TITLE OF THE INVENTION

TETRAHYDROIMIDAZO[1,5-d][1,4]OXAZEPINE DERIVATIVE

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present invention relates to a tetrahydroimidazo[1,5-d][1,4]oxazepine derivative having an antagonistic action against group II metabotropic glutamate receptor or a pharmaceutically acceptable acid addition salt thereof. The present invention also relates to a pharmaceutical composition comprising the compound as an active ingredient.

Related Background Art

[0002] Glutamic acid is known as one of principal excitatory neurotransmitters working for adjusting advanced functions of memory, learning and the like in a central nervous system of a mammal. Glutamate receptors are roughly classified into two types, that is, ionotropic glutamate receptors (iGlu receptors) and metabotropic glutamate receptors (mGlu receptors) coupled with G protein (see Non Patent Document 1).

The iGlu receptors are classified, on the basis of types of their agonists, into three types, that is, N-methyl-D-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and kainate receptors. On the other hand, the mGlu receptors have 8 subtypes (mGluR1 to 8) and are classified, on the basis of a signaling system to be conjugated and pharmacological characteristics, into group I (mGluR1, mGluR5), group II (mGluR2, mGluR3) and group III (mGluR4, mGluR6, mGluR7 and mGluR8).

The group II and group III mGluRs are expressed as an autoreceptor or a heteroreceptor mainly at the nerve terminal, so as to suppress adenylate cyclase via Gi protein and regulate a specific K^+ or Ca^{2+} channel activity (see Non Patent Document 2).

Antagonists against group II mGluRs, among these glutamate receptors, show an action to improve the cognitive function in animal models and also show an antidepressant action and an antianxiety action, and therefore, it is suggested that group II mGluR antagonists are effective as a novel cognitive function enhancer or antidepressant (see Non Patent Documents 3, 4 and 5).

Citation List

Non-Patent Literatures

[0003]

[Non-Patent Literature 1] Science, 258, 597-603, 1992

[Non-Patent Literature 2] Trends Pharmacol. Sci., 14, 13 (1993)

[Non-Patent Literature 3] Neuropharmacol., 46 (7), 907-917 (2004)

[Non-Patent Literature 4] Pharmacol. Therapeutics, 104(3), 233-244 (2004)

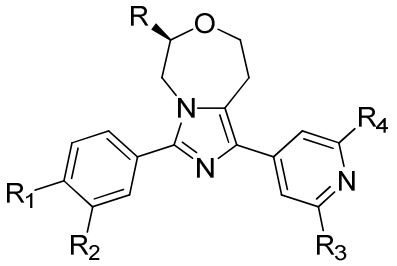
[Non-Patent Literature 5] Neuropharmacol., 66, 40-52 (2013)

SUMMARY OF THE INVENTION

[0004] An object of the present invention is to provide a tetrahydroimidazo[1,5-d][1,4]oxazepine derivative or a pharmaceutically acceptable salt thereof having an antagonistic action against group II metabotropic glutamate receptors, and a pharmaceutical composition comprising the same.

[0005] The present invention relate to [1] to [29] below:

[1] A compound represented by the following formula (I) or a pharmaceutically acceptable acid addition salt thereof:



(I)

wherein R is a hydrogen atom or a C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms, wherein

when R is a hydrogen atom,

R_1 is a chlorine atom, a bromine atom, a trifluoromethyl group, an ethyl group, a trifluoromethoxy group, a methoxy group substituted with a phenyl group, a methoxy group substituted with a C_{3-8} cycloalkyl group, an ethoxy group optionally substituted with 1 to 3 fluorine atoms, or C_{3-8} cycloalkyloxy group,

R_2 is a fluorine atom, a chlorine atom, a methyl group optionally substituted with 2 to 3 fluorine atoms, a methoxy group optionally substituted with 1 to 3 fluorine atoms, or an ethoxy group optionally substituted with 1 to 3 fluorine atoms,

R_3 is a hydrogen atom or a methyl group, and

R_4 is a fluorine atom or a methyl group optionally substituted with 1 to 3 fluorine atoms, or

when R is a C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms,

R_1 is a hydrogen atom, a halogen atom, a C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms, a C_{1-6} alkoxy group

optionally substituted with 1 to 3 substituents selected from a fluorine atom and a C_{3-8} cycloalkyl group, a C_{3-8} cycloalkyloxy group, or a 4- to 6-membered heterocycloalkyloxy group,

R_2 is a hydrogen atom, a cyano group, a halogen atom, a C_{1-6} alkyl group optionally substituted with 1 to 3 substituents selected from a fluorine atom and a hydroxyl group, or a C_{1-6} alkoxy group optionally substituted with 1 to 3 substituents selected from a fluorine atom, a C_{3-8} cycloalkyl group and a 4- to 6-membered heterocycloalkyl group,

R_3 is a hydrogen atom or a C_{1-6} alkyl group, and

R_4 is a C_{1-6} alkyl group optionally substituted with 1 to 3 substituents selected from a fluorine atom and a hydroxyl group, or a C_{1-6} alkoxy group.

[2] The compound or a pharmaceutically acceptable acid addition salt thereof according to [1], wherein

R is a C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms,

R_1 is a hydrogen atom, a halogen atom, a C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms, a C_{1-6} alkoxy group optionally substituted with 1 to 3 substituents selected from a fluorine atom and a C_{3-8} cycloalkyl group, a C_{3-8} cycloalkyloxy group, or a 4- to 6-membered heterocycloalkyloxy group,

R_2 is a hydrogen atom, a cyano group, a halogen atom, a C_{1-6} alkyl group optionally substituted with 1 to 3 substituents selected from a fluorