(M + H)^+$;

[0425] ^{1}H-NMR($CDCl_3$) : δ 8.89, 8.73, 8.55, 8.36, 8.15, 7.98 - 8.04, 7.87, 7.73, 5.65 - 5.76, 4.51, 2.69.

[0426] Example 3

[0427] 5-chloro-N-{(1ξ)-2-[(2-methyl-5-pyrimidinyl)oxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide

[0428] The compound (100 mg) prepared in Reference Example 10 was separated by supercritical fluid chromatography (SFC) to give two isomers.

[0429] SFC was carried out under the following condition.

[0430] Column: Chiralpak AD-3 50x4.6mm I.D., 3μm;

[0431] Mobile phase: A: CO_2, B: ethanol (0.05% DEA);

[0432] Gradient: from 5% to 40% of B in 2 min and hold 40% for 1.2 min, then 5% of B for 0.8 min;

[0433] Flow rate: 4 mL/min;

[0434] Column temperature: 35°C;

[0435] Back pressure regulator (BPR): 1500 psi.

[0436] Whereby the title compound (48 mg) was obtained in the first peak (retention time : 2.07 min).

[0437] LCMS (C) Retention time (min) : 0.883 ;

[0438] MS (ESI, Pos.) 438 $(M + H)^+$;

[0439] ^{1}H-NMR($CDCl_3$) : δ 8.88, 8.73, 8.55, 8.36, 8.15, 8.01, 7.87, 7.73, 5.64 - 5.76, 4.46 - 4.55, 2.69.

[0440] Reference Example 11

[0441] 2-(4-chloro-3-fluorophenoxy)-N-methoxy-N-methylacetamide

[0442] 4-chloro-3-fluorophenol (200 mg) (CAS No.: 348-60-7) was used instead of 4-hydroxybenzotrifluoride and subjected to the same reaction as in Reference Example 1 to give the title compound (300 mg).

[0443] LCMS (C) Retention time (min) : 0.857 ;

[0444] MS (ESI, Pos.) 248 $(M + H)^+$.

[0445] Reference Example 12

[0446] 2-(4-chloro-3-fluorophenoxy)-1-[6-(trifluoromethyl)-3-pyridinyl]ethanone

[0447] The compound (365 mg) prepared in Reference Example 11 was used instead of the compound prepared in Reference Example 7 and subjected to the same reaction as in Reference Example 8 to give the title compound (214 mg).

[0448] LCMS (C) Retention time (min) : 0.986 ;

[0449] MS (ESI, Pos.) *m/z* 375 $(M + CH_3CN + H)^+$.

[0450] Reference Example 13

[0451] 2-(4-chloro-3-fluorophenoxy)-1-[6-(trifluoromethyl)-3-pyridinyl]ethanamine

[0452] The compound (214 mg) prepared in Reference Example 12 was used instead of the compound prepared in Reference Example 8 and subjected to the same reaction as in Reference Example 9 to give the title compound (50 mg).

[0453] LCMS (A) Retention time (min) : 0.700 ;

[0454] MS (ESI, Pos.) 335 $(M + H)^+$.

[0455] Example 4

[0456] N-{2-(4-chloro-3-fluorophenoxy)-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-5-fluoro-2-pyridinecarboxamide

[0457] To a solution of 5-fluoro-2-pyridinecarboxylic acid (26 mg) (CAS No.: 107504-08-5) in DMF (1 mL) was added DIEA (0.07 mL) and HATU (69 mg) at 25°C. The reaction mixture was stirred for 10 min. Then, the compound (50 mg) prepared in Reference Example 13 was added. The reaction mixture was stirred for 1 h at 25°C to give a yellow solution. LCMS showed that the starting material was consumed completely. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (5 mL x3). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over sodium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (petroleum ether: ethyl acetate = 6 : 1) to give the title compound (54.8 mg).

[0458] LCMS (A) Retention time (min) : 0.944 ;

[0459] MS (ESI, Pos.) 458 $(M + H)^+$;

[0460] ^{1}H-NMR(DMSO-d_6) : δ 9.33, 8.91, 8.65, 8.22, 8.11, 7.84 - 7.93, 7.43, 7.08, 6.85, 5.54 - 5.67, 4.57 - 4.65, 4.49.

[0461] Reference Example 14

[0462] N-methoxy-N-methyl-2-{[2-(trifluoromethyl)-4-pyridinyl]oxy}acetamide

[0463] 2-(trifluoromethyl)pyridine-4-ol (1 g) (CAS No.: 170886-13-2) was used instead of 4-hydroxybenzotrifluoride and subjected to the same reaction as in Reference Example 1 to give the title compound (1.5 g).

[0464] ^{1}H-NMR(DMSO-d_6) : δ 8.51 - 8.59, 7.43 - 7.47, 7.24 - 7.27, 5.19, 3.77, 3.13.

[0465] Reference Example 15

[0466] 1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-4-pyridinyl]oxy}ethanone

[0467] The compound (1.5 g) prepared in Reference Example 14 was used instead of the compound prepared in Reference Example 7 and subjected to the same reaction as in Reference Example 8 to give the title compound (1.4 g).

[0468] ^{1}H-NMR(DMSO-d_6) : δ 9.32 - 9.33, 8.60 - 8.64, 8.16, 7.61 - 7.64, 7.38 - 7.40, 5.95.

[0469] Reference Example 16

[0470] 1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-4-pyridinyl]oxy}ethanamine

[0471] The compound (1 g) prepared in Reference Example 15 was used instead of the compound prepared in Reference Example 5 and subjected to the same reaction as in Reference Example 6 to give the title compound (440 mg).

[0472] LCMS (C) Retention time (min) : 0.762 ;

[0473] MS (ESI, Pos.) 352 $(M + H)^+$.

[0474] Example 5

[0475] 5-chloro-N-(1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-4-pyridinyl]oxy}ethyl)-2-pyridinecarboxamide

[0476] The compound (200 mg) prepared in Reference Example 16 was used instead of the compound prepared in Reference Example 6 and subjected to the same reaction as in Example 2 to give the title compound (180 mg).

[0477] LCMS (C) Retention time (min) : 0.979 ;

[0478] MS (ESI, Pos.) 491 $(M + H)^+$;

[0479] ^{1}H-NMR(DMSO-d_6) : δ 9.77, 8.96, 8.74, 8.56, 8.24, 8.15, 8.03, 7.95, 7.52, 7.32, 5.68, 4.77, 4.58.

[0480] Example 6

[0481] 5-chloro-N-[(1ξ)-1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-4-pyridinyl]oxy}ethyl]-2-pyridinecarboxamide

[0482] The compound (180 mg) prepared in Example 5 was separated by SFC to give two isomers.

[0483] SFC was carried out under the following condition.

[0484] Column: Chiralpak AD-3 50x4.6mm I.D., 3μm;

[0485] Mobile phase: A: CO_2, B: ethanol (0.05% DEA);

[0486] Gradient: from 5% to 40% of B in 2 min and hold 40% for 1.2 min, then 5% of B for 0.8 min;

[0487] Flow rate: 4 mL/min;

[0488] Column temperature: 35°C;

[0489] BPR: 1500 psi.

[0490] Whereby the title compound (62.7 mg) was obtained in the first peak (retention time : 1.13 min).

[0491] LCMS (C) Retention time (min) : 0.990 ;

[0492] MS (ESI, Pos.) 491 $(M + H)^+$;

[0493] ^{1}H-NMR(DMSO-d_6) : δ 9.75, 8.96, 8.75, 8.57, 8.25, 8.15, 8.04, 7.96, 7.52, 7.33, 5.69, 4.78, 4.60.

[0494] Reference Example 17

[0495] N-methoxy-N-methyl-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}acetamide

[0496] To a solution of 2-(trifluoromethyl)pyrimidine-5-ol (2 g) (CAS No.: 100991-09-1) and in DMF (25 mL) was added potassium carbonate (3.4 g), 2-chloro-N-methoxy-N-methylacetamide (2 mL). The reaction mixture was stirred at 25°C for 16 h to give a white mixture. LCMS showed part of reactant remained. Then the mixture stirred at 40°C for 2 h to give a white mixture. The reaction was diluted with water (40 mL) and ethyl acetate (50 mL x3). The organic layer was washed with water (50 mL x3) and brine (50 mL x2), dried over sodium sulfate, concentrated in vacuum to give crude oil. The residue was purified by silica gel column chromatography (25-50% ethyl acetate in petroleum ether) to give the title compound (2.65 g).

[0497] LCMS (C) Retention time (min) : 0.773 ;

[0498] MS (ESI, Pos.) 266 $(M + H)^+$;

[0499] Reference Example 18

[0500] 1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethanone

[0501] To a solution of 5-bromo-2-(trifluoromethyl)pyridine (1.73 g) in THF (9.3 mL) was added iPrMgCl.LiCl (5.9 mL, 1.3M in THF) at 0°C. The mixture was stirred at 0°C for 2 h. The compound (1.35 g) prepared in Reference Example 17 in THF (10 mL) was added the above mixture. The reaction mixture was stirred at 0°C for 1 h to give a yellow solution. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x3). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was combined with another batch for purification. The crude product was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 80 : 20) to give the title compound (2 g).

[0502] ^{1}H-NMR($CDCl_3$) : δ 9.28, 8.55, 8.45 - 8.48, 7.91, 5.52.

[0503] Reference Example 19

[0504] 1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethanamine

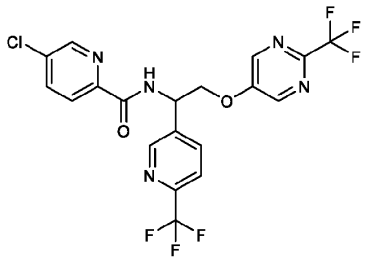
[0505] To a solution of the compound (2 g) prepared in Reference Example 18 in methanol (18 mL) was added ammonium acetate (4.39 g) and sodium cyanoborohydride (716 mg), the mixture stirred at 40°C for 1 h to give a yellow solution. The reaction mixture was concentrated. The crude product was purified by silica gel column

chromatography (15-25% ethyl acetate in petroleum ether) to give the crude compound (1000 mg). The crude compound was purified by silica gel column chromatography (ethyl acetate : methanol = 95 : 5) to give the title compound (600 mg).

[0506] ^{1}H-NMR($CDCl_3$) : δ 8.87, 8.51, 8.06 - 8.08, 7.75, 4.69 - 4.72, 4.26 - 4.33.

[0507] Example 7

[0508] 5-chloro-N-(1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl)-2-pyridinecarboxamide



[0509] To a solution of 5-chloro-2-pyridinecarboxylic acid (407 mg) in DMF (15 mL) was added DIEA (0.89 mL), HATU (983 mg) and the compound (1.3 g) prepared in Reference Example 19. The mixture was stirred at 20°C for 1 h to give a brown solution. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x3). The combined organic layers were washed with water (30 mL x3) and brine (50 mL x2), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was combined with another batch for purification. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 80 : 20 → dichloromethane : ethyl acetate = 80 : 20) to give the title compound (1.19 g).

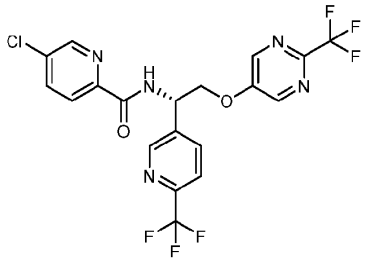
[0510] LCMS (C) Retention time (min) : 0.979 ;

[0511] MS (ESI, Pos.) 492 $(M + H)^+$;

[0512] ^{1}H-NMR($CDCl_3$) : δ 8.90, 8.69, 8.57, 8.54, 8.16, 7.99 - 8.06, 7.88, 7.76, 5.73 - 5.80, 4.64.

[0513] Example 8

[0514] 5-chloro-N-[(1S)-1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-2-pyridinecarboxamide



[0515] The compound (1 g) prepared in Example 7 was separated by SFC to give two isomers.

[0516] SFC was carried out under the following condition.

[0517] Column: Chiralcel OJ-3 100x4.6mm I.D., 3μm;

[0518] Mobile phase: A: CO_2, B: ethanol (0.05% DEA);

[0519] Isocratic: 40%B

[0520] Flow rate: 2.8 mL/min;

[0521] Column temperature: 35°C;

[0522] BPR: 1500 psi.

[0523] Whereby the title compound (419 mg) was obtained in the first peak (retention time : 1.07 min) .

[0524] LCMS (C) Retention time (min) : 0.980 ;

[0525] MS (ESI, Pos.) 492 $(M + H)^+$;

[0526] ^{1}H-NMR($CDCl_3$) : δ 8.89, 8.68, 8.51 - 8.58, 8.15, 8.01, 7.87, 7.75, 5.71 - 5.80, 4.63.

[0527] Example 9

[0528] 5-fluoro-N-(1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl)-2-pyridinecarboxamide

[0529] To a solution of 5-fluoro-2-pyridinecarboxylic acid (58 mg), the compound (120 mg) prepared in Reference Example 19 and DIEA (0.12 mL) in DMF (1 mL) was added HATU (156 mg) at 0°C. The reaction was stirred at 0°C for 2 h to give brown solution. The reaction was diluted with ethyl acetate (5 mL) and water (5 mL). The organic layer was washed with water (5 mL x2) and brine (5 mL), then dried over sodium sulfate, concentrated in vacuum to give crude residue, which was purified by prep-TLC (petroleum ether: ethyl acetate = 2 : 1) to give the title compound (98.5 mg).

[0530] LCMS (C) Retention time (min) : 0.946 ;

[0531] MS (ESI, Pos.) 476 $(M + H)^+$;

[0532] ^{1}H-NMR(DMSO-d_6) : δ 9.72, 8.97, 8.83, 8.69, 8.26, 8.11, 7.89 - 7.98, 5.71, 4.85, 4.68.

[0533] Example 10

[0534] 5-methyl-N-(1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl)-2-pyridinecarboxamide

[0535] A solution of 5-methy-2-pyridinecarboxylic acid (47 mg) (CAS No.: 4434-13-3), DIEA (74 mg) and HATU (130 mg) in DMF (2 mL) was stirred at 20°C for 10 min. Then, the solution was treated with the compound (100 mg) prepared in Reference Example 19. The reaction was stirred at 20°C for 2 h to give pale yellow solution. The reaction was diluted with ethyl acetate (6 mL) and water (6 mL). The organic layer was washed with water (6 mL x 2) and brine (6 mL). The organic layer was dried over sodium sulfate, concentrated in vacuum to give crude residue, which was purified by prep-TLC (petroleum ether: ethyl acetate = 1 : 1) to give the title compound (88.2 mg).

[0536] LCMS (C) Retention time (min) : 0.954 ;

[0537] MS (ESI, Pos.) 472 $(M + H)^+$;

[0538] ^{1}H-NMR(DMSO-d_6) : δ 9.68, 8.96, 8.82, 8.52, 8.25, 7.89 - 7.98, 7.82, 5.66 - 5.75, 4.85, 4.68, 2.39.

[0539] Example 11

[0540] N-(1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl)-1,3-thiazole-2-carboxamide

[0541] To a solution of the compound (100 mg) prepared in Reference Example 19, thiazole-2-carboxylic acid (48 mg) (CAS No.: 14190-59-1), DIEA (0.14 mL) in DMF (1 mL) was added HATU (142 mg) at 0°C. The reaction mixture was stirred for 1 h at 0°C. LCMS showed desired MS. The reaction mixture was diluted with water (3 mL) and extracted with ethyl acetate (3 mL x3). The combined organic layers were washed with water (5 mL x2) and brine (3 mL), dried over sodium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (petroleum ether: ethyl acetate = 5 : 1) to give the title compound (60.8 mg).

[0542] LCMS (C) Retention time (min) : 0.915 ;

[0543] MS (ESI, Pos.) 464 $(M + H)^+$;

[0544] ^{1}H-NMR(DMSO-d_6) : δ 9.87, 8.97, 8.84, 8.26, 8.09 - 8.12, 8.05 - 8.07, 7.98, 5.69, 4.80, 4.65.

[0545] Reference Example 20

[0546] methyl 5-chloro-1,3-thiazole-2-carboxylate

[0547] To a solution of 2-bromo-5-chlorothiazole (3 g) (CAS No.: 16629-15-5) in methanol (90 mL) was added 1,1'-bis(diphenylphosphino)ferrocene (0.84 g) (CAS No.: 12150-46-8), triethylamine (3.2 mL), palladium(II) acetate (0.68 g) was stirred at 60 ºC.

The reaction was stirred at 60°C for 24 h under CO at 45 Psi. LCMS showed the reaction was completed. The mixture was thermally filtered and washed with methanol (45 mL x2). The filtrate was concentrated. The mixture was diluted with water (60 mL), extracted by dichloromethane (50 mL x3), the organic layer was washed with brine (40 mL x3) and concentrated. The crude product was purified by silica gel column chromatography (0 to 3% ethyl acetate in petroleum ether) to give the title compound (3.2 g).

[0548] LCMS (C) Retention time (min) : 0.756 ;

[0549] MS (ESI, Pos.) 178 $(M + H)^+$.

[0550] Reference Example 21

[0551] lithium 5-chloro-1,3-thiazole-2-carboxylate

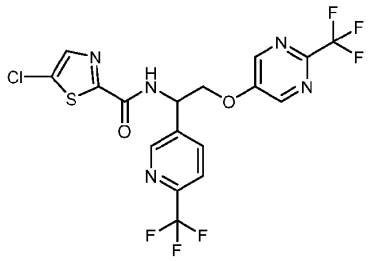
[0552] To a solution of the compound (3.1 g) prepared in Reference Example 20 in THF (66 mL) and water (17 mL) were added lithium hydroxide (788 mg) at 0°C. The reaction was stirred at 20°C for 12 h. LCMS showed the desired MS. The reaction was concentrated. Then the reaction was lyophilizated to give the title compound (3 g).

[0553] LCMS (B) Retention time (min) : 0.686 ;

[0554] ^{1}H-NMR(DMSO-d_6) : δ 7.66.

[0555] Example 12

[0556] 5-chloro-N-(1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl)-1,3-thiazole-2-carboxamide



[0557] To a solution of the compound (120 mg) prepared in Reference Example 21 in DMF (2.5 mL) was added DIEA (0.24 mL), HATU (270 mg) and the compound (250 mg) prepared in Reference Example 19. The mixture was stirred at 20°C for 1 h to give a brown solution. Then the compound (60 mg) prepared in Reference Example 21, HATU (135 mg) was added and stirred at 20°C for 1 h to give a brown solution. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (10 mL x3). The combined organic layers were washed with water (15 mL x3) and brine (15 mL x2), dried over sodium sulfate, filtered and concentrated under reduced pressure.

The residue was combined with another batch for purification. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 80 : 20) to give the title compound (280 mg).

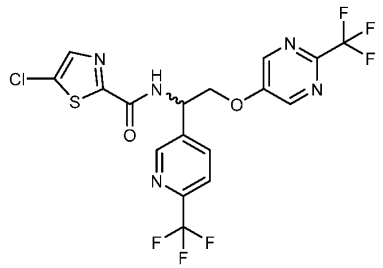
[0558] LCMS (C) Retention time (min) : 0.997 ;

[0559] MS (ESI, Pos.) 498 $(M + H)^+$;

[0560] ^{1}H-NMR($CDCl_3$) : δ 8.88, 8.56, 8.00, 7.88, 7.75, 7.70, 5.65 - 5.78, 4.56 - 4.67.

[0561] Example 13

[0562] 5-chloro-N-[(1ξ)-1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-1,3-thiazole-2-carboxamide



[0563] The compound (960 mg) prepared in Example 12 was separated by SFC to give two isomers.

[0564] SFC was carried out under the following condition.

[0565] Column: Chiralcel OD-3 150x4.6mm I.D., 3μm;

[0566] Mobile phase: A: CO_2, B: ethanol (0.05% DEA);

[0567] Gradient: from 5% to 40% of B in 4 min and from 40% to 5% of B in 0.2 min, hold 5% of B for 1.8 min;

[0568] Flow rate: 2.5 mL/min;

[0569] Column temperature: 35°C;

[0570] BPR: 1500 psi.

[0571] Whereby the title compound (336 mg) was obtained in the first peak (retention time : 3.81 min) .

[0572] LCMS (C) Retention time (min) : 0.993 ;

[0573] MS (ESI, Pos.) 498 $(M + H)^+$;

[0574] ^{1}H-NMR($CDCl_3$) : δ 8.87, 8.56, 8.00, 7.90, 7.75, 7.70, 5.67 - 5.76, 4.58 - 4.65.

[0575] Reference Example 22

[0576] 1-[2-(trifluoromethyl)-4-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethanone

[0577] 4-bromo-2-(trifluoromethyl) pyridine (CAS No.: 887583-90-6) (1.7 g) was used instead of 5-bromo-2-(trifluoromethyl)pyridine and subjected to the same reaction as in Reference Example 18 to give the title compound (1 g).

[0578] ^{1}H-NMR($CDCl_3$) : δ 9.03 - 9.04, 8.55, 8.14, 7.94 - 7.98, 5.55.

[0579] Reference Example 23

[0580] 1-[2-(trifluoromethyl)-4-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethanamine

[0581] To a solution of the compound (1 g) prepared in Reference Example 22 in methanol (10 mL) was added ammonium acetate (2.2 g) and the mixture was stirred at 40°C for 1 h. Then sodium cyanoborohydride (358 mg). The mixture stirred at 20°C for 1 h to give a yellow solution. The reaction was concentrated directly. The residue was diluted with water (5 mL) and extracted with ethyl acetate (5 mL x3). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate : methanol = 95 : 5) to give the title compound (580 mg).

[0582] LCMS (C) Retention time (min) : 0.751 ;

[0583] MS (ESI, Pos.) 353 $(M + H)^+$.

[0584] Example 14

[0585] 5-chloro-N-(1-[2-(trifluoromethyl)-4-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl)-1,3-thiazole-2-carboxamide

[0586] The compound (300 mg) prepared in Reference Example 23 was used instead of the compound prepared in Reference Example 19 and subjected to the same reaction as in Example 12 to give the title compound (275 mg).

[0587] LCMS (C) Retention time (min) : 0.981 ;

[0588] MS (ESI, Pos.) 498 $(M + H)^+$;

[0589] ^{1}H-NMR($CDCl_3$) : δ 8.80, 8.55, 7.90, 7.74, 7.59, 5.64 - 5.74, 4.60.

[0590] Example 15

[0591] 5-chloro-N-[(1ξ)-1-[2-(trifluoromethyl)-4-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-1,3-thiazole-2-carboxamide

[0592] The compound (190 mg) prepared in Example 14 was separated by SFC to give two isomers.

[0593] SFC was carried out under the following condition.

[0594] Column: Chiralpak AD-3 50x4.6mm I.D., 3μm;

[0595] Mobile phase: A: CO_2, B: ethanol (0.05% DEA);

[0596] Gradient: from 5% to 40% of B in 2 min and hold 40% for 1.2 min, then 5% of B for 0.8 min;

[0597] Flow rate: 4 mL/min;

[0598] Column temperature: 35°C;

[0599] BPR: 1500 psi.

[0600] Whereby the title compound (68 mg) was obtained in the second peak (retention time : 1.18 min) .

[0601] LCMS (C) Retention time (min) : 0.990 ;

[0602] MS (ESI, Pos.) 498 $(M + H)^+$;

[0603] ^{1}H-NMR($CDCl_3$) : δ 8.81, 8.56, 7.93, 7.71 - 7.81, 7.60, 5.63 - 5.76, 4.61.

[0604] Reference Example 24

[0605] 5-chloro-N-(1-[2-(trifluoromethyl)-4-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl)-2-pyridinecarboxamide

[0606] To a solution of the compound (300 mg) prepared in Reference Example 23 and 5-chloro-2-pyridinecarboxylic acid (148 mg) in DMF (3 mL) was added DIEA (0.29 mL), HATU (357 mg) at 0°C. The mixture was stirred at 0°C for 1 h to give a brown solution. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (5 mL x3). The combined organic layers were washed with water (5 mL x4) and brine (10 mL x2), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 80 : 20) to give the title compound (300 mg).

[0607] LCMS (C) Retention time (min) : 0.976 ;

[0608] MS (ESI, Pos.) 492 $(M + H)^+$;

[0609] ^{1}H-NMR($CDCl_3$) : δ 8.79, 8.70, 8.56, 8.16, 7.89, 7.77, 7.61, 5.70 - 5.76, 4.61.

[0610] Example 16

[0611] 5-chloro-N-[(1ξ)-1-[2-(trifluoromethyl)-4-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-2-pyridinecarboxamide

[0612] The compound (100 mg) prepared in Reference Example 24 was separated by SFC to give two isomers.

[0613] SFC was carried out under the following condition.

[0614] Column: Chiralpak AD-3 150x4.6mm I.D., 3μm;

[0615] Mobile phase: A: CO_2, B: ethanol (0.05% DEA);

[0616] Gradient: from 5% to 40% of B in 4.5 min and then 40% of B for 2 min, and 5% of B for 1.5 min;

[0617] Flow rate: 2.5 mL/min;

[0618] Column temperature: 40°C;

[0619] BPR: 100 bar.

[0620] Whereby the title compound (42 mg) was obtained in the second peak (retention time : 5.00 min).

[0621] LCMS (C) Retention time (min) : 0.984 ;

[0622] MS (ESI, Pos.) 492 $(M + H)^+$;

[0623] ^{1}H-NMR($CDCl_3$) : δ 8.80, 8.72, 8.57, 8.17, 7.90, 7.78, 7.62, 5.70 - 5.79, 4.62.

[0624] Reference Example 25

[0625] 2-[3-chloro-4-(methylthio)phenoxy]-N-methoxy-N-methylacetamide

[0626] To a solution of 3-chloro-4-(methylthio)phenol (200 mg) (CAS No.: 13560-43-5) and in DMF (3 mL) was added potassium carbonate (317 mg), 2-chloro-N-methoxy-N-methylacetamide (220 mg). The reaction mixture was stirred at 20 ℃ for 16 h to give a yellow solution. The reaction was quenched with water (5 mL), extracted with ethyl acetate (5 mL x3). The organic layer was washed water (5 mL x4), brine (5 mL x2) and dried over sodium sulfate, concentrated. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 78 : 22) to give the title compound (300 mg).

[0627] ^{1}H-NMR($CDCl_3$) : δ 7.16 - 7.26, 6.98 - 6.99, 6.86, 4.79, 3.76, 3.24, 2.47.

[0628] Reference Example 26

[0629] 2-[3-chloro-4-(methylthio)phenoxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethanone

[0630] To a solution of 5-bromo-2-(trifluoromethyl) pyridine (160 mg) and TMEDA (0.1 mL) in MTBE (1 mL) were added n-butyllithium (0.37 mL, 2.5M) drop-wise at -78°C. The reaction was stirred at -78°C for 10 min. Then, the reaction was treated with a solution of the compound (207 mg) prepared in Reference Example 25 in MTBE (2.5 mL) drop-wise at -78°C. The reaction was stirred at -78°C for 2 h to give a brown solution. The reaction was quenched with water (5 mL), extracted with ethyl acetate (5 mL x2). The organic layer was washed with water (5 mL) and brine (5 mL), then, dried over sodium sulfate, concentrated in vacuum to give crude residue. The residue was purified by prep-TLC (petroleum ether: ethyl acetate = 3 : 1) to give the title compound (30 mg).

[0631] LCMS (C) Retention time (min) : 0.993 ;

[0632] MS (ESI, Pos.) 362 $(M + H)^+$;

[0633] Reference Example 27

[0634] 2-[3-chloro-4-(methylthio)phenoxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethanamine

[0635] To a solution of the compound (65 mg) prepared in Reference Example 26 in methanol (1.5 mL) was added ammonium acetate (151 mg) and sodium

cyanoborohydride (30 mg), the mixture stirred at 65 °C for 2 h to give a yellow solution. LCMS showed the reaction was completed. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (5 mL x3). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to give the title compound (70 mg).

[0636] LCMS (A) Retention time (min) : 0.723 ;

[0637] MS (ESI, Pos.) *m/z* 404 $(M + CH_3CN + H)^+$.

[0638] Reference Example 28

[0639] 5-chloro-N-{2-[3-chloro-4-(methylthio)phenoxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide

[0640] To a solution of 5-chloro-2-pyridinecarboxylic acid (22 mg) in DMF (1 mL) was added DIEA (0.07 mL), HATU (74 mg) and the compound (70 mg) prepared in Reference Example 27, the mixture was stirred at 20°C for 1 h to give a brown solution. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (5 mL x3). The combined organic layers were washed with water (5 mL x4) and brine (5 mL x2), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (petroleum ether: ethyl acetate = 3 : 1) to give the title compound (25 mg).

[0641] LCMS (C) Retention time (min) : 1.067 ;

[0642] MS (ESI, Pos.) 502 $(M + H)^+$.

[0643] Example 17

[0644] 5-chloro-N-{2-[3-chloro-4-(methylsulfonyl)phenoxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide

[0645] To a solution of the compound (25 mg) prepared in Reference Example 28 in 1-propanol (1 mL) and water (0.1 mL) was added oxone (16 mg) at 0°C. After stirred at 0°C for 1 h, and oxone (16 mg) was added and the reaction was stirred at 0°C for further 5 h to give pale yellow mixture. LCMS showed sulfoxide as the majority. Then oxone (16 mg) was added, the mixture stirred at 0°C for 4 h to give pale yellow mixture. TLC (petroleum ether: ethyl acetate = 1 : 1) showed the sulfoxide as the major. Then oxone (16 mg) was added, the mixture stirred at 0°C for 6 h to give pale yellow mixture. LCMS showed the desired MS as the majority. The reaction was diluted with ethyl acetate (10 mL), washed with water (10 mL) and brine (10 mL). The organic layer was purified by prep-TLC (petroleum ether: ethyl acetate = 1 : 1) to give the title compound (10.47 mg).

[0646] LCMS (C) Retention time (min) : 0.944 ;

[0647] MS (ESI, Pos.) 534 $(M + H)^+$;

[0648] ^{1}H-NMR($CDCl_3$) : δ 8.87, 8.68, 8.54, 8.06 - 8.16, 7.99, 7.87, 7.72, 7.12, 6.98, 5.65 - 5.75, 4.44 - 4.55, 3.22.

[0649] Reference Example 29

[0650] 5-chloro-N-{2-[3-chloro-4-(methylthio)phenoxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-1,3-thiazole-2-carboxamide

[0651] The compound (36 mg) prepared in Reference Example 21 was used instead of 5-chloropyridine-2-carboxylic acid and subjected to the same reaction as in Reference Example 28 to give the title compound (50 mg).

[0652] LCMS (C) Retention time (min) : 1.078 ;

[0653] MS (ESI, Pos.) 508 $(M + H)^+$.

[0654] Example 18

[0655] 5-chloro-N-{2-[3-chloro-4-(methylsulfonyl)phenoxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-1,3-thiazole-2-carboxamide

[0656] To a solution of the compound (50 mg) prepared in Reference Example 29 and sodium periodate ($NaIO_4$) (71 mg) in dichloromethane (1 mL), acetonitrile (0.5 mL) and water (0.5 mL) were charged, and under ice cooling, ruthenium chloride ($RuCl_3$,CAS No.: 10049-08-8) (1 mg) was added. After that, and the mixture was stirred at 25°C for 16 h to give a black mixture. The reaction mixture was diluted with water (5 mL) and extracted with dichloromethane (8 mL x3). The combined organic layers were washed with brine (5 mL x2), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (petroleum ether: ethyl acetate = 1 : 1) to give the title compound (18.4 mg).

[0657] LCMS (A) Retention time (min) : 0.879 ;

[0658] MS (ESI, Pos.) 540 $(M + H)^+$;

[0659] ^{1}H-NMR($CDCl_3$) : δ 8.85, 8.08, 7.88 - 8.01, 7.68 - 7.76, 7.11, 6.97, 5.59 - 5.72, 4.45 - 4.55, 3.23.

[0660] Reference Example 30

[0661] 5-[4-(benzyloxy)-2-fluorophenyl]-2-methyl-2H-tetrazole

[0662] A mixture of (4-benzyloxy-2-fluoro-phenyl)boronic acid (1.36 g) (CAS No.: 166744-78-1), 5-bromo-2-methyl-2H-1,2,3,4-tetrazole (600 mg) (CAS No.: 16681-80-4), 1,1'-bis(diphenylphophino)ferrocenepalladium(II) dichloride ($Pd(dppf)Cl_2$) (135 mg) and sodium bicarbonate (0.62 g) in 1,4-dioxane (20 mL) and water (2 mL) were purged with N_2, then, heated at 85°C for 12 h to give brown mixture. LCMS showed desired MS. The reaction was diluted with dichloromethane (50 mL) and water (10 mL). The precipitate was filtered off. The organic layer was dried over sodium

sulfate, concentrated in vacuum to give crude residue, which was purified by prep-TLC (petroleum ether: ethyl acetate = 3 : 1) to give the title compound (700 mg).

[0663] ^{1}H-NMR($CDCl_3$) : δ 8.06, 7.40 - 7.46, 6.81 - 6.92, 5.13, 4.43.

[0664] Reference Example 31

[0665] 3-fluoro-4-(2-methyl-2H-tetrazol-5-yl)phenol

[0666] To a solution of the compound (300 mg) prepared in Reference Example 30 in dichloromethane (3 mL) and methanol (3 mL) was added 10% palladium on activated carbon (50 mg), the mixture was stirred at 20°C under H_2 for 3 h to give black mixture. LCMS showed the reaction was complete. The suspension was filtered through a pad of Celite (Registered Trademark) or silica gel and the pad or filter cake was washed with dichloromethane (10 mL x3). The combined filtrates were concentrated to give the title compound (155 mg).

[0667] ^{1}H-NMR($CDCl_3$) : δ 8.00, 6.67 - 6.78, 4.43.

[0668] Reference Example 32

[0669] 2-[3-fluoro-4-(2-methyl-2H-tetrazol-5-yl)phenoxy]-N-methoxy-N-methylacetamide

[0670] The compound (620 mg) prepared in Reference Example 31 was used instead of 2-(trifluoromethyl)pyrimidine-5-ol and subjected to the same reaction as in Reference Example 17 to give the title compound (356 mg).

[0671] ^{1}H-NMR(DMSO-d_6) : δ 7.95, 7.02 - 7.06, 6.86 - 6.97, 5.05, 4.42, 3.77, 3.14.

[0672] Reference Example 33

[0673] 2-[3-fluoro-4-(2-methyl-2H-tetrazol-5-yl)phenoxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethanone

[0674] The compound (545 mg) prepared in Reference Example 32 was used instead of the compound prepared in Reference Example 17 and subjected to the same reaction as in Reference Example 18 to give the title compound (30 mg).

[0675] LCMS (C) Retention time (min) : 0.906 ;

[0676] MS (ESI, Pos.) 382 $(M + H)^+$;

[0677] ^{1}H-NMR(DMSO-d_6) : δ 9.34, 8.63 - 8.65, 8.16, 7.97, 7.22 - 7.26, 7.08 - 7.10, 5.82, 4.43.

[0678] Reference Example 34

[0679] 2-[3-fluoro-4-(2-methyl-2H-tetrazol-5-yl)phenoxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethanamine

[0680] To a solution of the compound (300 mg) prepared in Reference Example 33 in methanol (1.5 mL) was added acetic acid, ammonium acetate (606 mg) stirred at 50°C for 1 h. Then sodium cyanoborohydride (129 mg) was added and the reaction was

stirred at 20°C for 1 h. LCMS showed the reactant was remained and the desired compound was detected. The reaction was concentrated to remove solvent, then quenched with water (8 mL), then potassium carbonate was added, diluted with ethyl acetate (10 mL x3). The organic layer was washed with water (10 mL x3) and brine (10 mL x3), then, dried over sodium sulfate, concentrated in vacuum to give crude residue. The residue was purified by silica gel column chromatography (0~10% ethyl acetate in dichloromethane) to give the title compound (130 mg).

[0681] LCMS (C) Retention time (min) : 0.764 ;

[0682] MS (ESI, Pos.) 383 $(M + H)^+$.

[0683] Reference Example 35

[0684] 5-chloro-N-{2-[3-fluoro-4-(2-methyl-2H-tetrazol-5-yl)phenoxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide

[0685] The compound (81 mg) prepared in Reference Example 34 was used instead of the compound prepared in Reference Example 19 and subjected to the same reaction as in Example 7 to give the title compound (103 mg).

[0686] LCMS (C) Retention time (min) : 0.979 ;

[0687] MS (ESI, Pos.) 522 $(M + H)^+$.

[0688] Example 19

[0689] 5-chloro-N-{(1ξ)-2-[3-fluoro-4-(2-methyl-2H-tetrazol-5-yl)phenoxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl]-2-pyridinecarboxamide

[0690] The compound (103 mg) prepared in Reference Example 35 was separated by SFC to give two isomers.

[0691] SFC was carried out under the following condition.

[0692] Column: Chiralpak IG-3 50x4.6mm I.D., 3μm;

[0693] mobile phase: A: CO_2 B: ethanol (0.05% DEA);

[0694] Isocratic: 40% B;

[0695] Flow rate: 4 mL/min;

[0696] Column temperature: 35°C;

[0697] BPR: 1500 psi.

[0698] Whereby the title compound (35 mg) was obtained in the first peak (retention time : 0.947 min).

[0699] LCMS (C) Retention time (min) : 0.965 ;

[0700] MS (ESI, Pos.) 522 $(M + H)^+$;

[0701] ^{1}H-NMR(DMSO-d_6) : δ 9.72, 8.95, 8.75, 8.25, 8.15, 8.04, 7.92 - 7.98, 7.13, 7.01, 5.67, 4.67, 4.49, 4.42.

[0702] Reference Example 36

[0703] 5-(2-chloro-4-methoxyphenyl)-2-methyl-2H-tetrazole

[0704] 2-chloro-4-methoxyphenylboronic acid (856 mg) (CAS No.: 219735-99-6) was used instead of (4-benzyloxy-2-fluoro-phenyl)boronic acid and subjected to the same reaction as in Reference Example 30 to give the title compound (570 mg).

[0705] LCMS (C) Retention time (min) : 0.845 ;

[0706] MS (ESI, Pos.) 225 $(M + H)^+$.

[0707] Reference Example 37

[0708] 3-chloro-4-(2-methyl-2H-tetrazol-5-yl)phenol

[0709] The compound (700 mg) prepared in Reference Example 36 was dissolved in dichloromethane (7 mL). Boron tribromide (7.8 mL) was added dropwise at 0°C. After addition, the reaction mixture was warmed to room temperature and stirred for 4 h. LCMS showed desired MS. The reaction was quenched by adding water (15 mL). The reaction mixture was extracted with ethyl acetate (20 mL x2) and the organic phase was washed with water (15 mL x2) and brine (15 mL), dried over anhydrous sodium sulfate, filtered and then the filtrate was concentrated in vacuum. The residue was purified by silica gel column chromatography (dichloromethane : methanol = 10 : 1) to give the title compound (670 mg).

[0710] LCMS (C) Retention time (min) : 0.736 ;

[0711] MS (ESI, Pos.) 211 $(M + H)^+$.

[0712] Reference Example 38

[0713] 2-[3-chloro-4-(2-methyl-2H-tetrazol-5-yl)phenoxy]-N-methoxy-N-methylacetamide

[0714] The compound (670 mg) prepared in Reference Example 37 was used instead of 2-(trifluoromethyl)pyrimidine-5-ol and subjected to the same reaction as in Reference Example 17 to give the title compound (690 mg).

[0715] LCMS (C) Retention time (min) : 0.792 ;

[0716] MS (ESI, Pos.) 312 $(M + H)^+$.

[0717] Reference Example 39

[0718] 2-[3-chloro-4-(2-methyl-2H-tetrazol-5-yl)phenoxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethanone

[0719] The compound (1 g) prepared in Reference Example 38 was used instead of the compound prepared in Reference Example 17 and subjected to the same reaction as in Reference Example 18 to give the title compound (715 mg).

[0720] LCMS (C) Retention time (min) : 0.921 ;

[0721] MS (ESI, Pos.) 398 $(M + H)^+$.

[0722] Reference Example 40

[0723] 2-[3-chloro-4-(2-methyl-2H-tetrazol-5-yl)phenoxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethanamine

[0724] The compound (400 mg) prepared in Reference Example 39 was used instead of the compound prepared in Reference Example 22 and subjected to the same reaction as in Reference Example 23 to give the title compound (154 mg).

[0725] LCMS (C) Retention time (min) : 0.767 ;

[0726] MS (ESI, Pos.) 399 $(M + H)^+$.

[0727] Reference Example 41

[0728] 5-chloro-N-{2-[3-chloro-4-(2-methyl-2H-tetrazol-5-yl)phenoxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide

[0729] The compound (154 mg) prepared in Reference Example 40 was used instead of the compound prepared in Reference Example 9 and subjected to the same reaction as in Reference Example 10 to give the title compound (110 mg).

[0730] LCMS (C) Retention time (min) : 0.998 ;

[0731] MS (ESI, Pos.) 538 $(M + H)^+$.

[0732] Example 20

[0733] 5-chloro-N-{(1ξ)-2-[3-chloro-4-(2-methyl-2H-tetrazol-5-yl)phenoxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide

[0734] The compound (110 mg) prepared in Reference Example 41 was separated by SFC to give two isomers.

[0735] SFC was carried out under the following condition.

[0736] Column: Chiralpak IG-3 50x4.6mm I.D., 3μm;

[0737] mobile phase: A: CO_2 B: ethanol (0.05% DEA);

[0738] Isocratic: 40% B;

[0739] Flow rate: 4 mL/min;

[0740] Column temperature: 35°C;

[0741] BPR: 1500 psi.

[0742] Whereby the title compound (39 mg) was obtained in the first peak (retention time : 1.02 min).

[0743] LCMS (C) Retention time (min) : 0.995 ;

[0744] MS (ESI, Pos.) 538 $(M + H)^+$;

[0745] ^{1}H-NMR($CDCl_3$) : δ 8.90, 8.76, 8.56, 8.15, 8.02, 7.93, 7.87, 7.72, 7.13, 6.98, 5.63 - 5.76, 4.42 - 4.53.

[0746] Reference Example 42

[0747] 1-(2,2-diethoxyethoxy)-3-fluorobenzene

[0748] To a solution of 3-fluorophenol (1 g) in N,N-dimethylacetamide (DMA) (15 mL) was added sodium hydride (428 mg, 60% in oil) at 0°C. The mixture was stirred for 15 min at 0°C. Then 2-bromo-1,1-diethoxy-ethane (1.85 g) (CAS No.: 2032-35-1) was added and the mixture was stirred for 16 h at 60°C. The reaction mixture was quenched with ammonium chloride aqueous solution and extracted with ethyl acetate. The organic layer was washed with potassium carbonate aqueous solution and brine, dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 97 : 3 to 90 : 10) to give the title compound (1.5 g).

[0749] ^{1}H-NMR($CDCl_3$) : δ 7.18 - 7.25, 6.62 - 6.72, 4.83, 3.99, 3.55 - 3.80, 1.24.

[0750] Reference Example 43

[0751] (3-fluorophenoxy)acetaldehyde

[0752] To a solution of the compound (1.5 g) prepared in Reference Example 42 in THF (10 mL) and acetone (10 mL) was added 2M HCl in water (10 mL). The mixture was stirred for 2 h at 85°C. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give the title compound.

[0753] ^{1}H-NMR($CDCl_3$) : δ 9.85, 7.18 - 7.31, 6.59 - 6.76, 4.57.

[0754] Reference Example 44

[0755] N-[(1E)-2-(3-fluorophenoxy)ethylidene]-2-methyl-2-propanesulfinamide

[0756] To a solution of the compound prepared in Reference Example 43 in dichloromethane (23 mL) was added 2-methyl-2-propanesulfinamide (956 mg) (CAS No.: 146374-27-8) and cupric sulfate (3.2 g). The mixture was stirred for 16 h at 20°C. The reaction mixture was filtered with Celite (Registered Trademark) and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (hexane : ethyl acetate = 97 : 3 to 70 : 30) to give the title compound (603 mg).

[0757] ^{1}H-NMR($CDCl_3$) : δ 8.19, 7.21 - 7.25, 6.62 - 6.73, 4.93, 1.19.

[0758] Reference Example 45

[0759] N-{2-(3-fluorophenoxy)-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-methyl-2-propanesulfinamide

[0760] To a solution of 5-bromo-2-(trifluoromethyl)pyridine (132 mg) in THF (2 mL) was added n-buthyllithium (0.37 mL, 1.6M in hexane) at -78°C. The mixture was stirred for 30 min at -78°C. Then the compound (100 mg) prepared in Reference Example 44 was added and the mixture was stirred for 1 h at -78°C. The reaction mixture was quenched with ammonium chloride aqueous solution and sodium

bicarbonate aqueous solution, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (hexane : ethyl acetate = 97 : 3 to 60 : 40) to give the title compound (43 mg).

[0761] ^{1}H-NMR($CDCl_3$) : δ 8.81, 7.91 - 7.94, 7.72, 7.19 - 7.31, 6.56 - 6.75, 4.98, 4.16 - 4.26, 3.49, 1.27.

[0762] Reference Example 46

[0763] 2-(3-fluorophenoxy)-1-[6-(trifluoromethyl)-3-pyridinyl]ethanamine hydrochloride

[0764] To a solution of the compound (43 mg) prepared in Reference Example 45 in ethyl acetate was 4M HCl in ethyl acetate and the mixture was stirred for 1 h at room temperature. The reaction mixture was concentrated under reduced pressure to give the title compound.

[0765] LCMS (B) Retention time (min) : 0.870 ;

[0766] MS (ESI, Pos.) 301 $(M + H)^+$.

[0767] Example 21

[0768] 5-chloro-N-{2-(3-fluorophenoxy)-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide

[0769] To a solution of the compound prepared in Reference Example 46 in DMF (1 mL) was added 5-chloro-2-pyridinecarboxylic acid (22 mg), DIEA (0.046 mL) and HATU (53 mg). The mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with 1M HCl solution. The crude residue was purified by UHPLC under the following condition to give the title compound (20 mg).

[0770] Column: YMC-Triart C_{18} 2.0 mm × 30 mm, 1.9 μm;

[0771] Flow rate: 1.0 mL/min;

[0772] Temperature: 30°C;

[0773] Mobile phase A: 0.1% TFA aqueous solution, B: 0.1% TFA acetonitrile solution;

[0774] Gradient (the ratio of the mobile phase (A) and the mobile phase (B) is described): 0 to 0.10 minutes: (95% : 5%), 0.10 to 1.20 minutes: from (95% : 5%) to (5% : 95%), 1.20 to 1.60 minutes: (5% : 95%);

[0775] LCMS (E) Retention time (min) : 1.253 ;

[0776] MS (ESI, Pos.) 440 $(M + H)^+$;

[0777] ^{1}H-NMR($CDCl_3$) : δ 8.88, 8.76, 8.54, 8.13, 8.00, 7.85, 7.70, 7.22 - 7.25, 6.64 - 6.75, 5.62 - 5.67, 4.35 - 4.44.

[0778] Reference Example 47

[0779] 2-bromo-1-[6-(trifluoromethyl)-3-pyridinyl]ethanone

[0780] To a solution of 1-(6-(trifluoromethyl)pyridine-3-yl)ethanone (9.85 g) (CAS No.: 358780-14-0) in THF (100 mL) was added phenyltrimethylammonium tribromide (20.6 g) (CAS No.: 4207-56-1) at 0°C. The mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with sodium bicarbonate aqueous solution and brine, dried over sodium sulfate and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (hexane : ethyl acetate = 100 : 0 to 70 : 30) to give the title compound (9.97 g).

[0781] LCMS (B) Retention time (min) : 1.025 ;

[0782] MS (ESI, Pos.) 268 $(M + H)^+$;

[0783] ^{1}H-NMR($CDCl_3$) : δ 9.29, 8.47, 7.85, 4.44.

[0784] Reference Example 48

[0785] 2-(4-chloro-3-fluorophenoxy)-1-[6-(trifluoromethyl)-3-pyridinyl]ethanone

[0786] To a solution of 4-chloro-3-fluorophenol (6 g) in DMF (50 mL) was added potassium carbonate (7.7 g). The mixture was stirred for 10 min at room temperature. Then the compound (9.97 g) prepared in Reference Example 47 in DMF (20 mL) was added and the mixture was stirred for 10 min at 0°C. The reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (hexane : ethyl acetate = 100 : 0 to 80 : 20) and the slurry was washed (hexane : ethyl acetate = 12 mL: 2 mL) to give the title compound (3.08 g).

[0787] LCMS (B) Retention time (min) : 1.186 ;

[0788] MS (ESI, Pos.) 334 $(M + H)^+$;

[0789] ^{1}H-NMR($CDCl_3$) : δ 9.29, 8.46, 7.86, 7.31, 6.76, 6.65 - 6.70, 5.21.

[0790] Reference Example 49

[0791] 2-(4-chloro-3-fluorophenoxy)-N-(2,4-dimethoxybenzyl)-1-[6-(trifluoromethyl)-3-pyridinyl]ethanamine

[0792] To a solution of the compound (3.08 g) prepared in Reference Example 48 in dichloromethane (18 mL) was added 2,4-dimethoxybenzylamine (2.3 g) (CAS No.: 20781-20-8) and acetic acid (1.1 mL). The mixture was stirred for 30 min at room temperature. Then sodium triacetoxyborohydride (3.9 g) was added and the mixture was stirred for 16 h at room temperature. The reaction mixture was quenched with sodium bicarbonate aqueous solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated under reduced

pressure. The crude residue was purified by amino silica gel column chromatography (hexane : ethyl acetate = 100 : 0 to 70 : 30) to give the title compound (1.35 g).

[0793] LCMS (B) Retention time (min) : 1.063 ;

[0794] MS (ESI, Pos.) 485 $(M + H)^+$;

[0795] ^{1}H-NMR($CDCl_3$) : δ 8.75, 8.01, 7.70, 7.22-7.27, 6.95, 6.62, 6.56, 6.45, 6.41, 4.15 - 4.21, 3.95-3.99, 3.81, 3.80, 3.74, 3.49.

[0796] Reference Example 50

[0797] 2-(4-chloro-3-fluorophenoxy)-1-[6-(trifluoromethyl)-3-pyridinyl]ethanamine

[0798] To the compound (1.35 g) prepared in Reference Example 49 was added trifluoroacetic acid (9 mL). The mixture was stirred for 1.5 h at 70°C. The reaction mixture was concentrated under reduced pressure, azeotropic with toluene. Sodium bicarbonate aqueous solution was added to the residue and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure to give the title compound (959 mg).

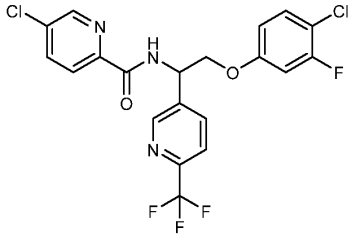
[0799] LCMS (B) Retention time (min) : 0.924 ;

[0800] MS (ESI, Pos.) 335 $(M + H)^+$;

[0801] ^{1}H-NMR($CDCl_3$) : δ 8.81, 8.03, 7.71, 7.25 - 7.30, 6.70, 6.63, 4.56, 4.03 - 4.06, 3.93 - 3.98.

[0802] Example 22

[0803] 5-chloro-N-{2-(4-chloro-3-fluorophenoxy)-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide



[0804] To a solution of the compound (959 mg) prepared in Reference Example 50 in DMF (9 mL) was added 5-chloro-2-pyridinecarboxylic acid (526 mg), DIEA (1.4 mL) and HATU (1.59 g). The mixture was stirred for 5.5 h at room temperature. The reaction mixture was extracted with ethyl acetate and the organic layer was washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure. The crude residue was purified by amino silica gel column chromatography (hexane : ethyl acetate = 100 : 0 to 70 : 30). The slurry was washed (hexane : ethyl acetate = 4 mL : 2 mL) to give the title compound (728 mg).

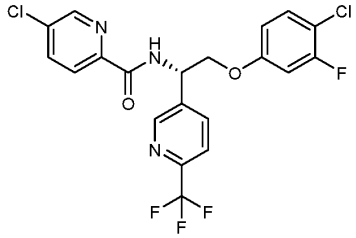
[0805] LCMS (B) Retention time (min) : 1.288 ;

[0806] MS (ESI, Pos.) 474 $(M + H)^+$;

[0807] ^{1}H-NMR($CDCl_3$) : δ 8.86, 8.72, 8.54, 8.13, 7.98, 7.85, 7.70, 7.30, 6.76, 6.69, 5.62 - 5.68, 4.30 - 4.46.

[0808] Example 23

[0809] 5-chloro-N-{(1S)-2-(4-chloro-3-fluorophenoxy)-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide



[0810] The compound (728 mg) prepared in Example 22 was separated by SFC to give two isomers.

[0811] SFC was carried out under the following condition.

[0812] Column: DAICEL CHIRALPAK IA 10x250mm, 5μm;

[0813] mobile phase: A: CO_2, B: methanol;

[0814] Isocratic: 15% B;

[0815] Flow rate: 30 mL/min;

[0816] Column temperature: 35°C;

[0817] BPR: 100 bar.

[0818] Whereby the title compound (324 mg) was obtained in the first peak (retention time : 3.2 min).

[0819] LCMS (B) Retention time (min) : 1.289 ;

[0820] MS (ESI, Pos.) 474 $(M + H)^+$;

[0821] ^{1}H-NMR($CDCl_3$) : δ 8.86, 8.71, 8.54, 8.13, 7.98, 7.86, 7.70, 7.27 - 7.32, 6.76, 6.68, 5.62 - 5.67, 4.34-4.43.

[0822] Reference Example 51

[0823] 1-(4-fluorophenyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethanone

[0824] To a solution of 2-(trifluoromethyl)pyrimidin-5-ol (CAS No.: 100991-09-1) (533 mg) and in DMF (4 mL), was added potassium carbonate (640 mg), 2-chloro-4'-fluoroacetophenone (400 mg) (CAS No.: 456-04-2). The reaction mixture was stirred at 20°C for 16 h to give a white mixture. LCMS showed desired MS. The reaction mixture was poured into water (10 mL), extracted with ethyl acetate (20 mL x3) and washed with water (20 mL x3) and brine (20 mL x2). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give crude

product. The residue was purified by silica gel column chromatography (ethyl acetate = 100%) to give the title compound (523 mg).

[0825] LCMS (C) Retention time (min) : 0.902 ;

[0826] MS (ESI, Pos.) 301 $(M + H)^+$.

[0827] Reference Example 52

[0828] 1-(4-fluorophenyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethanamine

[0829] To a solution of the compound (250 mg) prepared in Reference Example 51 and in methanol (3 mL), was added ammonium acetate (642 mg), sodium cyanoborohydride (79 mg). The reaction mixture was stirred at 40°C for 1 h to give a yellow solution. LCMS showed the desired MS. The reaction mixture was poured into water (10 mL), added potassium carbonate, diluted with brine (30 mL), extracted with ethyl acetate (20 mL x3) and washed with water (20 mL x3). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (0~5% MeOH in ethyl acetate) and lyophilized to give the title compound (156 mg).

[0830] LCMS (C) Retention time (min) : 0.758 ;

[0831] MS (ESI, Pos.) *m/z* 343 $(M + CH_3CN + H)^+$.

[0832] Example 24

[0833] 5-chloro-N-[1-(4-fluorophenyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-1,3-thiazole-2-carboxamide

[0834] To a solution of HATU (136 mg), the compound (86 mg) prepared in Reference Example 21, the compound (78 mg) prepared in Reference Example 52 in DMF (2 mL) was added DIEA (0.13 mL) at 20°C. The mixture was stirred for 1 h at 20°C. LCMS showed desired MS. The reaction mixture was concentrated under reduced pressure, poured into water (20 mL), extracted with ethyl acetate (30 mL x3), washed with brine (30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The crude was purified by prep-TLC (petroleum ether: ethyl acetate = 4 : 3) to give the title compound (15 mg).

[0835] LCMS (C) Retention time (min) : 1.007 ;

[0836] MS (ESI, Pos.) 447 $(M + H)^+$;

[0837] ^{1}H-NMR($CDCl_3$) : δ 8.54, 7.65 - 7.72, 7.44, 7.08 - 7.17, 5.57, 4.50 - 4.59.

[0838] Reference Example 53

[0839] 4,4-difluoro-N-methoxy-N-methylcyclohexanecarboxamide

[0840] To a solution of 4,4-difluorocyclohexanecarboxylic acid (8 g) (CAS No.: 122665-97-8) in dichloromethane (100 mL) was added DIEA (20 mL) at 0°C and HATU (22.4 g) and stirred at 0°C for 10 min. Then N,O-dimethylhydroxylamine

hydrochloride (5.3 g) was added in the reaction mixture and stirred at 0°C for 1 h, then stirred at 20°C for 12 h to give a yellow orange solution. The mixture was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with water (100mL x3) and brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give compound as a crude product. The residue was purified by silica gel column chromatography (0~20% ethyl acetate in petroleum ether) to give the title compound (9.6 g).

[0841] ^{1}H-NMR($CDCl_3$) : δ 3.72, 3.19, 2.65 - 2.80, 1.81 - 2.20.

[0842] Reference Example 54

[0843] 1-(4,4-difluorocyclohexyl)ethanone

[0844] To a solution of the compound (7.2 g) prepared in Reference Example 53 in THF (70 mL) under N_2 was added methyl magnesium bromide (10 mL, 3M in 2-methyltetrahydrofuran) dropwise at 0°C. Then the temperature of the reaction system was slowly raised to room temperature and stirred for 2 h to give a yellow solution. The mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (50mL x3) and brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the title compound (5 g).

[0845] ^{1}H-NMR($CDCl_3$) : δ 2.35 - 2.50, 2.18, 1.72 - 2.18.

[0846] Reference Example 55

[0847] 2-bromo-1-(4,4-difluorocyclohexyl)ethanone

[0848] To a solution of the compound (1.5 g) prepared in Reference Example 54 in methanol (15 mL) was added bromine (0.95 mL) at 0°C. The reaction was stirred at 0°C for 2 h, then water (7 mL) was added, the mixture was stirred at 0°C for 2 h to give yellow solution. The mixture was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with water (100 mL x3） and brine (200 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the title compound (2 g).

[0849] ^{1}H-NMR($CDCl_3$) : δ 3.96, 2.86 - 2.87, 2.19, 1.79 - 2.18.

[0850] Reference Example 56

[0851] 1-(4,4-difluorocyclohexyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethanone

[0852] To a solution of the compound (900 mg) prepared in Reference Example 55 in DMF (3 mL) was added 2-(trifluoromethyl)pyrimidin-5-ol (520 mg) and potassium carbonate (0.17 mL). The mixture was stirred at 20°C for 12 h to give yellow mixture. The mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The

organic layer was washed with water (50 mL x3) and brine (50 mL), dried over sodium sulfate, concentrated to give crude residue, which was purified by silica gel column chromatography (0~30% ethyl acetate in petroleum ether) to give the title compound (600 mg).

[0853] LCMS (C) Retention time (min) : 0.916 ;

[0854] MS (ESI, Pos.) 325 $(M + H)^+$.

[0855] Reference Example 57

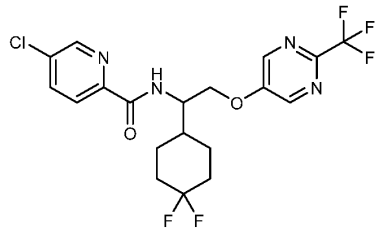
[0856] 1-(4,4-difluorocyclohexyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethanamine To a solution of the compound (600 mg) prepared in Reference Example 56 in methanol (5 mL) was added ammonium acetate (710 mg), sodium cyanoborohydride (175 mg). The reaction mixture was stirred at 40°C for 1 h to give a yellow solution. The mixture was concentrated under reduced pressure, partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (50 mL x3) and brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give compound as a crude product. The residue was purified by silica gel column chromatography (0~5% MeOH in dichloromethane) to give the title compound (520 mg).

[0857] LCMS (C) Retention time (min) : 0.766 ;

[0858] MS (ESI, Pos.) 326 $(M + H)^+$.

[0859] Example 25

[0860] 5-chloro-N-[1-(4,4-difluorocyclohexyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-2-pyridinecarboxamide



[0861] A solution of 5-chloro-2-pyridinecarboxylic acid (349 mg), HATU (1.0 g), and DIEA (0.76 mL) in DMF (7 mL) was stirred at 20°C for 10 min. Then the compound (720 mg) prepared in Reference Example 57 was added. The mixture was stirred at 20°C for 1h to give yellow solution. The mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (50 mL x3) and brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give crude residue, which was purified by silica gel column

chromatography (0~30% ethyl acetate in petroleum ether) to give the title compound (620 mg).

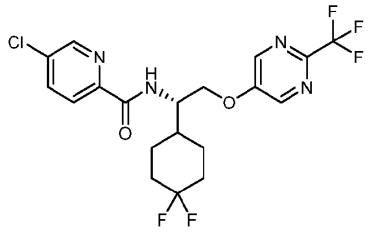
[0862] LCMS (C) Retention time (min) : 1.000 ;

[0863] MS (ESI, Pos.) 465 $(M + H)^+$;

[0864] ^{1}H-NMR($CDCl_3$) : δ 8.56, 8.50 - 8.54, 8.16, 7.86, 4.37 - 4.45, 4.28 - 4.34, 2.18, 1.87 - 2.06, 1.63 - 1.85.

[0865] Example 26

[0866] 5-chloro-N-[(1S)-1-(4,4-difluorocyclohexyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-2-pyridinecarboxamide



[0867] The compound (550 mg) prepared in Example 25 was separated by SFC to give two isomers.

[0868] SFC was carried out under the following condition.

[0869] Column: Chiralcel OJ-3 150x4.6mm I.D., 3μm;

[0870] Mobile phase: A: CO_2, B: ethanol (0.05% DEA);

[0871] Gradient: from: 5% to 40% of B in 4 min and from 40% to 5% of B in 0.2 min, hold 5% of B for 1.8 min;

[0872] Flow rate: 2.5 mL/min;

[0873] Column temperature: 35°C;

[0874] BPR: 1500 psi.

[0875] Whereby the title compound (207 mg) was obtained in the first peak (retention time : 3.30 min).

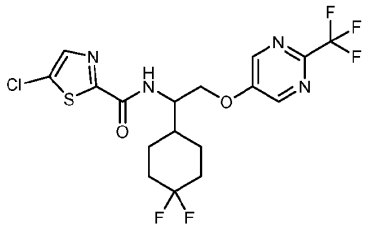
[0876] LCMS (A) Retention time (min) : 0.923 ;

[0877] MS (ESI, Pos.) 465 $(M + H)^+$;

[0878] ^{1}H-NMR($CDCl_3$) : δ 8.56, 8.52, 8.13 - 8.20, 7.86, 4.27 - 4.46, 2.18, 1.65 - 2.06, 1.53.

[0879] Example 27

[0880] 5-chloro-N-[1-(4,4-difluorocyclohexyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-1,3-thiazole-2-carboxamide



[0881] To a solution of DIEA (0.27 mL), the compound (100 mg) prepared in Reference Example 21, the compound (169 mg) prepared in Reference Example 57 in DMF (3 mL) was added HATU (237 mg) at 0°C. The mixture was stirred for 1 h at 20°C. LCMS showed desired MS. The mixture was partitioned with ethyl acetate (10 mL x3) and water (10 mL). The combined organic layers were washed with water (10 mL x 3), brine (6 mL), dried with sodium sulfate and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 3 : 1) to give the title compound (177 mg).

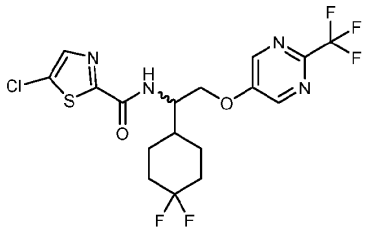
[0882] LCMS (C) Retention time (min) : 1.003 ;

[0883] MS (ESI, Pos.) 471 $(M + H)^+$;

[0884] ^{1}H-NMR($CDCl_3$) : δ 8.55, 7.67, 7.36, 4.34 - 4.43, 4.27 - 4.33, 2.19, 1.88 - 2.03, 1.70 - 1.87, 1.47 - 1.56.

[0885] Example 28

[0886] 5-chloro-N-[(1ξ)-1-(4,4-difluorocyclohexyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-1,3-thiazole-2-carboxamide



[0887] The compound (177 mg) prepared in Example 27 was separated by SFC to give two isomers.

[0888] SFC was carried out under the following condition.

[0889] Column: Chiralcel OD-3 150x4.6mm I.D., 3μm;

[0890] Mobile phase: A: CO_2, B: ethanol (0.05% DEA);

[0891] Gradient: from: 5% to 40% of B in 4 min and from 40% to 5% of B in 0.2 min, hold 5% of B for 1.8 min;

[0892] Flow rate: 2.5 mL/min;

[0893] Column temperature: 35°C;

[0894] BPR: 1500 psi.

[0895] Whereby the title compound (59.96 mg) was obtained in the first peak (retention time : 3.20 min).

[0896] LCMS (C) Retention time (min) : 0.986 ;

[0897] MS (ESI, Pos.) 471 $(M + H)^+$;

[0898] ^{1}H-NMR(DMSO-d_6) : δ 9.02, 8.77, 8.08, 4.46 - 4.52, 4.23 - 4.33, 1.99 - 2.13, 1.72 - 1.94, 1.29 - 1.42.

[0899] Reference Example 58

[0900] 3,3-difluorocyclopentanecarbonyl chloride

[0901] To a solution of 3,3-difluorocyclopentanecarboxylic acid (1 g) (CAS No.: 1260897-05-9) and DMF (5 μL) in dichloromethane (15 mL) was added oxalyl dichloride (1.5 mL) at 0°C. The mixture was stirred at 20°C for 4 h to give a mixture. The mixture was concentrated under residue pressure to give crude the title compound (1.12 g). The residue was used directly without purification

[0902] Reference Example 59

[0903] 2-diazo-1-(3,3-difluorocyclopentyl)ethanone

[0904] To a solution of the compound (1.12 g) prepared in Reference Example 58 in MTBE (20 mL) was added trimethylsilyldiazomethane (17 mL, 2M in hexane) at 0°C. The reaction mixture was warmed to 20°C and stirred at 20°C for 16 h to give a yellow mixture. The mixture was used directly without purification.

[0905] Reference Example 60

[0906] 2-bromo-1-(3,3-difluorocyclopentyl)ethanone

[0907] To crude solution prepared in Reference Example 59 was added HBr at 0°C, the solution was stirred at 20°C for 3 h to give yellow solution. TLC (petroleum ether: ethyl acetate = 3 : 1) showed reactant was consumed completed and a new spot was formed. The solution was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (50 mL x3) and brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the title compound (1.2 g).

[0908] ^{1}H-NMR(DMSO-d_6) : δ 4.49, 2.29 - 2.50, 2.07 - 2.09, 1.83 - 1.85.

[0909] Reference Example 61

[0910] 1-(3,3-difluorocyclopentyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethanone

[0911] The compound (1.2 g) prepared in Reference Example 60 was used instead of the compound prepared in Reference Example 55 and subjected to the same reaction as in Reference Example 56 to give the title compound (1.1 g).

[0912] ^{1}H-NMR(DMSO-d_6) : δ 8.76, 5.24 - 5.39, 2.31 - 2.50, 1.92 – 2.14.

[0913] Reference Example 62

[0914] 1-(3,3-difluorocyclopentyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethanamine

[0915] To a solution of the compound (1.1 g) prepared in Reference Example 61 in methanol (11 mL) was added ammonium acetate (2.8 g) and sodium cyanoborohydride (580 mg). The mixture was stirred at 70°C for 1 h to give a mixture. LCMS showed the reaction was completed and the desired compound was detected. The mixture was concentrated under reduced pressure to give a residue. The reaction mixture was diluted by water (20 mL) and potassium carbonate (2 g) was added. Then the mixture was extracted with ethyl acetate (20 mL x3). The combined organic layers were washed with brine (20 mL x3), dried over sodium sulfate filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (50~80% ethyl acetate in petroleum ether) to give the title compound (600 mg).

[0916] ^{1}H-NMR(DMSO-d_6) : δ 8.78, 4.16 - 4.19, 4.01 - 4.05, 2.95 - 2.96, 1.55 - 2.20.

[0917] Reference Example 63

[0918] 5-chloro-N-[1-(3,3-difluorocyclopentyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-2-pyridinecarboxamide

[0919] The compound (200 mg) prepared in Reference Example 62 was used instead of the compound prepared in Reference Example 57 and subjected to the same reaction as in Example 25 to give the title compound.

[0920] Example 29

[0921] 5-chloro-N-[(1ξ)-1-[(1ξ)-3,3-difluorocyclopentyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-2-pyridinecarboxamide

[0922] The compound (200 mg) prepared in Reference Example 63 was separated by SFC to give four isomers.

[0923] SFC was carried out under the following condition.

[0924] Column: ChiralPak IG-3 100x4.6mm I.D., 3μm;

[0925] Mobile phase: A: CO_2, B: ethanol (0.05% DEA);

[0926] Gradient: from: 5% to 40% of B in 4.5 min, then 5% of B for 1.5 min;

[0927] Flow rate: 2.5 mL/min;

[0928] Column temperature: 40°C;

[0929] BPR: 100 bar.

[0930] Whereby the title compound (27.6 mg) was obtained in the fourth peak (retention time : 2.89 min) .

[0931] LCMS (C) Retention time (min) : 0.989 ;

[0932] MS (ESI, Pos.) 451 $(M + H)^+$;

[0933] ^{1}H-NMR(DMSO-d_6) : δ 8.93, 8.75, 8.68, 8.09 - 8.16, 8.00 - 8.09, 4.36 - 4.47, 2.51 - 2.61, 2.23 - 2.38, 2.07 - 2.21, 1.94 - 2.07, 1.86, 1.54 - 1.66.

[0934] Reference Example 64

[0935] 5-chloro-N-[1-(3,3-difluorocyclopentyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-1,3-thiazole-2-carboxamide

[0936] The compound (350 mg) prepared in Reference Example 62 was used instead of the compound prepared in Reference Example 57 and subjected to the same reaction as in Example 27 to give the title compound (400 mg).

[0937] LCMS (C) Retention time (min) : 0.989 ;

[0938] MS (ESI, Pos.) 457 $(M + H)^+$.

[0939] Example 30, Example 31

[0940] 5-chloro-N-[(1ξ)-1-[(1ξ)-3,3-difluorocyclopentyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-1,3-thiazole-2-carboxamide

[0941] The compound (200 mg) prepared in Reference Example 64 was separated by SFC to give two impure isomers. SFC showed these two compounds were hard to separate by one-time separation. Then these two impure compounds were separated by second SFC and then to give four isomers.

[0942] SFC was carried out under the following condition.

[0943] Column: Chiralcel OJ-3 150x4.6mm I.D., 3μm;

[0944] Mobile phase: A: CO_2, B: ethanol (0.05% DEA);

[0945] Gradient: from: 5% to 40% of B in 4.5 min, then 5% of B for 1.5 min;

[0946] Flow rate: 2.5 mL/min;

[0947] Column temperature: 40℃;

[0948] BPR: 100 bar.

[0949] Whereby the title compound (Example 30) (28.4 mg) was obtained in the third peak (retention time : 3.56 min).

[0950] LCMS (C) Retention time (min) : 0.991 ;

[0951] MS (ESI, Pos.) 457 $(M + H)^+$;

[0952] ^{1}H-NMR(DMSO-d_6) : δ 9.11, 8.78, 8.09, 4.35 - 4.43, 2.53 - 2.61, 2.13 - 2.27, 2.01 - 2.08, 1.89 - 2.01, 1.57 - 1.69.

[0953] The title compound (Example 31) (26.3 mg) was obtained in the fourth peak (retention time : 3.71 min).

[0954] LCMS (C) Retention time (min) : 0.993 ;

[0955] MS (ESI, Pos.) 457 $(M + H)^+$;

[0956] ^{1}H-NMR (DMSO-d_6) : δ 9.02 - 9.14, 8.77, 8.08, 4.32 - 4.40, 2.54 - 2.59, 2.24 - 2.35, 1.88 - 2.18, 1.53 - 1.67.

[0957] Reference Example 65

[0958] 2-(trifluoromethyl)-5-vinylpyrimidine

[0959] To a solution of palladium acetate (460 mg), potassium trifluoro(vinyl)borate (3.54 g) (CAS No.: 13682-77-4), cesium carbonate (21.5 g), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)-biphenyl (1.21 g) (CAS No.: 213697-53-1) were mixed and 5-bromo-2-(trifluoromethyl)pyrimidine (5 g) (CAS No.: 799557-86-1) in THF (70 mL). The mixture was stirred at 70°C for 12 h to give yellow solution. The reaction mixture was poured into water (30 mL), extracted with ethyl acetate (30 mL x3) and washed with brine (30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give crude product. The residue was purified by silica gel column chromatography (0~3% ethyl acetate in petroleum ether) to give the title compound (2.3 g).

[0960] LCMS (C) Retention time (min) : 0.793 ;

[0961] MS (ESI, Pos.) 175 $(M + H)^+$.

[0962] Reference Example 66

[0963] 2-bromo-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethanol

[0964] To a solution of the compound (2.3 g) prepared in Reference Example 65, ammonium acetate (170 mg) in acetone (23 mL) was mixed. Then a solution of N-bromosuccinimide (NBS) (2.6 g) in water (7 mL) was added and stirred at 25°C for 2 h to give yellow solution. LCMS showed desired MS. The mixture was partitioned with ethyl acetate (20 mL x3) and water (30 mL), the organic layer was washed with brine (20 mL), dried with sodium sulfate and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (0~20% ethyl acetate in petroleum ether) to give the title compound (2.4 g).

[0965] LCMS (C) Retention time (min) : 0.764 ;

[0966] MS (ESI, Pos.) 271 $(M + H)^+$.

[0967] Reference Example 67

[0968] 2-(3-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethanol

[0969] To a solution of the compound (230 mg) prepared in Reference Example 66, in toluene (2 mL), was added potassium carbonate (118 mg), potassium iodide (57 mg) and 3-fluorophenol (143 mg) in sequence. The mixture was stirred for 2 h in microwave oven at 150°C to give yellow solution. LCMS showed desired MS. The reaction mixture was poured into water (5 mL), extracted with ethyl acetate (5 mL x3) and washed with brine (5 mL). The combined organic layers were dried over sodium

sulfate and concentrated under reduced pressure to give crude product. The residue was purified by silica gel column chromatography (0~16% ethyl acetate in petroleum ether) to give the title compound (80 mg).

[0970] LCMS (C) Retention time (min) : 0.891 ;

[0971] MS (ESI, Pos.) 303 $(M + H)^+$.

[0972] Reference Example 68

[0973] 2-{2-(3-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-1H-isoindole-1,3(2H)-dione

[0974] To a solution of the compound (30 mg) prepared in Reference Example 67, phthalimide (16 mg) and triphenylphosphine (39 mg) in THF (0.3 mL) was added drop-wise a solution of DEAD (26 mg) in toluene (0.05 mL) at 0°C. The reaction was stirred at 20°C for 12 h to give yellow solution. LCMS showed desired MS. The reaction was diluted with ethyl acetate (6 mL), washed with water (3 mL x 2) and brine (3 mL). The organic layer was dried over sodium sulfate, concentrated in vacuum to give crude residue, which was purified by prep-TLC (petroleum ether : ethyl acetate = 3 : 1) to give the title compound (6 mg).

[0975] Reference Example 69

[0976] 2-(3-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethanamine

[0977] To a solution of the compound (6 mg) prepared in Reference Example 68 in ethanol (0.06 mL) and THF (0.06 mL) was added hydrazine hydrate (7 mg). The reaction was stirred at 20°C for 12 h to give a yellow solution. LCMS showed desired MS. The precipitate was filtered off. The filtrate was concentrated in vacuum to give the title compound (7 mg).

[0978] LCMS (C) Retention time (min) : 0.786 ;

[0979] MS (ESI, Pos.) 302 $(M + H)^+$.

[0980] Example 32

[0981] 5-chloro-N-{2-(3-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide

[0982] A solution of the compound (4.6 mg) prepared in Reference Example 69 in DMF (0.5 mL) was stirred with HATU (38 mg) and DIEA (10 mg) at 20°C for 10 min. Then, the solution was treated with 5-chloro-2-pyridinecarboxylic acid (4.6 mg). The reaction was stirred at 20°C for 2 h to give pale yellow solution. LCMS showed desired MS. The reaction was diluted with ethyl acetate (5 mL) and water (5 mL). The organic layer was washed with water (5 mL x2) and brine (5 mL), dried over sodium sulfate, concentrated in vacuum to give crude residue, which was purified by prep-TLC (petroleum ether : ethyl acetate = 1 : 1) to give the title compound (3.05 mg).

[0983] LCMS (C) Retention time (min) : 1.007 ;

[0984] MS (ESI, Pos.) 441 $(M + H)^+$;

[0985] ^{1}H-NMR(DMSO-d_6) : δ 9.69, 9.23, 8.75, 8.15, 8.03, 7.25 - 7.35, 6.70 - 6.95, 5.60 - 5.70, 4.55-4.65, 4.40-4.50.

[0986] Reference Example 70

[0987] 3-{2-hydroxy-2-[2-(trifluoromethyl)-5-pyrimidinyl]ethoxy}benzonitrile

[0988] To a solution of the compound (500 mg) prepared in Reference Example 66 in toluene (5 mL) was added potassium carbonate (382 mg), potassium iodide (123 mg) and 3-cyanophenol (330 mg) (CAS No.: 873-62-1) in sequence. The mixture was stirred for 2 h in microwave oven at 150°C. The reaction was combined with another batch, poured into water (5 mL), extracted with ethyl acetate (5 mL x3). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 90 : 10) to give the title compound (550 mg).

[0989] LCMS (C) Retention time (min) : 0.854 ;

[0990] MS (ESI, Pos.) 310 $(M + H)^+$.

[0991] Reference Example 71

[0992] 3-{2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-[2-(trifluoromethyl)-5-pyrimidinyl]ethoxy}benzonitrile

[0993] To a solution of the compound (550 mg) prepared in Reference Example 70, phthalimide (288 mg) and triphenylphosphine (699 mg) in THF (4 mL) was added drop-wise a solution of DEAD (465 mg) in toluene (4 mL) at 0°C. The reaction was partitioned with ethyl acetate (10 mL x2) and water (5 mL). The combined organic layer was washed with water (3 mL x2), brine (3 mL), dried over sodium sulfate and concentrated in vacuum to give crude residue. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 90 : 10) to give the title compound (474 mg).

[0994] LCMS (C) Retention time (min) : 0.971 ;

[0995] MS (ESI, Pos.) 439 $(M + H)^+$.

[0996] Reference Example 72

[0997] 3-{2-amino-2-[2-(trifluoromethyl)-5-pyrimidinyl]ethoxy}benzonitrile

[0998] To a solution of the compound (470 mg) prepared in Reference Example 71 in ethanol (5 mL) and THF (5 mL) was added hydrazine hydrate (1.61 g). The reaction was stirred at 20°C for 16 h to give a yellow solution. LCMS showed desired MS. The mixture was filtered and the filtrate was partitioned with ethyl acetate (20 mL x2)

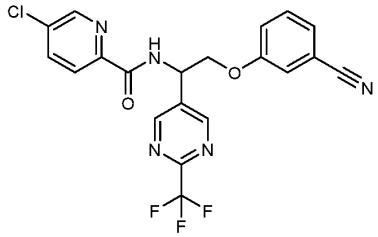
and water (4 mL). The organic layers were washed with brine (4 mL), dried with sodium sulfate and concentrated under reduced pressure to give the title compound (252 mg), which was used directly in the next step.

[0999] LCMS (C) Retention time (min) : 0.749 ;

[01000] MS (ESI, Pos.) *m/z* 350 $(M + CH_3CN + H)^+$.

[01001] Example 33

[01002] 5-chloro-N-{2-(3-cyanophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide



[01003] To a solution of DIEA (0.37 mL), the compound (227 mg) prepared in Reference Example 72, 5-chloro-2-pyridinecarboxylic acid (128 mg) in DMF (2 mL) was added HATU (420 mg) at 0°C. The mixture was stirred at 20°C for 1 h. LCMS showed desired MS. The reaction was diluted with ethyl acetate (3 mL x3) and water (5 mL). The organic layers were washed with water (5 mL x2) and brine (5 mL), dried over sodium sulfate, concentrated in vacuum to give crude residue. The crude was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 85 : 15) to give the title compound (256 mg).

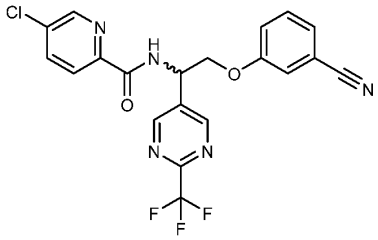
[01004] LCMS (C) Retention time (min) : 0.957 ;

[01005] MS (ESI, Pos.) 448 $(M + H)^+$;

[01006] ^{1}H-NMR(DMSO-d_6) : δ 9.72, 9.24, 8.74, 8.15, 8.04, 7.40 - 7.56, 7.33, 5.64 - 5.73, 4.66, 4.52.

[01007] Example 34

[01008] 5-chloro-N-{(1ξ)-2-(3-cyanophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide



[01009] The compound (256 mg) prepared in Example 33 was separated by SFC to give two isomers.
[01010] SFC was carried out under the following condition.
[01011] Column: Chiralpak IC-3 150x4.6mm I.D., 3μm;
[01012] Mobile phase: A: CO_2, B: ethanol (0.05% DEA);
[01013] Isocratic: 40% B;
[01014] Flow rate: 2.5 mL/min;
[01015] Column temperature: 35°C;
[01016] BPR: 1500 psi.
[01017] Whereby the title compound (63 mg) was obtained in the second peak (retention time : 2.10 min).
[01018] LCMS (C) Retention time (min) : 0.969 ;
[01019] MS (ESI, Pos.) 448 $(M + H)^+$;
[01020] ^{1}H-NMR(DMSO-d_6) : δ 9.70, 9.25, 8.75, 8.15, 8.05, 7.46 - 7.47, 7.41 - 7.45, 7.34, 5.65 - 5.74, 4.62 - 4.72, 4.53.
[01021] Reference Example 73
[01022] 2-(4-chloro-3-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethanol
[01023] 4-chloro-3-fluorophenol (649 mg) was used instead of 3-fluorophenol and subjected to the same reaction as in Reference Example 67 to give the title compound (489 mg).
[01024] LCMS (C) Retention time (min) : 0.940 ;
[01025] MS (ESI, Pos.) *m/z* 378 $(M + CH_3CN + H)^+$.
[01026] Reference Example 74
[01027] 2-{2-(4-chloro-3-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-1H-isoindole-1,3(2H)-dione
[01028] The compound (487 mg) prepared in Reference Example 73 was used instead of the compound prepared in Reference Example 67 and subjected to the same reaction as in Reference Example 68 to give the title compound (392 mg).
[01029] LCMS (C) Retention time (min) : 1.045 ;
[01030] MS (ESI, Pos.) 466 $(M + H)^+$.
[01031] Reference Example 75
[01032] 2-(4-chloro-3-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethanamine
[01033] The compound (392 mg) prepared in Reference Example 74 was used instead of the compound prepared in Reference Example 68 and subjected to the same reaction as in Reference Example 69 to give the title compound (192 mg).
[01034] LCMS (C) Retention time (min) : 0.793 ;

[01035] MS (ESI, Pos.) 336 $(M + H)^+$.

[01036] Reference Example 76

[01037] 5-chloro-N-{2-(4-chloro-3-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide

[01038] The compound (195 mg) prepared in Reference Example 75 was used instead of the compound prepared in Reference Example 69 and subjected to the same reaction as in Example 32 to give the title compound (293 mg).

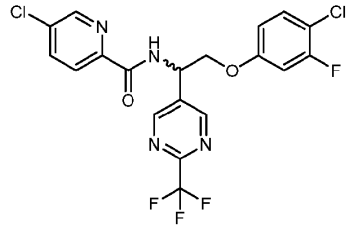
[01039] LCMS (C) Retention time (min) : 1.043 ;

[01040] MS (ESI, Pos.) 475 $(M + H)^+$;

[01041] ^{1}H-NMR(DMSO-d_6) : δ 9.67, 9.21, 8.72, 8.12, 8.01, 7.51, 7.45, 7.14, 6.85, 5.90, 5.65, 4.43 - 4.62.

[01042] Example 35

[01043] 5-chloro-N-{(1ξ)-2-(4-chloro-3-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide



[01044] The compound (293 mg) prepared in Reference Example 76 was separated by SFC to give two isomers.

[01045] SFC was carried out under the following condition.

[01046] Column: Chiralpak IC-3 150x4.6mm I.D., 3μm;

[01047] Mobile phase: A: CO_2, B: ethanol (0.05% DEA);

[01048] Isocratic: 40% B;

[01049] Flow rate: 2.5 mL/min;

[01050] Column temperature: 35℃;

[01051] BPR: 1500 psi.

[01052] Whereby the title compound (85.2 mg) was obtained in the second peak (retention time : 1.31 min).

[01053] LCMS (C) Retention time (min) : 1.040 ;

[01054] MS (ESI, Pos.) 475 $(M + H)^+$;

[01055] ^{1}H-NMR(DMSO-d_6) : δ 9.69, 9.23, 8.74, 8.13 - 8.15, 8.02 - 8.04, 7.47, 7.14 - 7.17, 6.88, 5.67, 4.61, 4.48.

[01056] Reference Example 77

[01057] 2-(4-chloro-2-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethanol

[01058] 4-chloro-2-fluorophenol (811 mg) (CAS No.: 348-62-9) was used instead of 3-fluorophenol and subjected to the same reaction as in Reference Example 67 to give the title compound (548 mg).

[01059] LCMS (C) Retention time (min) : 0.932 ;

[01060] MS (ESI, Pos.) 337 $(M + H)^+$.

[01061] Reference Example 78

[01062] 2-{2-(4-chloro-2-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-1H-isoindole-1,3(2H)-dione

[01063] The compound (548 mg) prepared in Reference Example 77 was used instead of the compound prepared in Reference Example 67 and subjected to the same reaction as in Reference Example 68 to give the title compound (370 mg).

[01064] LCMS (C) Retention time (min) : 1.031 ;

[01065] MS (ESI, Pos.) 466 $(M + H)^+$.

[01066] Reference Example 79

[01067] 2-(4-chloro-2-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethanamine

[01068] The compound (370 mg) prepared in Reference Example 78 was used instead of the compound prepared in Reference Example 68 and subjected to the same reaction as in Reference Example 69 to give the title compound (200 mg).

[01069] LCMS (C) Retention time (min) : 0.804 ;

[01070] MS (ESI, Pos.) 336 $(M + H)^+$.

[01071] Example 36

[01072] 5-chloro-N-{2-(4-chloro-2-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide

[01073] The compound (200 mg) prepared in Reference Example 79 was used instead of the compound prepared in Reference Example 69 and subjected to the same reaction as in Example 32 to give the title compound (200 mg).

[01074] LCMS (C) Retention time (min) : 1.044 ;

[01075] MS (ESI, Pos.) 475 $(M + H)^+$;

[01076] ^{1}H-NMR(DMSO-d_6) : δ 9.71, 9.22, 8.75, 8.15, 8.03, 7.42, 7.27 - 7.34, 7.20 - 7.26, 5.64 - 5.73, 4.61 - 4.70, 4.54.

[01077] Example 37

[01078] 5-chloro-N-{(1ξ)-2-(4-chloro-2-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide

[01079] The compound (190 mg) prepared in Example 36 was separated by SFC to give two isomers.

[01080] SFC was carried out under the following condition.
[01081] Column: Chiralpak AD-3 50x4.6mm I.D., 3μm;
[01082] Mobile phase: A: CO_2, B: ethanol (0.05% DEA);
[01083] Gradient: from: 5% to 40% of B in 2 min and hold 40% for 1.2 min, then 5% of B for 0.8 min;
[01084] Flow rate: 4 mL/min;
[01085] Column temperature: 35°C;
[01086] BPR: 1500 psi.
[01087] Whereby the title compound (71.6 mg) was obtained in the first peak (retention time : 1.56 min).
[01088] LCMS (C) Retention time (min) : 1.046 ;
[01089] MS (ESI, Pos.) 475 $(M + H)^+$;
[01090] ^{1}H-NMR(DMSO-d_6) : δ 9.70, 9.22, 8.75, 8.15, 8.03, 7.42, 7.27 - 7.33, 7.19 - 7.26, 5.64 - 5.73, 4.62 - 4.70, 4.51 - 4.58.
[01091] Example 38
[01092] 5-chloro-N-{2-(4-chloro-2-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-1,3-thiazole-2-carboxamide
[01093] The compound (18 mg) prepared in Reference Example 21 was used instead of 5-chloropyridine-2-carboxylic acid and subjected to the same reaction as in Example 36 to give the title compound (19 mg).
[01094] LCMS (C) Retention time (min) : 1.067 ;
[01095] MS (ESI, Pos.) 481 $(M + H)^+$;
[01096] ^{1}H-NMR(DMSO-d_6) : δ 9.85, 9.22, 8.14, 7.43, 7.26 - 7.34, 7.20 - 7.25, 5.61 - 5.69, 4.57 - 4.64, 4.48 - 4.55.
[01097] Reference Example 80
[01098] 2-(4-chlorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethanol
[01099] To a solution of the compound (100 mg) prepared in Reference Example 66 in toluene (2 mL), 4-chlorophenol (72 mg) (CAS No.: 106-48-9), potassium iodide (25 mg) and potassium carbonate (51 mg) was added. The reaction was stirred in microwave oven at 150°C for 16 h to give yellow solution. LCMS showed desired MS. The reaction was diluted with water (6 mL), ethyl acetate (3 mL x 2) and brine (3 mL). The organic layer was dried over sodium sulfate, concentrated in vacuum to give crude residue, which was purified by prep-TLC (petroleum ether: ethyl acetate = 4 : 1) to give the title compound (100 mg).
[01100] LCMS (C) Retention time (min) : 0.920 ;
[01101] MS (ESI, Pos.) *m/z* 360 $(M + CH_3CN + H)^+$.

[01102] Reference Example 81

[01103] 2-{2-(4-chlorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-1H-isoindole-1,3(2H)-dione

[01104] To a solution of the compound (40 mg) prepared in Reference Example 80, phthalimide (21 mg) and triphenylphosphine (50 mg) in THF (1.5 mL) was added drop-wise a solution of DEAD (33 mg) at 0°C. The reaction was stirred at 25°C for 2 h to give yellow solution. LCMS showed desired MS. The reaction was diluted with ethyl acetate (3 mL), washed with water (3 mL x 2) and brine (3 mL). The organic layer was dried over sodium sulfate, concentrated in vacuum to give crude residue, which was purified by prep-TLC (petroleum ether: ethyl acetate = 4 : 1) to give the title compound (20 mg).

[01105] LCMS (C) Retention time (min) : 1.051 ;

[01106] MS (ESI, Pos.) 448 $(M + H)^+$.

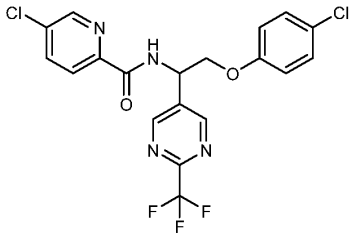
[01107] Reference Example 82

[01108] 2-(4-chlorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethanamine

[01109] To a solution of the compound (60 mg) prepared in Reference Example 81 in ethanol (0.5 mL) and THF (0.5 mL) was added hydrazine hydrate (67 mg). The reaction was stirred at 20°C for 12 h to give a yellow solution. LCMS showed desired MS. The precipitate was filtered off. The filtrate was diluted with ethyl acetate (3 mL), washed with water (3 mL x2) and brine (3 mL). The organic layer was dried over sodium sulfate, concentrated in vacuum to give crude the title compound (50 mg).

[01110] Example 39

[01111] 5-chloro-N-{2-(4-chlorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide



[01112] A solution 5-chloro-2-pyridinecarboxylic acid (13 mg) in DMF (0.5 mL) was stirred with the compound (26 mg) prepared in Reference Example 82 and DIEA (22 mg) at 25°C for 10 mins. Then, the solution was treated with HATU (16 mg). The reaction was stirred at 25°C for 2 h to give pale yellow solution. LCMS showed desired MS. The reaction was diluted with ethyl acetate (5 mL) and water (5 mL). The organic layer was washed with water (5 mL x2) and brine (5 mL), then dried over

sodium sulfate, concentrated in vacuum to give crude residue, which was purified by prep-TLC (petroleum ether: ethyl acetate = 3 : 1) to give the title compound (25.1 mg).

[01113] LCMS (C) Retention time (min) : 1.047 ;

[01114] MS (ESI, Pos.) 457 $(M + H)^+$;

[01115] ^{1}H-NMR(DMSO-d_6) : δ 9.68, 9.23, 8.75, 8.12 - 8.18, 8.01 - 8.06, 7.33, 7.01, 5.65, 4.53 - 4.61, 4.42 - 4.48.

[01116] Reference Example 83

[01117] 5-(2-oxiranyl)-2-(trifluoromethyl)pyrimidine

[01118] To a solution of the compound (2 g) prepared in Reference Example 66 in DMF (60 mL) was added potassium carbonate (1.33 g) at 20°C. The mixture was stirred for 1.5 h at 20°C. LCMS showed desired MS. The mixture was partitioned with ethyl acetate (100 mL x3) and water (20 mL). The organic layers were washed with water (10 mL x2), brine (10 mL), dried with sodium sulfate and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 93 : 7) to give the title compound (850 mg).

[01119] ^{1}H-NMR(DMSO-d_6) : δ 9.00, 4.19- 4.21, 3.27 - 3.28, 3.12 - 3.13.

[01120] Reference Example 84

[01121] 2-(4-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethanol

[01122] To a solution of 4-fluorophenol (384 mg) in acetonitrile (10 mL) was added potassium carbonate (545 mg). The mixture was stirred for 0.5 h. Then strontium perchlorate trihydrate ($Sr(ClO_4)_2 \cdot 3H_2O$) (924 mg) (CAS No.: 15650-09-6) and the compound (500 mg) prepared in Reference Example 83 was added. The reaction was stirred at 80°C for 16 h. The reaction mixture was filtered and diluted with water (5 mL) and extracted with ethyl acetate (20 mL x3). The organic layer was washed with brine (5 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 90 : 10) to give the title compound (492 mg).

[01123] ^{1}H-NMR(DMSO-d_6) : δ 9.14, 7.08 - 7.12, 6.21, 5.17 - 5.21, 4.18 - 4.19.

[01124] Reference Example 85

[01125] 2-{2-(4-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-1H-isoindole-1,3(2H)-dione

[01126] To a solution of the compound (715 mg) prepared in Reference Example 84, phthalimide (383 mg) and triphenylphosphine (930 mg) in THF (8 mL) was added drop-wise a solution of DEAD (618 mg) in toluene (5 mL) at 0°C. The reaction was stirred at 20°C for 12 h to give yellow solution. LCMS showed desired MS. The reaction was diluted with ethyl acetate (6 mL), washed with water (3 mL x2) and brine (3 mL).

The organic layer was dried over sodium sulfate, concentrated in vacuum to give crude residue. The crude was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 92 : 8) to give the title compound (500 mg).

[01127] LCMS (C) Retention time (min) : 1.019 ;

[01128] MS (ESI, Pos.) 432 $(M + H)^+$.

[01129] Reference Example 86

[01130] 2-(4-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethanamine

[01131] To a solution of the compound (845 mg) prepared in Reference Example 85 in ethanol (8 mL) and THF (8 mL) was added hydrazine hydrate (2.74 g). The reaction was stirred at 20°C for 12 h to give a yellow solution. LCMS showed desired MS and reactant was detected. Hydrazine hydrate (490 mg) was added and stirred. The precipitate was filtered off. The filtrate was partitioned with ethyl acetate (15 mL x2) and water (5 mL). The organic layers were washed with brine (3 mL), dried with sodium sulfate and concentrated to give the title compound (590 mg).

[01132] LCMS (C) Retention time (min) : 0.754 ;

[01133] MS (ESI, Pos.) 302 $(M + H)^+$.

[01134] Reference Example 87

[01135] 5-chloro-N-{2-(4-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide

[01136] To a solution of DIEA (0.97 mL), 5-chloro-2-pyridinecarboxylic acid (324 mg), the compound (590 mg) prepared in Reference Example 86 in DMF (8 mL) was added HATU (820 mg) at 20°C. The mixture was stirred for 1 h at 20°C. LCMS showed desired MS. The reaction mixture was concentrated under reduced pressure, poured into water (20 mL), extracted with ethyl acetate (30 mL x3). The combined organic layer was washed with brine (30 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 88 : 12) to give the title compound (424 mg).

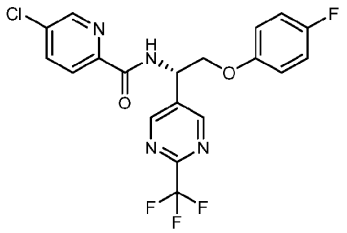
[01137] LCMS (C) Retention time (min) : 1.007 ;

[01138] MS (ESI, Pos.) 441 $(M + H)^+$;

[01139] ^{1}H-NMR(DMSO-d_6) : δ 9.67, 9.23, 8.76, 8.15, 8.04, 7.08 - 7.16, 6.97 - 7.03, 5.61 - 5.69, 4.56, 4.44.

[01140] Example 40

[01141] 5-chloro-N-{(1S)-2-(4-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide



[01142] The compound (424 mg) prepared in Reference Example 87 was separated by SFC to give two isomers.

[01143] SFC was carried out under the following condition.

[01144] Column: ChiralPak AD-3 150x4.6mm I.D., 3μm;

[01145] Mobile phase: A: CO_2, B: ethanol (0.05% DEA);

[01146] Isocratic: 40% B;

[01147] Flow rate: 2.5 mL/min;

[01148] Column temperature: 40°C;

[01149] BPR: 100 bar.

[01150] Whereby the title compound (159 mg) was obtained in the first peak (retention time : 2.01 min).

[01151] LCMS (C) Retention time (min) : 1.010 ;

[01152] MS (ESI, Pos.) 441 $(M + H)^+$;

[01153] ^{1}H-NMR(DMSO-d_6) : δ 9.67, 9.23, 8.75, 8.15, 8.04, 7.08 - 7.16, 6.96 - 7.02, 5.64, 4.52 - 4.58, 4.43.

[01154] Example 41

[01155] 5-fluoro-N-{2-(4-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide

[01156] To a solution of DIEA (0.03 mL), the compound (17 mg) prepared in Reference Example 86, 5-fluoro-2-pyridinecarboxylic acid (16 mg) in DMF (0.5 mL) was added HATU (28 mg) at 20°C. The mixture was stirred for 1 h at 20°C. LCMS showed desired MS. The reaction mixture was concentrated under reduced pressure, poured in to water (20 mL), alkalified with sodium bicarbonate (20 mL), extracted with ethyl acetate (30 mL x3), washed with brine (30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The crude was purified by prep-TLC (petroleum ether: ethyl acetate = 3 : 1) to give the title compound (7.5 mg).

[01157] LCMS (C) Retention time (min) : 0.975 ;

[01158] MS (ESI, Pos.) 425 $(M + H)^+$;

[01159] ^{1}H-NMR(DMSO-d_6) : δ 9.60, 9.23, 8.70, 8.11, 7.93, 7.09 - 7.16, 6.97 - 7.01, 5.60 - 5.67, 4.52 - 4.58, 4.43.

[01160] Reference Example 88

[01161] 4-(2-methyl-2H-tetrazol-5-yl)phenol

[01162] A mixture of (4-hydroxyphenyl)boronic acid (508 mg) (CAS No.: 71597-85-8), 5-bromo-2-methyl 2H-1,2,3,4-tetrazole (400 mg), Pd(dppf)Cl_2 (90 mg) and sodium bicarbonate (413 mg) in 1,4-dioxane (8 mL) and water (0.8 mL) was purged with N_2, then, heated at 85°C for 12 h to give brown mixture. The reaction was diluted with dichloromethane (20 mL) and water (10 mL). The organic layer was dried over sodium sulfate, concentrated in vacuum to give crude residue, which was purified by prep-TLC (dichloromethane: methanol = 10 : 1) to give the title compound (160 mg).

[01163] LCMS (C) Retention time (min) : 0.688 ;

[01164] MS (ESI, Pos.) 177 $(M + H)^+$.

[01165] Reference Example 89

[01166] 2-[4-(2-methyl-2H-tetrazol-5-yl)phenoxy]-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethanol

[01167] To a solution of the compound (334 mg) prepared in Reference Example 88 in acetonitrile (6 mL) was added potassium carbonate (327 mg). The mixture was stirred for 0.5 h. Then magnesium perchrorate ($Mg(ClO_4)_2$) (554 mg) (CAS No.: 10034-81-8) and the compound (300 mg) prepared in Reference Example 83 were added. The reaction was stirred at 90°C for 16 h to give yellow solution. LCMS showed the desired MS. The reaction mixture was filtered and diluted with water (10 mL) and extracted with ethyl acetate (10 mL x3) the organic layer was washed with brine (10 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0~20% ethyl acetate in petroleum ether) to give the title compound (360 mg).

[01168] LCMS (C) Retention time (min) : 0.855 ;

[01169] MS (ESI, Pos.) 367 $(M + H)^+$.

[01170] Reference Example 90

[01171] 2-{2-[4-(2-methyl-2H-tetrazol-5-yl)phenoxy]-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-1H-isoindole-1,3(2H)-dione

[01172] To a solution of the compound (396 mg) prepared in Reference Example 89, phthalimide (175 mg) and triphenylphosphine (425 mg) in THF (4 mL) was added drop-wise a solution of DEAD (283 mg) in toluene (2 mL) at 0°C. The reaction was stirred at 20°C for 2 h to give yellow solution showed desired MS. The reaction mixture was filtered and diluted with water (10 mL) and extracted with ethyl acetate (10 mL x3) the

organic layer was washed with brine (10 mL), dried over sodium sulfate and concentrate under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate = 70 : 30) to give the title compound (500 mg).

[01173] LCMS (C) Retention time (min) : 0.973 ;

[01174] MS (ESI, Pos.) 496 $(M + H)^+$;

[01175] Reference Example 91

[01176] 2-[4-(2-methyl-2H-tetrazol-5-yl)phenoxy]-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethanamine

[01177] To a solution of the compound (500 mg) prepared in Reference Example 90 in ethanol (6 mL) and THF (6 mL) was added hydrazine hydrate (656 mg). The reaction was stirred at 20°C for 12 h to give a yellow solution showed desired MS. The precipitate was filtered off. The filtrate was diluted with ethyl acetate (15 mL), washed with water (15 mL x 2) and brine (15 mL). The organic layer was dried over sodium sulfate, concentrated in vacuum to give the title compound (450 mg).

[01178] Reference Example 92

[01179] 5-chloro-N-{2-[4-(2-methyl-2H-tetrazol-5-yl)phenoxy]-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide

[01180] To a solution of 5-chloro-2-pyridinecarboxylic acid (187 mg) in DMF (4 mL) was stirred with the compound (360 mg) prepared in Reference Example 91 and DIEA (255 mg) at 20°C for 10 min. Then, the solution was treated with HATU (450 mg). The reaction was stirred at 20°C for 2 h to give pale yellow solution. LCMS showed desired MS. The reaction was diluted with ethyl acetate (10 mL) and water (10 mL). The organic layer was washed with water (10 mL x 2) and brine (10 mL), then dried over sodium sulfate, concentrated in vacuum to give crude residue, which was purified by prep-TLC (petroleum ether: ethyl acetate = 1 : 1) after prep-HPLC to give the title compound (83 mg).

[01181] LCMS (C) Retention time (min) : 0.964 ;

[01182] MS (ESI, Pos.) 505 $(M + H)^+$;

[01183] ^{1}H-NMR(DMSO-d_6) : δ 9.72, 9.26, 8.75, 8.14 - 8.16, 8.05, 7.98, 7.16, 5.68 - 5.73, 4.64 - 4.69, 4.29 - 4.56, 4.39.

[01184] Example 42

[01185] 5-chloro-N-{(1ξ)-2-[4-(2-methyl-2H-tetrazol-5-yl)phenoxy]-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide

[01186] The compound (83 mg) prepared in Reference Example 92 was separated by SFC to give two isomers.

[01187] SFC was carried out under the following condition.
[01188] Column: Chiralcel OD-3 50x4.6mm I.D., 3μm;
[01189] mobile phase: A: CO_2 B: ethanol (0.05% DEA);
[01190] Gradient: from: 5% to 40% of B in 2 min and hold 40% for 1.2 min, then 5% of B for 0.8 min;
[01191] Flow rate: 4 mL/min;
[01192] Column temperature: 35°C;
[01193] BPR: 1500 psi.
[01194] Whereby the title compound (29.5 mg) was obtained in the first peak (retention time : 1.93 min).
[01195] LCMS (C) Retention time (min) : 0.970 ;
[01196] MS (ESI, Pos.) 505 $(M + H)^+$;
[01197] ^{1}H-NMR(DMSO-d_6) : δ 9.72, 9.26, 8.75, 8.15, 8.05, 7.98, 7.16, 5.66 - 5.75, 4.67, 4.54, 4.39.
[01198] Reference Example 93
[01199] 2-{[6-(trifluoromethyl)-3-pyridinyl]oxy}-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethanol
[01200] 6-(trifluoromethyl)pyridine-3-ol (870 mg) (CAS No.: 216766-12-0) was used instead of the compound prepared in Reference Example 88 and subjected to the same reaction as in Reference Example 89 to give the title compound (930 mg).
[01201] LCMS (C) Retention time (min) : 0.877 ;
[01202] MS (ESI, Pos.) 354 $(M + H)^+$.
[01203] Reference Example 94
[01204] 2-(2-{[6-(trifluoromethyl)-3-pyridinyl]oxy}-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl)-1H-isoindole-1,3(2H)-dione
[01205] The compound (1 g) prepared in Reference Example 93 was used instead of the compound prepared in Reference Example 89 and subjected to the same reaction as in Reference Example 90 to give the title compound (792 mg).
[01206] LCMS (C) Retention time (min) : 1.003 ;
[01207] MS (ESI, Pos.) 483 $(M + H)^+$.
[01208] Reference Example 95
[01209] 2-{[6-(trifluoromethyl)-3-pyridinyl]oxy}-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethanamine
[01210] The compound (792 mg) prepared in Reference Example 94 was used instead of the compound prepared in Reference Example 90 and subjected to the same reaction as in Reference Example 91 to give the title compound (259 mg).

[01211] LCMS (C) Retention time (min) : 0.749 ;
[01212] MS (ESI, Pos.) 353 $(M + H)^+$.
[01213] Example 43
[01214] 5-chloro-N-(2-{[6-(trifluoromethyl)-3-pyridinyl]oxy}-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl)-2-pyridinecarboxamide
[01215] The compound (259 mg) prepared in Reference Example 95 was used instead of the compound prepared in Reference Example 91 and subjected to the same reaction as in Reference Example 92 to give the title compound (249 mg).
[01216] LCMS (C) Retention time (min) : 0.991 ;
[01217] MS (ESI, Pos.) 492 $(M + H)^+$;
[01218] ^{1}H-NMR($CDCl_3$) : δ 9.06, 8.77, 8.55, 8.45, 8.09 - 8.16, 7.88, 7.67, 7.38, 5.73, 4.58 - 4.63, 4.52 - 4.57.
[01219] Example 44
[01220] 5-chloro-N-{(1ξ)-2-{[6-(trifluoromethyl)-3-pyridinyl]oxy}-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide
[01221] The compound (193 mg) prepared in Example 43 was separated by SFC to give two isomers.
[01222] SFC was carried out under the following condition.
[01223] Column: Chiralpak IG-3 50x4.6mm I.D., 3μm;
[01224] mobile phase: A: CO_2 B: ethanol (0.05% DEA);
[01225] Gradient: from: 5% to 40% of B in 2 min and hold 40% for 1.2 min, then 5% of B for 0.8 min;
[01226] Flow rate: 4 mL/min;
[01227] Column temperature: 35°C;
[01228] BPR: 1500 psi.
[01229] Whereby the title compound (68.6 mg) was obtained in the first peak (retention time : 1.58 min).
[01230] LCMS (C) Retention time (min) : 0.979 ;
[01231] MS (ESI, Pos.) 492 $(M + H)^+$;
[01232] ^{1}H-NMR(DMSO-d_6) : δ 9.76, 9.25, 8.74, 8.48, 8.15, 8.04, 7.86, 7.68, 5.68 - 5.78, 4.73 - 4.81, 4.65.
[01233] Example 45
[01234] 5-chloro-N-(2-{[6-(trifluoromethyl)-3-pyridinyl]oxy}-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl)-1,3-thiazole-2-carboxamide

[01235] The compound (9.6 mg) prepared in Reference Example 21 was used instead of 5-chloropyridine-2-carboxylic acid and subjected to the same reaction as in Example 43 to give the title compound (7.0 mg).
[01236] LCMS (A) Retention time (min) : 0.921 ;
[01237] MS (ESI, Pos.) 498 $(M + H)^+$;
[01238] ^{1}H-NMR(DMSO-d_6) : δ 9.90, 9.25, 8.48, 8.13, 7.86, 7.68, 5.70, 4.68 - 4.75, 4.62.
[01239] Reference Example 96
[01240] 2-{[2-(trifluoromethyl)-4-pyridinyl]oxy}-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethanol
[01241] 2-(trifluoromethyl)pyridin-4-ol (452 mg) was used instead of 3-fluorophenol and subjected to the same reaction as in Reference Example 67 to give the title compound (190 mg).
[01242] LCMS (C) Retention time (min) : 0.861 ;
[01243] MS (ESI, Pos.) 354 $(M + H)^+$.
[01244] Reference Example 97
[01245] 2-(2-{[2-(trifluoromethyl)-4-pyridinyl]oxy}-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl)-1H-isoindole-1,3(2H)-dione
[01246] The compound (190 mg) prepared in Reference Example 96 was used instead of the compound prepared in Reference Example 89 and subjected to the same reaction as in Reference Example 90 to give the title compound (76 mg).
[01247] LCMS (C) Retention time (min) : 0.983 ;
[01248] MS (ESI, Pos.) 483 $(M + H)^+$.
[01249] Reference Example 98
[01250] 2-{[2-(trifluoromethyl)-4-pyridinyl]oxy}-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethanamine
[01251] The compound (76 mg) prepared in Reference Example 97 was used instead of the compound prepared in Reference Example 90 and subjected to the same reaction as in Reference Example 91 to give the title compound (36 mg).
[01252] LCMS (C) Retention time (min) : 0.768 ;
[01253] MS (ESI, Pos.) *m/z* 394 $(M + CH_3CN + H)^+$.
[01254] Example 46
[01255] 5-chloro-N-(2-{[2-(trifluoromethyl)-4-pyridinyl]oxy}-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl)-2-pyridinecarboxamide

[01256] The compound (36 mg) prepared in Reference Example 98 was used instead of the compound prepared in Reference Example 91 and subjected to the same reaction as in Reference Example 92 to give the title compound (20.6 mg).
[01257] LCMS (D) Retention time (min) : 2.015 ;
[01258] MS (ESI, Pos.) 492 $(M + H)^+$;
[01259] ^{1}H-NMR($CDCl_3$) : δ 9.06, 8.75, 8.62, 8.56, 8.15, 7.89, 7.28, 7.05, 5.75, 4.53 - 4.64.
[01260] Example 47
[01261] 5-chloro-N-{(1ξ)-2-{[2-(trifluoromethyl)-4-pyridinyl]oxy}-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide
[01262] The compound (190 mg) prepared in Example 46 was separated by SFC to give two isomers.
[01263] SFC was carried out under the following condition.
[01264] Column: (S,S)whelk-01 100x4.6mm I.D., 5μm;
[01265] Mobile phase: A: CO_2, B: ethanol (0.05% DEA);
[01266] Isocratic: 40% B;
[01267] Flow rate: 2.5 mL/min;
[01268] Column temperature: 40°C;
[01269] BPR: 100 bar.
[01270] Whereby the title compound (53.4 mg) was obtained in the first peak (retention time : 0.931 min).
[01271] LCMS (C) Retention time (min) : 0.972 ;
[01272] MS (ESI, Pos.) 492 $(M + H)^+$;
[01273] ^{1}H-NMR($CDCl_3$) : δ 9.06, 8.76, 8.62, 8.56, 8.14, 7.83 - 7.97, 7.28, 7.05, 5.75, 4.48 - 4.69.
[01274] Example 48
[01275] 5-chloro-N-(2-{[2-(trifluoromethyl)-4-pyridinyl]oxy}-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl)-1,3-thiazole-2-carboxamide
[01276] The compound (174 mg) prepared in Reference Example 21 was used instead of 5-chloro-2-pyridinecarboxylic acid and subjected to the same reaction as in Example 46 to give the title compound (325 mg).
[01277] LCMS (C) Retention time (min) : 0.979 ;
[01278] MS (ESI, Pos.) 498 $(M + H)^+$;
[01279] ^{1}H-NMR(DMSO-d_6) : δ 9.90, 9.25, 8.58, 8.14, 7.54, 7.34, 5.70, 4.69 - 4.79, 4.58 - 4.66.
[01280] Example 49

[01281] 5-chloro-N-{(1ξ)-2-{[2-(trifluoromethyl)-4-pyridinyl]oxy}-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-1,3-thiazole-2-carboxamide

[01282] The compound (410 mg) prepared in Example 48 was separated by SFC to give two isomers.

[01283] SFC was carried out under the following condition.

[01284] Column: Chiralpak AD-3 50x4.6mm I.D., 3μm;

[01285] mobile phase: A: CO_2 B: ethanol (0.05% DEA);

[01286] Gradient: from: 5% to 40% of B in 2 min and hold 40% for 1.2 min, then 5% of B for 0.8 min;

[01287] Flow rate: 4 mL/min;

[01288] Column temperature: 35°C;

[01289] BPR: 1500 psi.

[01290] Whereby the title compound (112 mg) was obtained in the first peak (retention time : 0.98 min).

[01291] LCMS (C) Retention time (min) : 0.983 ;

[01292] MS (ESI, Pos.) 498 $(M + H)^+$;

[01293] ^{1}H-NMR($CDCl_3$) : δ 9.06, 8.63, 7.98, 7.72, 7.25 - 7.27, 7.04, 5.71, 4.58 - 4.64, 4.51 - 4.57.

[01294] Reference Example 99

[01295] 2-methyl-2-propanyl [6-(trifluoromethyl)-3-pyridinyl]acetate

[01296] To a solution of solution of 5-bromo-2-(trifluoromethyl)pyridine (5 g), tris(dibenzylidenacetone)dipalladium ($Pd_2(dba)_3$) (1.0 g) and 2-dicyclohexylphosphino-2'4'6'-triisopropylbiphenyl (Xphos) (1.0 g) in THF (4 mL) was added bromo-(2-tert-butoxy-2-oxo-ethyl)zinc (66.4 mL, 1M) at 20°C. The reaction was purged with N_2, then, heated at 60°C for 12 h under N_2 atmosphere. LCMS showed desired MS as the major peak. The reaction was poured onto ice-water (50 mL) and ethyl acetate (60 mL). The precipitate was filtered off. The organic layer was washed with water (40 mL) and brine (40 mL). The organic layer was dried over sodium sulfate, concentrated in vacuum to give crude residue, which was purified by silica gel column chromatography (0~4% ethyl acetate in petroleum ether) to give the title compound (5.7 g).

[01297] ^{1}H-NMR($CDCl_3$) : δ 8.63, 7.82 - 7.87, 7.63 - 7.68, 3.63, 1.46.

[01298] Reference Example 100

[01299] 2-methyl-2-propanyl bromo[6-(trifluoromethyl)-3-pyridinyl]acetate

[01300] To a solution of the compound (2.45 g) prepared in Reference Example 99 and N-bromosuccinimide (2.0 g) in carbon tetrachloride (30 mL) was add benzoyl peroxide

(BPO) (227 mg). The reaction was heated at 80°C for 12 h to give yellow mixture. The reaction was diluted with dichloromethane (20 mL), washed with water (20 mL x2) and brine (20 mL). The organic layer was dried over sodium sulfate, concentrated in vacuum to give crude residue. The residue was purified by prep-TLC (petroleum ether : ethyl acetate = 12 : 1) to give the title compound (2.3 g).

[01301] ^{1}H-NMR($CDCl_3$) : δ 8.79, 8.16 - 8.18, 7.72, 5.29, 1.49.

[01302] Reference Example 101

[01303] 2-methyl-2-propanyl amino[6-(trifluoromethyl)-3-pyridinyl]acetate

[01304] To a solution of the compound (2.3 g) prepared in Reference Example 100 in THF (25 mL) was added ammonia in methanol (14.5 mL, 7M) at 0°C. The mixture was stirred at 0°C for 1 h and was stirred at 20°C for 1 h. LCMS showed the reaction was completed. The solution was concentrated under reduced pressure to give the title compound (1.85 g). The crude product was directly used in the next reaction.

[01305] Reference Example 102

[01306] 2-methyl-2-propanyl ({[(2-methyl-2-propanyl)oxy]carbonyl}amino)[6-(trifluoromethyl)-3-pyridinyl]acetate

[01307] To a solution of the compound (1.85 g) prepared in Reference Example 101 in water (20 mL) and dichloromethane (20 mL) was added sodium hydrogencarbonate (844 mg) and di-tert-butyl dicarbonate (3.0 g) at 20°C. The mixture was stirred at 20°C for 2 h to give a colorless mixture. The reaction mixture diluted with water (10 mL) and extracted with dichloromethane (10 mL x3). The combined organic layers were washed with brine (10 mL x3), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (0~2% ethyl acetate in petroleum ether) to give the title compound (2 g).

[01308] ^{1}H-NMR($CDCl_3$) : δ 8.76, 7.88, 7.68, 5.70 - 5.85, 1.41.

[01309] Reference Example 103

[01310] 2-methyl-2-propanyl {2-hydroxy-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}carbamate

[01311] To a solution of the compound (1.8 g) prepared in Reference Example 102 in THF (36 mL) was added diisobutylalluminium hydride (DIBAL-H) (14.4 mL, 1M in toluene) at -78°C, the mixture was stirred at -78°C for 10 min, then slowly warmed to 0°C and stirred at 0°C for 5 h to give a white mixture. TLC (petroleum ether : ethyl acetate = 3 : 1) showed the reaction was completed. The mixture was quenched by adding saturated aqueous sodium potassium tartrate solution (5 mL) at 0°C, then extracted with ethyl acetate (10 mL x3). The combined organic layers were washed

with brine (10 mL x3), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (0~30% ethyl acetate in petroleum ether) to give the title compound (800 mg).

[01312] ^{1}H-NMR($CDCl_3$) : δ 8.71, 7.86, 7.68, 5.40 - 5.55, 4.80 - 4.90, 3.88 - 4.01, 1.44.

[01313] Reference Example 104

[01314] 2-amino-2-[6-(trifluoromethyl)-3-pyridinyl]ethanol trifluoroacetate

[01315] To a solution of the compound (95 mg) prepared in Reference Example 103 in dichloromethane (1 mL) was added trifluoroacetic acid (TFA) (0.46 mL), the mixture was stirred at 20°C for 1 h. TLC (petroleum ether : ethyl acetate = 2 : 1) showed starting material was consumed completely. The reaction mixture was concentrated under reduced pressure to give the title compound (64 mg).

[01316] Reference Example 105

[01317] 5-chloro-N-{2-hydroxy-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide

[01318] A solution 5-chloro-2-pyridinecarboxylic acid (46 mg) in DMF (0.5 mL) was stirred with HATU (110 mg) and DIEA (0.14 mL) at 20°C for 10 mins. Then, the solution was treated with the compound (64 mg) prepared in Reference Example 104. The reaction was stirred at 20°C for 2 h to give pale yellow solution. LCMS showed desired MS. The reaction was diluted with ethyl acetate (8 mL) and water (5 mL). The organic layer was washed with water (5 mL x2) and brine (5 mL), then, dried over sodium sulfate, concentrated in vacuum to give crude residue, which was purified by prep-TLC (petroleum ether : ethyl acetate = 2 : 1) to give the title compound (60 mg).

[01319] LCMS (C) Retention time (min) : 0.834 ;

[01320] MS (ESI, Pos.) 346 $(M + H)^+$.

[01321] Example 50

[01322] 5-chloro-N-(2-{[5-(trifluoromethyl)-2-pyrazinyl]oxy}-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl)-2-pyridinecarboxamide

[01323] To a solution of the compound (30 mg) prepare in Reference Example 105 in THF (1 mL) was added sodium hydride (6.9 mg, 60% in oil) at 0°C, the mixture was stirred at 0°C for 0.5 h. Then, 2-chloro-5-(trifluoromethyl) pyrazine (20.5 mg) (CAS No.: 799557-87-2) was added. The reaction mixture was stirred at 20°C for 4 h to give a yellow solution. TLC (petroleum ether : ethyl acetate = 1 : 2) showed a new spot was formed. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x3). The combined organic layers were washed with brine (20

mL x3), dried over sodium sulfate, filtered and concentrated under reduced pressure to give the title compound (14.89 mg).

[01324] LCMS (C) Retention time (min) : 1.009 ;

[01325] MS (ESI, Pos.) 492 $(M + H)^+$;

[01326] ^{1}H-NMR($CDCl_3$) : δ 8.87, 8.78, 8.54, 8.49, 8.35, 8.13, 7.98, 7.86, 7.72, 5.69 - 5.81, 4.81 - 4.93.

[01327] Reference Example 106

[01328] N-[(1E)-2-{[dimethyl(2-methyl-2-propanyl)silyl]oxy}ethylidene]-2-methyl-2-propanesulfinamide

[01329] To a solution of (tert-butyldimethylsilyloxy)acetaldehyde (5 g) (CAS No.: 102191-92-4) and 2-methyl-2-propanesulfinamide (4.17 g) in dichloromethane (80 mL) was added cupric sulfate (11.45g), the mixture was stirred at 20°C for 3 h to give green blue mixture. The solid was filtered off, the residue was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether : ethyl acetate=19 : 1 to 6 : 1) to give the title compound (6.8 g).

[01330] LCMS (C) Retention time (min) : 1.049 ;

[01331] MS (ESI, Pos.) 278 $(M + H)^+$.

[01332] Reference Example 107

[01333] N-(2-{[dimethyl(2-methyl-2-propanyl)silyl]oxy}-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl)-2-methyl-2-propanesulfinamide

[01334] To a solution of 5-bromo-2-(trifluoromethyl)pyridine (1.3 g) in THF (10 mL), was added iPrMgCl·LiCl (3.9 mL, 1.3M in THF) at 0°C. The mixture was stirred at 0°C for 1.5 h. The compound (1.0 g) prepared in Reference Example 106 in THF (20 mL) was added to the above solution drop-wise. The reaction mixture was stirred at 0°C for 2 h to give a yellow solution. LCMS showed the reaction was completed and the desired compound was detected. The reaction mixture was quenched with ice-water (40 mL), diluted with ethyl acetate (60 mL). The organic layer was washed with water (40 mL x2) and brine (40 mL), then, dried over sodium sulfate, concentrated in vacuum to give crude residue. The residue was purified by silica gel column chromatography (0~30% ethyl acetate in petroleum ether) to give the title compound (1000 mg).

[01335] LCMS (C) Retention time (min) : 1.067 ;

[01336] MS (ESI, Pos.) 425 $(M + H)^+$.

[01337] Reference Example 108

[01338] 2-{[dimethyl(2-methyl-2-propanyl)silyl]oxy}-1-[6-(trifluoromethyl)-3-pyridinyl]ethanamine

[01339] To a solution of the compound (300 mg) prepared in Reference Example 107 in 1,4-dioxane (15 mL) was added 4M HCl in dioxane (0.88 mL) at 0°C. The solution was stirred at 20°C for 10 min to give white mixture. The solution partitioned with ethyl acetate (20 mL) and water (20 mL). The aqueous layer was basified with sodium bicarbonate to pH=8, extracted with ethyl acetate (20 mL x3). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the title compound (184 mg).

[01340] LCMS (C) Retention time (min) : 0.838 ;

[01341] MS (ESI, Pos.) 321 $(M + H)^+$.

[01342] Reference Example 109

[01343] 5-chloro-N-(2-{[dimethyl(2-methyl-2-propanyl)silyl]oxy}-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl)-1,3-thiazole-2-carboxamide

[01344] To a solution of the compound (200 mg) prepare in Reference Example 108, the compound (212 mg) prepared in Reference Example 21 in DMF (1 mL) was added DIEA (0.31 mL), HATU (333 mg) at 20°C. The mixture was stirred for 16 h at 20°C. The reaction mixture was concentrated under reduced pressure, poured into water (20 mL), alkalified with sodium bicarbonate (20 mL), extracted with ethyl acetate (30 mL x 3). The combined organic layer was washed with brine (30 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (0~10% ethyl acetate in petroleum ether) to give the title compound (190 mg).

[01345] ^{1}H-NMR($CDCl_3$) : δ 8.79, 8.03, 7.90, 7.70, 7.67, 5.22 - 5.26, 4.06 - 4.10, 3.93 - 3.97, 0.89, 0.06, -0.01.

[01346] Reference Example 110

[01347] 5-chloro-N-{2-hydroxy-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-1,3-thiazole-2-carboxamide

[01348] To a solution of the compound (190 mg) prepared in Reference Example 109 in THF (2 mL) was added tetra-N-butylammonium fluoride (TBAF, 1M in THF) (0.17 mL). The mixture was stirred at 20°C for 2 h to give a yellow solution. TLC (petroleum ether : ethyl acetate = 4 : 1) showed the reaction was completed. The reaction mixture diluted with water (10 mL) and extracted with ethyl acetate (10 mL x3). The combined organic layers were washed with brine (10 mL x3), dried over sodium sulfate, filtered and concentrated under reduced pressure to give the title compound (130 mg).

[01349] ^{1}H-NMR($CDCl_3$) : δ 8.81, 7.93 - 8.00, 7.69 - 7.70, 5.30 - 5.33, 4.04 - 4.25.

[01350] Example 51

[01351] 5-chloro-N-(1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[5-(trifluoromethyl)-2-pyrimidinyl]oxy}ethyl)-1,3-thiazole-2-carboxamide

[01352] To a solution of the compound (30 mg) prepared in Reference Example 110 in THF (1 mL) was added sodium hydride (6.8 mg, 60% in oil) at 0°C. The mixture was stirred at 0°C for 0.5 h. Then, 2-chloro-5-(trifluoromethyl) pyrimidine (21 mg) (CAS No.: 69034-12-4) was added. The reaction mixture was stirred at 20°C for 2 h to give a yellow solution. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x3). The combined organic layers were washed with brine (20 mL x3), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (petroleum ether : ethyl acetate = 2 : 1) to give the title compound (27.2 mg).

[01353] LCMS (C) Retention time (min) : 0.998 ;

[01354] MS (ESI, Pos.) 498 $(M + H)^+$;

[01355] ^{1}H-NMR($CDCl_3$) : δ 8.86, 8.79, 8.22, 8.02, 7.71, 7.68, 5.64-5.75, 4.83 - 4.95.

[01356] Example 52

[01357] 5-chloro-N-(2-{[5-(trifluoromethyl)-2-pyrazinyl]oxy}-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl)-1,3-thiazole-2-carboxamide

[01358] 2-chloro-5-(trifluoromethyl) pyrazine (21 mg) was used instead of 2-chloro-5-(trifluoromethyl) pyrimidine and subjected to the same reaction as in Example 51 to give the title compound (26.6 mg).

[01359] LCMS (C) Retention time (min) : 1.030 ;

[01360] MS (ESI, Pos.) 498 $(M + H)^+$;

[01361] ^{1}H-NMR($CDCl_3$) : δ 8.86, 8.50, 8.35, 8.12, 7.97, 7.73, 7.69, 5.64-5.73, 4.81 - 4.92.

[01362] Reference Example 111

[01363] N-[(E)-(5-chloro-2-pyridinyl)methylene]-2-methyl-2-propanesulfinamide

[01364] To a solution of 5-chloro-2-formylpyridine (2 g) (CAS No.: 31181-89-2) in THF (20 mL) was added 2-methylpropane-2-sulfinamide (1.88 g) and titanium ethoxide ($Ti(OEt)_4$) (5.91 mL). The mixture was stirred at 20°C under N_2 for 16 h to give a yellow mixture. Brine (20 mL) was added to quench the reaction and then the mixture was filtered through a pad of Celite (Registered Trademark) cake, the cake was washed with ethyl acetate (15 mL x2). The combined filtrate was diluted with water (30 mL), extracted with ethyl acetate (30 mL x3). The combined organic layers were washed with brine (30 mL x3), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column

chromatography (0~10% ethyl acetate in petroleum ether) to give the title compound (2.4 g).

[01365] ^{1}H-NMR (DMSO-d_6): δ 8.00, 7.65, 7.27 - 7.33, 0.38.

[01366] Reference Example 112

[01367] N-[(5-chloro-2-pyridinyl)(3,4-dichlorophenyl)methyl]-2-methyl-2-propanesulfinamide

[01368] To a solution of 4-bromo-1, 2-dichlorobenzene (240 mg) (CAS No.: 18282-59-2) in THF (2 mL) was added *i*PrMgCl·LiCl (0.82 mL, 1.3M in THF) under N_2 at 0°C. The mixture was stirred at 20°C for 1 h to give a brown mixture. The compound (200 mg) prepared in Reference Example 111 in THF (1 mL) was added into the mixture. The mixture was stirred at 0°C for 2 h to give a brown mixture. LCMS showed the desired compound was detected. The reaction mixture was quenched by water (10 mL) and extracted with ethyl acetate (15 mL x3). The combined organic layers were washed with brine (15 mL x3), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (0~20% ethyl acetate in petroleum ether) to give the title compound (190 mg).

[01369] ^{1}H-NMR (DMSO-d_6): δ 8.57, 7.96 - 7.98, 7.58 - 7.68, 7.37, 6.26, 5.70, 1.14.

[01370] Reference Example 113

[01371] 1-(5-chloro-2-pyridinyl)-1-(3,4-dichlorophenyl)methanamine dihydrochloride

[01372] To a solution of the compound (240 mg) prepared in Reference Example 112 in methanol (3 mL) was added 4M HCl in methanol (6 mL). The mixture was stirred at 20°C for 2 h to give a mixture. LCMS showed the reaction was completed and the desired compound was detected. The mixture was concentrated under reduced pressure to give the title compound (200 mg).

[01373] ^{1}H-NMR (DMSO-d_6): δ 9.24 - 9.28, 8,74, 8.04, 7.89, 7.72, 7.60, 7.39, 5.80 - 5.95.

[01374] Reference Example 114

[01375] 5-chloro-N-[(5-chloro-2-pyridinyl)(3,4-dichlorophenyl)methyl]nicotinamide

[01376] To a solution of 5-chloropyridine-3-carboxylic acid (121 mg) (CAS No.: 22620-27-5) in DMF (2 mL) was added HATU (291 mg), DIEA (0.36 mL) and the compound (200 mg) prepared in Reference Example 113 at 20°C. The mixture was stirred at 20°C for 2 h to give a mixture. LCMS showed the reaction was completed and the desired compound was detected. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (15 mL x3). The combined organic layers were washed with brine (15 mL x6), dried over sodium sulfate filtered and concentrated

under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (0~25% ethyl acetate in petroleum ether) to give the title compound (210 mg).

[01377] LCMS (A) Retention time (min): 0.939;

[01378] MS (ESI, Pos.) 428 $(M + H)^+$.

[01379] Comparative Example A

[01380] 5-chloro-N-[(R)-(5-chloro-2-pyridinyl)(3,4-dichlorophenyl)methyl]nicotinamide

[01381] and

[01382] Comparative Example B

[01383] 5-chloro-N-[(S)-(5-chloro-2-pyridinyl)(3,4-dichlorophenyl)methyl]nicotinamide

[01384] The compound (210 mg) prepared in Reference Example 114 was separated by SFC to give two isomers.

[01385] SFC was carried out under the following condition.

[01386] Column: Chiralpak AD-3 150x4.6mm I.D., 3μm;

[01387] Mobile phase: A: CO_2, B: ethanol (0.05% DEA);

[01388] Isocratic: 60% B

[01389] Flow rate: 2 mL/min;

[01390] Column temperature: 35°C;

[01391] BPR: 1500 psi.

[01392] Whereby the title compound (Comparative Example A) (83 mg) was obtained in the first peak (retention time : 3.06 min).

[01393] LCMS (C) Retention time (min): 1.018;

[01394] MS (ESI, Pos.) 428 $(M + H)^+$;

[01395] ^{1}H-NMR (DMSO-d_6): δ 9.64, 8.99, 8.81, 8.62, 8.41, 7.97, 7.74, 7.59 - 7.67, 7.44, 6.45.

[01396] Title compound (Comparative Example B) (76 mg) was obtained in the second peak (retention time : 4.90 min).

[01397] LCMS (A) Retention time (min): 0.950;

[01398] MS (ESI, Pos.) 428 $(M + H)^+$;

[01399] ^{1}H-NMR (DMSO-d_6) δ: 9.65, 8.98, 8.80, 8.62, 8.41, 7.96, 7.74, 7.60 - 7.64, 7.45, 6.44.

[01400] Comparative Example A and Comparative Example B are the isomers of the compound (Compound ID : CYM 52467) described in Patent Literature 1.

[Biological Examples]

[01401] Hereinafter, Biological Experimental Examples will be shown, and the effects of the compound of the present disclosure were confirmed based on these experimental methods.

[01402] Biological Experimental Example 1: Evaluation of $S1P_3$ receptor antagonistic activity of the compound of the present disclosure by monitoring intracellular calcium concentration

[01403] Chinese hamster ovary (hereinafter, CHO) cells in which each of a human $S1P_3$ was overexpressed were cultured in Ham's F-12 medium (Wako Pure Chemical, 087-08335) containing 10% fetal bovine serum (hereinafter, FBS) (Thermo), penicillin/streptomycin (Nacalai Tesque), and geneticin (0.25 mg/mL) (Thermo). The culture medium was replaced three days before performing a calcium assay and on the day of the assay. 4 hours after the culture medium replacement, the culture medium was removed, and washing was performed once with phosphate-buffered saline. After the cells were detached by adding 0.25% trypsin ethylene diamine tetra-acetic acid (hereinafter, EDTA) (Wako Pure Chemical, 209-16941), the cells were recovered by adding a culture medium. The recovered cell suspension was centrifuged to remove the supernatant, and the cells were suspended in phosphate-buffered saline, and the cell number was counted. The cells were suspended in a Hank's Balanced Salt Solution (Wako Pure Chemical, 084-08965) containing Calcium 6 Assay Reagent (Molecular Devices, LLC, R8191), 20 mM HEPES (Wako Pure Chemical), and 2.5 mM probenecid (Sigma Aldrich, P8761) at a cell density of 1.0×10^6 cells/mL, and the suspension was incubated at 37°C for about 1 hour. Thereafter, the supernatant was removed by centrifugation, and the cells were suspended in a Hank's Balanced Salt Solution containing 20 mM HEPES, 2.5 mM probenecid, and 0.1% bovine serum albumin (hereinafter, BSA) (Sigma Aldrich) at a cell density of 0.5×10^6 cells/mL. The suspension was inoculated in a 96-well plate at 80 μL/well. The plate was set on a fluorescent drug screening system (FDSS 7000, Hamamatsu), and the test compounds and S1P (Cayman, 62570) were sequentially added thereto, and an increase in intracellular calcium concentration between before and after the addition was measured at an excitation wavelength of 480 nm and a fluorescence wavelength of 540 nm. The increase in intracellular calcium concentration was evaluated by the signal intensity at the fluorescence wavelength, and the antagonistic activity of each compound was calculated by assuming the signal intensity when S1P was added to be 0% activity and S1P was not added to be 100% activity. Furthermore, Comparative Example A and Comparative Example B were used as comparative compound.

[01404] [Results]

[01405] $S1P_3$ receptor antagonistic activities (IC_{50} values) of the test compounds of the present disclosure are shown in Table 1. $S1P_3$ receptor antagonistic activities of compound of the present disclosure was stronger than that of Comparative Examples.

[01406] [Table 1]

Compound	IC_{50} (nmol/L)	Compound	IC_{50} (nmol/L)
Comparative Example A	111	Example 26	7
Comparative Example B	1128	Example 27	6
Example 1	2	Example 28	1
Example 6	6	Example 31	9
Example 7	7	Example 33	2
Example 8	2	Example 34	<1
Example 12	4	Example 38	9
Example 13	1	Example 39	9
Example 15	2	Example 40	1
Example 16	4	Example 42	1
Example 18	9	Example 44	<1
Example 19	1	Example 47	4
Example 20	2	Example 49	1
Example 22	1	Example 52	9
Example 23	<1	-	-

[01407] Biological Experimental Example 2 : Evaluation of $S1P_3$ receptor inverse agonistic activity of the compound of the present disclosure by membrane protein activity measurement method

[01408] Reporter cells were cultured utilizing Dulbecco's Modified Eagle Medium (DMEM) (Nacclai tesque) supplemented with 10% fetal calf serum (FCS) (Serana) and penicillin/streptomycin (Nacclai tesque). To liberate the cells, trypsin-EDTA (Nacclai tesque, 26253-84) was employed. Subsequently, the cells were transitioned to DMEM supplemented with 10% dialysis FCS. The cells were then suspended and evenly distributed at a concentration of 24,000 cells per well on 96-well white microplates. Ensuring proper adherence of the seeded cells to the bottom of the microplate, the cultivation was carried out at a temperature of 37 °C in the presence of 5% carbon dioxide (CO_2). The cells were allowed to grow overnight. Plasmids expressing $S1P_3$

receptor and luciferase reporters were combined and transfected into the cells at a total dosage of 100 ng per well using transfection reagents (FuGene 6, Promega, E2691). Afterward, the cells were cultured overnight at a temperature of 37 °C in the presence of 5% CO_2. 300 times the concentration of each final test, test compound solutions were prepared. Immediately prior to the assay, the test compound solutions were diluted to 6 times the concentration of each final test using DMEM containing 10% dialysis FCS. A test compound solution, prepared just before, with a concentration 6 times higher than the desired final test concentration was added to each well. Subsequently, the solution was cultured at a temperature of 37°C for a duration of 6 hours in the presence of 5% CO_2. Following the 6-hour period of test compound stimulation, the medium was subsequently aspirated. To quantify luciferase, a luciferase quantification reagent (Steady-Glo, Promega, E2510) was introduced into the well. The emitted luciferase light was then measured using a plate reader (Victor Nivo, Perkin Elmer). The above experimental method was referred to Reference Example A6 in Patent Publication No. WO2020/026979.

[01409] Data analysis was performed using the Scipy which is Python scientific computing library and the Hill equation was approximated by non-linear least squares for measurement results that showed concentration dependence. The parameters used were EC_{50}, Hill coefficient, curve bottom, and curve top.

$$\text{Reporter activity} = \frac{(\text{Curve top} - \text{Curve bottom}) \times \text{Conc}^{\text{Hill}}}{\text{Conc}^{\text{Hill}} + \text{EC50}^{\text{Hill}}} + \text{Curve bottom}$$

[01410] [Results]

[01411] The compound of the present disclosure had potent $S1P_3$ receptor inverse agonistic activities (EC_{50} values).

[01412] Biological Experimental Example 3: Evaluation of stability in human liver microsomes

[01413] (1) Preparation of Test Compound Solutions

[01414] The test compound (10 mmol/L DMSO solution, 5 μL) was diluted with 195 μL of 50% acetonitrile solution to prepare a 0.25 mmol/L solution. Furthermore, 40 μL of the 0.25 mmol/L solution was collected and diluted with 160 μL of 50% acetonitrile solution to prepare a 0.05 mmol/L solution.

[01415] (2) Sample preparation at 0 minutes

[01416] To a reaction container, which was previously warmed to 37°C, 245 μL of 0.1 mol/phosphate buffer solution (pH7.4) containing 0.5 mg/mL human liver microsomes

(Xenotech Inc., H2610) and Nicotinamide Adenine Dinucleotide Phosphate (NADPH) (CORNING Inc., K5000) was added. After pre-incubation for 10 minutes, the aforementioned test compound solution (5 μL) was added to initiate the reaction. Immediately after the start, 50 μL of the solution was collected and added to 150 μL of an acetonitrile/ethanol =7/3 solution containing the internal standard (nicardipine, candesartan) to stop the reaction. After centrifugation of this solution at 3000 g for 3 minutes, 40 μL of the supernatant was collected and diluted with 160 μL of 50% acetonitrile solution to prepare a sample at 0 min for reaction.

[01417] (3) Sample preparation for 15 minutes

[01418] After incubation of the reaction solution at 37°C for 15 minutes, 50 μL of the solution was collected, and added to 150 μL of an acetonitrile/ethanol =7/3 solution containing the internal standard (nicardipine, candesartan,) to stop the reaction. After centrifugation of this solution at 3000 g for 3 minutes, 40 μL of the supernatant was collected and diluted with 160 μL of 50% acetonitrile solution to prepare a sample for 15 minutes of reaction.

[01419] (4) Sample preparation for 60 minutes

[01420] After incubation of the reaction solution at 37°C for 60 minutes, 50 μL of the solution was collected, and added to 150 μL of an acetonitrile/ethanol =7/3 solution containing the internal standard (nicardipine, candesartan,) to stop the reaction. After centrifugation of this solution at 3000 g for 3 minutes, 40 μL of the supernatant was collected and diluted with 160 μL of 50% acetonitrile solution to prepare a sample for 60 minutes of reaction.

[01421] (5) Evaluation method and results

[01422] The residual rate (%) was calculated by injecting 5 μL of the sample solution into the LC-MS system and dividing the peak area ratio (peak area of the test compound/internal standard substance) of the samples at 15 minutes and 60 minutes after reaction by the peak area ratio (peak area of the test compound/internal standard substance) of the sample at 0 minutes after reaction and multiplying by 100.

[01423] LCMS analysis conditions are as below.

[01424] [Reversed phase LCMS]

[01425] Reversed phased LCMS analysis was obtained on Thermo Q Exactive Focus with ESI source. MS parameters were as follows:

[01426] Mobile Phase: 0.2% formic acid in 5mM Ammonium Acetate aq. (solvent A) and acetonitrile (solvent B), using the elution gradient 5%-95% (solvent B) over 0.7minutes and holding at 95% for 0.5 minutes at flow of 0.6 ml/min;

[01427] Column: InertSustain C18 HP 3μm, 2.1 x 30mm;

[01428] Column temperature: 40℃, detector MS ionization: ESI.

[01429] Furthermore, Comparative Example A and Comparative Example B were used as comparative compound.

[01430] [Results]

[01431] The half-life (hereinafter, T1/2) of the compounds in human liver microsome are shown in Table 2. The compound of the present disclosure was stable in human liver microsome than Comparative Example A.

[01432] [Table 2]

Compound	T1/2 (min)	Compound	T1/2 (min)
Comparative Example A	<15	Example 26	>200
Comparative Example B	79	Example 27	>200
Example 1	>200	Example 28	>200
Example 6	>200	Example 31	>200
Example 7	>200	Example 33	92
Example 8	>200	Example 34	87
Example 12	>200	Example 38	>200
Example 13	>200	Example 39	>200
Example 15	>200	Example 40	>200
Example 16	>200	Example 42	196
Example 18	>200	Example 44	>200
Example 19	>200	Example 47	>200
Example 20	164	Example 49	>200
Example 22	141	Example 52	>200
Example 23	>200	-	-

[01433] Biological Experimental Example 4: Measurement of inhibitory activity of drug metabolizing enzyme (inhibition of human CYP3A4 (including TDI effect))

[01434] The term “TDI” herein refers to Time-dependent inhibition of 3A4.

[01435] “TDI effect” occurs after a period of time the inhibitor is incubated with the enzyme, so its effect is delayed. This assay reveals the potential mechanisms include the formation of inhibitory metabolites.

[01436] The reaction was performed on a 384 well plate. The positive control substance, ketoconazole (CYP3A4) and erythromycin (CYP3A4-TDI) was prepared with DMSO at 300 times the final concentration (ketoconazole: 0.006 and 0.06 mmol/L, erythromycin: 0.9 and 9 mmol/L) and diluted 75 times with purified water containing 2.7% acetonitrile to prepare a solution (ketoconazole: 0.08 and 0.8 μmol/L, erythromycin: 12 and 120 μmol/L). The test compounds were prepared at 0.3 and 3

mmol/L in DMSO and diluted 75 times with purified water containing 2.7% acetonitrile to prepare solutions at 4 and 40 μmol/L. Then, potassium phosphate buffer (pH7.4), magnesium chloride (5 mol/L), liver microsome (Cypex, 10 mg/mL, CYP/EZ010), and NADPH (CORNING Inc., K5000) were prepared.

[01437] For 3A4, after preincubation with 8 μL of Potassium Phosphate Buffer, pH7.4 and 5 mmol/L $MgCl_2 .6H_2O$ containing liver microsome for 10 minutes, 4 μL of NADPH and 4 μL of test compound and positive control substance solution were added to initiate the reaction. After incubation at 25°C for 30 minutes, 16 μL of the luciferase solution was added to stop the reaction and cause luciferin to emit light. Then, the emission intensity of the reaction solution was measured.

[01438] To evaluate the TDI effect of 3A4, 12 μL of Potassium Phosphate Buffer, pH7.4 and 5 mmol/L $MgCl_2 .6H_2O$ containing the liver microsome was preincubated for 10 minutes, and then 6 μL of the NADPH, test compound solution, and positive control substance solution were dispensed to each well for 30 minutes of incubation at 25°C. Then, 6 μL of Luciferun-IPA (Promega, V840B) was added and the mixture was incubated for another 30 minutes. Then, 24 μL of Luciferin Detection Reagent (Promega, V9002) was added to stop the reaction and emit luciferin to measure the luminescence intensity of the reaction mixture.

[01439] The inhibition rate was defined as the reduction rate of luminescence intensity (inhibition rate) compared with the control reacted with DMSO instead of the test compound solution and calculated by the following equation.

[01440] Inhibition rate (%) =100- {(Emission intensity after reaction of the test compound − Emission intensity before reaction of the test compound)/(Emission intensity after reaction of the control − Emission intensity before reaction of the control) x100}

[01441] The IC50 value was set to <1 μM when the inhibition rate was ≥ 50% at 1 μmol/L, >10 μmol/L when the inhibition rate was ≤ 50% at 10 μmol/L, and was calculated by the following formula for the interval (≤ 50% at 1 μmol/L and ≥ 50% at 10 μmol/L).

[01442] IC50 = (50 – b)/a

[01443] where a and b are the slope and intercept of the linear regression line y=ax+b passing through 2 points: 1 μmol/L concentration and inhibition rate, and 10 μmol/L concentration and inhibition rate.

[01444] Furthermore, Comparative Example A and Comparative Example B were used as comparative compound.

[01445] [Results]

[01446] The inhibitory activities of the compounds at 0 and 30 min are shown in Table 3. While Comparative Examples exhibited TDI effect, the compound of the present disclosure did not exhibit TDI effect.

[01447] [Table 3]

Compound	0 min, μM	30 min, μM	Compound	0 min, μM	30 min, μM
Comparative Example A	>10	<1	Example 26	>10	>10
Comparative Example B	6.1	<1	Example 27	>10	>10
Example 1	>10	>10	Example 28	>10	>10
Example 6	>10	>10	Example 31	>10	>10
Example 7	>10	>10	Example 33	>10	>10
Example 8	>10	>10	Example 34	>10	>10
Example 12	>10	>10	Example 38	>10	>10
Example 13	>10	>10	Example 39	>10	>10
Example 15	>10	>10	Example 40	>10	>10
Example 16	>10	>10	Example 42	>10	>10
Example 18	>10	>10	Example 44	>10	>10
Example 19	>10	>10	Example 47	>10	>10
Example 20	>10	>10	Example 49	>10	>10
Example 22	>10	>10	Example 52	>10	>10
Example 23	>10	>10	-	-	-

[01448] Biological Experimental Example 5: Effect on human ether-a-go-go related gene (hERG) channel current

[01449] Inhibition of hERG channel current is the most common mechanism responsible for pharmaceutical-induced prolongation of QT interval of the electrocardiogram. When the QT interval is prolonged, there is an increased risk of ventricular tachyarrhythmia, including torsade de pointes, particularly when combined with other risk factors (for example, hypokalemia, heart disease with structural changes, bradycardia). Therefore, the evaluation of effects on the hERG channel current is required for drug development (ICH-S7B Guideline), and inhibition of the hERG channel current is an indicator of cardiotoxicity.

[01450] Inhibitory effects on hERG current elicited by a test pulse were evaluated using Qube 384 automated patch clamp system (Sophion Bioscience A/S). Patch clamp technique is gold standard technique for evaluating hERG channel pharmacology. The detail method is described below.

[01451] After 2-3 days of culture, hERG-transfected CHO-K1 cells (Cytomyx Ltd.) were removed from the plate with a trypsin/EDTA solution and suspended in EX-CELL (Registered Trademark) ACF CHO Medium (Merck KGaA, C5467). This cell suspension was used for measurement of hERG current by means of the perforated patch-clamp technique in the presence of test compounds (final concentrations of test compounds: 1, 3, and 10 μmol/L; final concentration of DMSO: 0.1%). A test pulse was composed of three phases (i.e., hold voltage [−80 mV], depolarization voltage [+40 mV for 2 seconds], and repolarization voltage [−50 mV for 2 seconds]), and maximum tail current elicited after the repolarization phase was measured by Sophion Analyzer (Sophion Bioscience A/S). Test pulses were applied 20 times every 20 seconds before and after addition of test article, and the rate of change in the mean value of the maximum tail current for the last 3 times (vs. before addition of test compound) was determined. Inhibition rate of hERG current (%) was calculated using the following equation:

[01452] Inhibition rate of hERG current (%) = 100 × (1 – [Rate of change in the maximum tail current after versus before treatment with test article] / [Rate of change in the maximum tail current after versus before treatment with the veicle control])

[01453] [Results]

[01454] The compound of the present disclosure has a low hERG inhibitory activity.

[01455] Biological Experimental Example 6: Evaluation of mitochondrial membrane potential lowering effect and cytotoxic effect in cultured human hepatocytes

[01456] Mitochondrial dysfunction is known to affect organs and tissues in aerobic equilibrium, such as kidney and heart, and those that are exposed to high drug concentrations and undergo drug metabolism, such as liver (Drug Discovery Today12 (17-18), 777-785, 2007). Drug-induced decrease or loss of mitochondrial membrane potential can be caused by direct inhibition of the electron transport system, uncoupling of the electron transport to ATP synthase, or opening of the mitochondrial permeability transition pore. Therefore, the evaluation of mitochondrial membrane potential in hepatocytes can be a parameter of hepatotoxicity.

[01457] Human hepatocytes (BioIVT, F00995/M00995) were seeded into collagen-coated 96-well plates and cultured overnight in an incubator at 37°C with 5%CO_2 and 95% air. The cultured cells were stained with 5, 5', 6, 6' -Tetrachloro-1, 1', 3, 3' -tetraethylbenzimidazolylcarbocyanine iodide (also known as JC-1) (Calbiochem, 420200) for 1 h and then treated with the test compounds. The test compounds were dissolved in DMSO, diluted with the culture medium, Hepatocyte Culture Medium (HCM) (LONZA, CC-3198), and added to the cells. The concentrations of the test

compounds were 0, 6.25, 12.5, 25, 50, 100, 200, and 400 μmol/L. After 24 h of exposure to the test compounds, the fluorescence was measured with the SpectraMax (Registered Trademark) M5e plate reader (Molecular Device) at excitation/emission wavelengths of 485 nm/538 nm and 544 nm/590 nm. The mitochondrial membrane potential was calculated as the ratio of the measured value at 544 nm/590 nm to the measured value at 485 nm/538 nm. After that, the cellular ATP levels were measured using CellTiter-Glo (Registered Ttademark) Luminescent Cell Viability Assay kit (Promega, G7571) to evaluate the cytotoxic effects of the test compounds. The cells were lysed with assay buffer from the assay kit, and the concentration of ATP released from the cells was determined based on luciferin-luciferase enzyme activity. The luminescence was measured with the SpectraMax (Registered Ttademarl) M5e plate reader. The mitochondrial membrane potential lowering effect and the cytotoxic effect of test compounds were expressed as the concentration that decreased mitochondrial membrane potential and ATP concentration by 50% (IC_{50} value), respectively.

[01458] [Results]

[01459] The compound of the present disclosure had a low mitochondrial membrane potential lowering effect and a low cytotoxic effect.

[01460] Biological Experimental Example 7: Effectiveness in amyotrophic lateral sclerosis model mouse.

[01461] The male B6SJL-Tg (SOD1*G93A)dl1Gur / J mice (hereafter, SOD1 mice (The Jackson laboratory) or the male wild type mice (B6SJL mouse, hereafter, WT) (The Jackson laboratory) were used for the experiments.

[01462] Before the start of dosing (at 14 weeks old), the WT and SOD1 mice were grouped to balance the latency to fall on the rotarod, body weight, and the number of mutant SOD1 copies between groups. From 15 weeks of age, the vehicle (0.5 w/v% methylcellulose 400), the test compound or the positive control substance (riluzole) was administered orally once a day. The dose for each mouse was calculated based on their body weight measured weekly. After dosing began, blood plasma was collected at 27 and 30 weeks of age.

[01463] To assess neurodegeneration in the SOD1 mice, the levels of plasma Neurofilament Light chain (hereafter, NfL), which increases as neurodegeneration progresses, were measured using Simoa (Registered Trademark) HD-X (Quanterix, 103385). Figure 1 shows results thereof.

[01464] [Results]

[01465] The compound of the present disclosure exhibited a reduction in the plasma NfL levels in SOD1 mice.

[01466] Biological Experimental Example 8: Effectiveness in Multiple system atrophy model mouse

[01467] The male and female transgenic mice with oligodendroglial α-synuclein overexpression (hereafter, PLP-SYN) or the male and female wild-type mice (C57BL/6 mouse, hereafter, WT2) (Motac) were used for the experiments.

[01468] PLP-SYN mice were assigned to treatment groups based on strain, weight, sex, and results of the bar and notch tests. Treatment is started at 4 months of age and continued for 9 months of age.

[01469] Motor behavior was assessed by the beam test at baseline, at 3 months, at 5 months and at 7 months of treatment. The test was performed first, followed by administration of the test item. This test measures the ability to traverse a narrowing beam to reach the home cage. During training, 3 trials were performed using the beam. Mice then undergo the test where a grid was added on top of the beam. Mice performed three consecutive trials. The numbers of steps and sideslips were recorded on each trial.

[01470] Motor behavior was assessed by the notched bar test at baseline, at 3 months, at 5, 7 and 9 months of treatment. The test was performed first, followed by administration of the test item. (1) Mice were first trained on a "training" bar consisting of a piece 1.7 cm large and 50 cm long bearing terminal platforms of 6 cm×6 cm. Once they have successfully crossed the bar 10 times, they were (2) tested on a special notched bar having 12 intermediate raised steps equally distributed between the two platforms. Again, mice must cross the bar 10 times, but this time, the numbers of hind-paw slip outside of the steps were recorded. Data were given as percentage of errors on total number of crossed steps. The two sessions ((1) trained and (2) test) were done the same day, with intersessions time of 4 h. Figure 2 shows results thereof.

[01471] [Results]

[01472] The compound of the present disclosure inhibited progression of motor deficits in PLP-SYN mice.

[01473] Biological Experimental Example 9: Effectiveness in Alzheimer's disease model mouse.

[01474] APP (NL-G-F) mice (RIKEN BIO Co. Ltd.) with knock-in mutations of the Swedish (KM670/671NL), Iberian (I176F) and Arctic (E693G) types of APP or the male wild type mice (C57BL/6 mouse, hereafter, WT3) (RIKEN BIO Co. Ltd.) are used for the experiments.

[01475] Treatment is started at 3 months of age and continued for 3 months. After the treatment, the Y-Maze Test (hereafter, YMT) and the Novel Object Recognition Test (hereafter, NOR) are performed to evaluate the recognition.

[01476] In the YMT, a Y-shaped maze, constructed from three black vinyl chloride arms (10 cm x 35 cm) joined at identical angles, is utilized. The mice are positioned in the center of an arm and allowed to navigate for a duration of 8 minutes, with its activity being recorded by a video camera. Subsequently, the sequence and total number of entries into each arm are visually quantified from the recorded video. The instances where the mice sequentially entered all three arms without repetition are defined as alternation behaviors. The alternation behavior rate is then computed using the following formula:

[01477] Alternation behavior rate (%) = 100 x [number of alternation behaviors / (total number of entries - 2)]

[01478] In the NOR, an Econ Cage (CLEA Japan, Inc.) is employed. The test is conducted over a span of three days. On the first day, for acclimation to the experimental apparatus, the mice are placed in the Econ Cage and allowed to move freely for a duration of 10 minutes. On the second day, during the acquisition trial, two objects of identical color and shape are positioned in the Econ Cage, and the mouse is allowed to navigate for the same duration of 10 minutes. The two objects are placed apart on a line parallel to one long side of the cage. On the third day, during the evaluation trial, one of the objects used in the acquisition trial is substituted with a novel object of a different color and shape, and the mouse is allowed to move for another 10 minutes. The evaluation trial commences 24 hours after the acquisition trial. From the recorded video during the evaluation trial, the exploration time for each object is visually quantified.

[01479] The total exploration time and the novel object recognition ratio are calculated from the exploration times of the known and novel objects using the following formulas:

[01480] Total exploration time (seconds) = exploration time of known object + exploration time of novel object

[01481] Novel object recognition ratio (%) = 100 x (exploration time of novel object / total exploration time)

[01482] Biological Experimental Example 10: Effectiveness in amyotrophic lateral sclerosis model mouse.

[01483] The male B6SJL-Tg (SOD1*G93A)dl1Gur / J mice (hereafter, SOD1 mice) (The Jackson laboratory) or the male wild type mice (B6SJL mouse, hereafter, WT) (The Jackson laboratory) are used for the experiments.
[01484] Before the start of dosing (at 14 weeks old), the WT and SOD1 mice are grouped to body weight and the number of mutant SOD1 copies between groups. From 15 weeks of age, the vehicle (0.5 w/v% methylcellulose 400) or the test compound is administered orally once a day. The dose for each mouse is calculated based on their body weight measured weekly. After dosing began, blood plasma is collected at 24, 26, 28, 30, 32 and 34 weeks of age.
[01485] To assess neurodegeneration in the SOD1 mice, the levels of plasma Neurofilament Light chain (hereafter, NfL), which increases as neurodegeneration progresses, are measured using Simoa (Registered Trademark) HD-X (Quanterix, 103385) or Ella (ProteinSimple).
[01486] Biological Experimental Example 11: Effectiveness in amyotrophic lateral sclerosis patient cell.
[01487] Astrocyte cells differentiated from iPS cells of SOD1 mutant patients (Keio University) were used.
[01488] The astrocytes were treated with the test compound or the solvent DMSO (Kishida Chemical, 000-25425), followed by treatment with 1 μM S1P (Cayman Chemical, 62570) or the solvent MeOH (Kishida Chemical, 140-48663).
[01489] After 1 hour, RNA was extracted using the Cells-to-CT 1-Step TaqMan Kit (ThermoFisher, A25602).
[01490] To measure the expression levels of inflammatory cytokines, RT-qPCR was performed using the Cells-to-CT 1-Step TaqMan Kit (ThermoFisher, A25602), TaqMan probes for ACTB, CXCL8 and IL6 (ThermoFisher, 4531370), and the QuantStudio 5 (ThermoFisher, QS5-384). Figure 3 shows result thereof.
[01491] [Results]
[01492] The compound of the present disclosure inhibited inflammatory cytokine gene expression induced by S1P treatment in patient astrocyte cells.
[01493] Biological Experimental Example 12: Effectiveness in astrocytoma cell line.
[01494] The Human Brain Astocytoma cell line CCF-STTG1 (ECACC, 90021502) was used.
[01495] The astrocytoma cells were treated with the test compound or the solvent DMSO (Kishida Chemical, 000-25425), followed by treatment with 1 μM S1P (Cayman Chemical, 62570) or the solvent MeOH (Kishida Chemical, 140-48663).

[01496] After 1 hour, RNA was extracted using the Cells-to-CT 1-Step TaqMan Kit (ThermoFisher, A25602).

[01497] To measure the expression levels of inflammatory cytokines, RT-qPCR was performed using the Cells-to-CT 1-Step TaqMan Kit (ThermoFisher, A25602), TaqMan probes for ACTB, CXCL8 and IL6 (ThermoFisher, 4531370), and the QuantStudio 5 (ThermoFisher, QS5-384). Figure 4 and 5 shows results thereof.

[01498] [Results]

[01499] The compound of the present disclosure inhibited inflammatory cytokine gene expression induced by S1P treatment in astrocytoma cell line.

[Preparation Examples]

[01500] Preparation Example 1

[01501] By mixing the following components in a conventional manner and tableting, about 10,000 tablets each containing 10 mg of the active ingredient are obtained.

[01502] ■ 5-chloro-N-{(1S)-2-(4-chloro-3-fluorophenoxy)-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide ■■■ 100 g

[01503] ■ Carboxymethyl cellulose calcium (a disintegrating agent) ■■■ 20 g

[01504] ■ Magnesium stearate (a lubricant) ■■■ 10 g

[01505] ■ Microcrystalline cellulose ■■■ 870 g

[01506] Preparation Example 2

[01507] The following components were mixed in a conventional manner. Thereafter, the mixture is filtered through a dust filter, and 5 ml aliquots are charged into ampules. The ampules are heat sterilized by an autoclave to give 10,000 ampules each containing 20 mg of the active component.

[01508] ■ 5-chloro-N-{2-(3-fluorophenoxy)-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide ■■■ 200 g

[01509] ■ Mannitol ■■■ 20 g

[01510] ■ Distilled water ■■■ 50 L

[01511] It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the disclosure, which is defined solely by the appended claims and their equivalents.

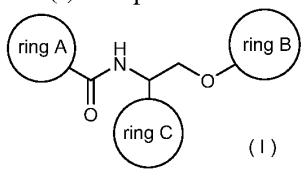
INDUSTRIAL APPLICABILITY

[01512] The compound of the present disclosure has a $S1P_3$ receptor antagonistic activity, and therefore, is useful for treating an $S1P_3$-mediated disease, for example,

neurodegenerative diseases, cancer, liver diseases, diseases of endocrine and metabolic system, cardiac diseases, respiratory disorders and the like.

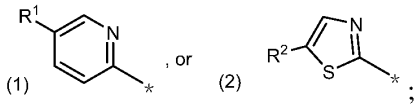
CLAIMS

[Claim 1] A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein ring A is



;

the * mark represents a bonding position with a carbonyl group;

ring B is 5-6 membered heterocyclic ring which may be substituted by 1 to 4 R^3 or 5-6 membered carbocyclic ring which may be substituted by 1 to 5 R^4;

when two or more R^3s are substituted, a plurality of R^3s may be the same or different;

when two or more R^4s are substituted, a plurality of R^4s may be the same or different;

ring C is 5-6 membered heterocyclic ring which may be substituted by 1 to 4 R^5 or 5-6 membered carbocyclic ring which may be substituted by 1 to 5 R^6;

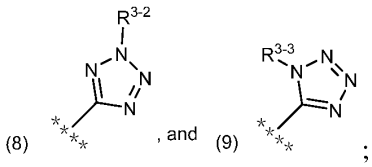
when two or more R^5s are substituted, a plurality of R^5s may be the same or different;

when two or more R^6s are substituted, a plurality of R^6s may be the same or different;

R^1 is selected from the group consisting of (1) a halogen atom, (2) C1-4 alkyl group and (3) C1-4 haloalkyl group;

R^2 is selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) C1-4 alkyl group and (4) C1-4 haloalkyl group;

R^3 is selected from the group consisting of (1) a halogen atom, (2) C1-4 alkyl group, (3) C1-4 haloalkyl group, (4) C1-4 alkoxy group, (5) C1-4 haloalkoxy group, (6) cyano, (7) $S(=O)_2$-R^{3-1},

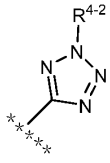
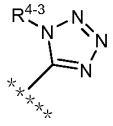


;

R^{3-1} is a hydrogen atom or C1-4 alkyl group;

when two or more R^3s are substituted, a plurality of R^{3-1}s may be the same or different;

R^{3-2} is a hydrogen atom or C1-4 alkyl group;
when two or more R^3s are substituted, a plurality of R^{3-2}s may be the same or different;
R^{3-3} is a hydrogen atom or C1-4 alkyl group;
when two or more R^3s are substituted, a plurality of R^{3-3}s may be the same or different;
the **** mark represents a bonding position with ring B;
R^4 is selected from the group consisting of (1) a halogen atom, (2) C1-4 alkyl group, (3) C1-4 haloalkyl group, (4) C1-4 alkoxy group, (5) C1-4 haloalkoxy group, (6) cyano, (7) $S(=O)_2$-R^{4-1},

(8)  , and (9)  ;

R^{4-1} is a hydrogen atom or C1-4 alkyl group;
when two or more R^4s are substituted, a plurality of R^{4-1}s may be the same or different;
R^{4-2} is a hydrogen atom or C1-4 alkyl group;
when two or more R^4s are substituted, a plurality of R^{4-2}s may be the same or different;
R^{4-3} is a hydrogen atom or C1-4 alkyl group;
when two or more R^4s are substituted, a plurality of R^{4-3}s may be the same or different;
the ***** mark represents a bonding position with ring B;
R^5 is selected from the group consisting of (1) a halogen atom, (2) C1-4 alkyl group, (3) C1-4 haloalkyl group, (4) C1-4 alkoxy group and (5) C1-4 haloalkoxy group;
R^6 is selected from the group consisting of (1) a halogen atom, (2) C1-4 alkyl group, (3) C1-4 haloalkyl group, (4) C1-4 alkoxy group and (5) C1-4 haloalkoxy group.

[Claim 2] The compound or a pharmaceutically acceptable salt thereof according to claim 1,
wherein ring B is selected from the group consisting of (1) a pyridine, (2) a pyrimidine, (3) a pyrazine, and (4) a benzene;
(1) to (3) in ring B may be substituted by 1 to 4 R^3;
when two or more R^3s are substituted, a plurality of R^3s may be the same or different;
(4) in ring B may be substituted by 1 to 5 R^4;
when two or more R^4s are substituted, a plurality of R^4s may be the same or different;
and the other symbols are as defined in claim 1.

[Claim 3] The compound or a pharmaceutically acceptable salt thereof according to claim 1 or claim 2,

wherein ring C is selected from the group consisting of (1) a pyridine, (2) a pyrimidine, (3) a benzene, (4) a cyclopentane, and (5) a cyclohexane;

(1) or (2) in ring C may be substituted by 1 to 4 R^5;

when two or more R^5s are substituted, a plurality of R^5s may be the same or different;

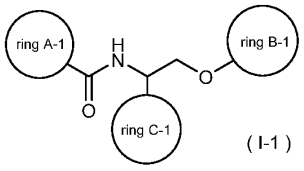
(3) to (5) in ring C may be substituted by 1 to 5 R^6;

when two or more R^6s are substituted, a plurality of R^6s may be the same or different;

and the other symbols are as defined in claim 1.

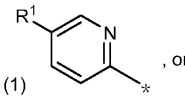
[Claim 4] The compound or a pharmaceutically acceptable salt thereof according to any one of claim 1 to claim 3,

wherein the compound is formula (I-1):

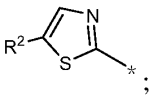


(I-1)

wherein ring A-1 is



(1) , or (2)



;

ring B-1 is selected from the group consisting of (1) a pyridine, (2) a pyrimidine, (3) a pyrazine, and (4) a benzene;

(1) to (3) in ring B-1 may be substituted by 1 to 4 R^3;

when two or more R^3s are substituted, a plurality of R^3s may be the same or different;

(4) in ring B-1 may be substituted by 1 to 5 R^4;

when two or more R^4s are substituted, a plurality of R^4s may be the same or different;

ring C-1 is selected from the group consisting of (1) a pyridine, (2) a pyrimidine, (3) a benzene, (4) a cyclopentane, and (5) a cyclohexane;

(1) or (2) in ring C-1 may be substituted by 1 to 4 R^5;

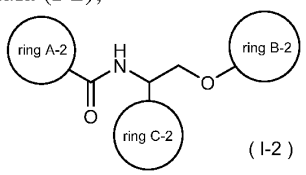
when two or more R^5s are substituted, a plurality of R^5s may be the same or different;

(3) to (5) in ring C-1 may be substituted by 1 to 5 R^6;

when two or more R^6s are substituted, a plurality of R^6s may be the same or different;

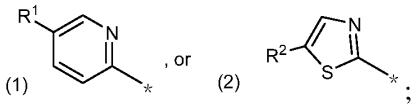
and the other symbols are as defined in claim 1.

[Claim 5] The compound or a pharmaceutically acceptable salt thereof according to any one of claim 1 to claim 4,
wherein the compound is formula (I-2);

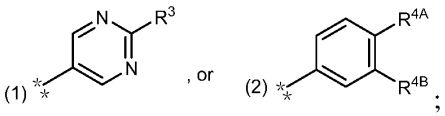


(I-2)

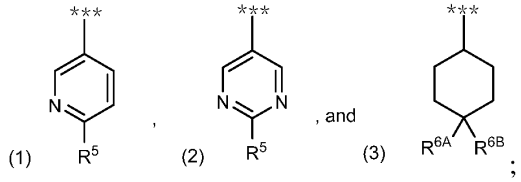
wherein ring A-2 is



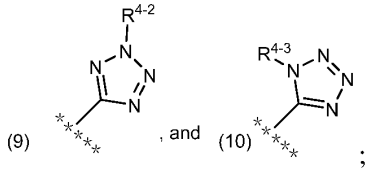
ring B-2 is



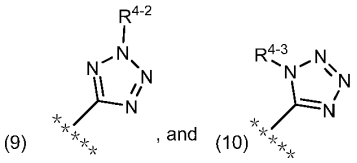
the ** mark represents a bonding position with an oxygen atom;
ring C-2 is selected from the group consisting of



the *** mark represents a bonding position with a carbon atom;
R^{4A} is selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) C1-4 alkyl group, (4) C1-4 haloalkyl group, (5) C1-4 alkoxy group, (6) C1-4 haloalkoxy group, (7) cyano, (8) $S(=O)_2$-R^{4-1},



R^{4B} is selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) C1-4 alkyl group, (4) C1-4 haloalkyl group, (5) C1-4 alkoxy group, (6) C1-4 haloalkoxy group, (7) cyano, (8) $S(=O)_2$-R^{4-1},



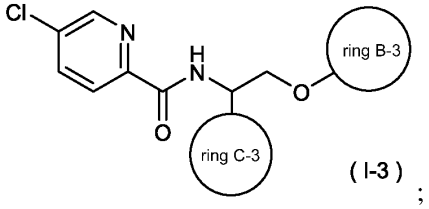
R^{6A} is selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) C1-4 alkyl group, (4) C1-4 haloalkyl group, (5) C1-4 alkoxy group and (6) C1-4 haloalkoxy group;

R^{6B} is selected from the group consisting of (1) a hydrogen atom, (2) a halogen atom, (3) C1-4 alkyl group, (4) C1-4 haloalkyl group, (5) C1-4 alkoxy group and (6) C1-4 haloalkoxy group;

and the other symbols are as defined in claim 1.

[Claim 6] The compound or a pharmaceutically acceptable salt thereof according to any one of claim 1 to claim 5,

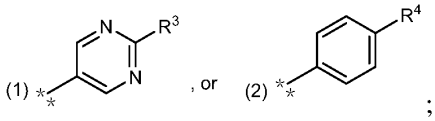
wherein the compound is formula (I-3):



;

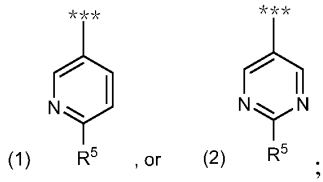
wherein

ring B-3 is



;

ring C-3 is



;

the ** mark represents a bonding position with an oxygen atom;

the *** mark represents a bonding position with a carbon atom;

and the other symbols are as defined in claim 1.

[Claim 7] The compound or a pharmaceutically acceptable salt thereof according to any one of claim 1 to claim 6, wherein the compound is
(1) 5-chloro-N-{2-[4-(trifluoromethyl)phenoxy]-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide;
(2) 5-chloro-N-(1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl)-2-pyridinecarboxamide;
(3) 5-chloro-N-[(1S)-1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-2-pyridinecarboxamide;
(4) 5-chloro-N-(1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl)-1,3-thiazole-2-carboxamide;
(5) 5-chloro-N-[(1ξ)-1-[6-(trifluoromethyl)-3-pyridinyl]-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-1,3-thiazole-2-carboxamide;
(6) 5-chloro-N-{2-(4-chloro-3-fluorophenoxy)-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide;
(7) 5-chloro-N-{(1S)-2-(4-chloro-3-fluorophenoxy)-1-[6-(trifluoromethyl)-3-pyridinyl]ethyl}-2-pyridinecarboxamide;
(8) 5-chloro-N-[1-(4,4-difluorocyclohexyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-2-pyridinecarboxamide;
(9) 5-chloro-N-[(1S)-1-(4,4-difluorocyclohexyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-2-pyridinecarboxamide;
(10) 5-chloro-N-[1-(4,4-difluorocyclohexyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-1,3-thiazole-2-carboxamide;
(11) 5-chloro-N-[(1ξ)-1-(4,4-difluorocyclohexyl)-2-{[2-(trifluoromethyl)-5-pyrimidinyl]oxy}ethyl]-1,3-thiazole-2-carboxamide;
(12) 5-chloro-N-{2-(3-cyanophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide;
(13) 5-chloro-N-{(1ξ)-2-(3-cyanophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide;
(14) 5-chloro-N-{(1ξ)-2-(4-chloro-3-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide;
(15) 5-chloro-N-{2-(4-chlorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide, or

(16) 5-chloro-N-{(1S)-2-(4-fluorophenoxy)-1-[2-(trifluoromethyl)-5-pyrimidinyl]ethyl}-2-pyridinecarboxamide.

[Claim 8] A pharmaceutical composition comprising the compound or a pharmaceutically acceptable salt thereof according to any one of claim 1 to claim 7.

[Claim 9] The pharmaceutical composition according to claim 8, which is a prophylactic and/or therapeutic agent for an $S1P_3$-mediated disease.

[Claim 10] The pharmaceutical composition according to claim 9, wherein the $S1P_3$-mediated disease is neurodegenerative disease, cancer, liver disease, disease of endocrine and metabolic system, cardiac disease, or respiratory disorder.

[Claim 11] The pharmaceutical composition according to claim 10, wherein the neurodegenerative disease is Alzheimer's Disease, dementia, Amyotrophic Lateral Sclerosis, Multiple System Atrophy, spinal cord injury, Cerebrovascular disease, Alexander disease, Sandhoff disease or Mucopolysaccharidosis type III.

[Claim 12] A method for preventing and/or treating an $S1P_3$-mediated disease comprising administering an effective amount of the compound or a pharmaceutically acceptable salt thereof according to any one of claim 1 to claim 7 to a mammal.

[Claim 13] The compound or a pharmaceutically acceptable salt thereof according to any one of claim 1 to claim 7 for use in preventing and/or treating an $S1P_3$-mediated disease.

[Claim 14] Use of the compound or a pharmaceutically acceptable salt thereof according to any one of claim 1 to claim 7 for manufacturing a prophylactic and/or therapeutic agent for an $S1P_3$-mediated disease.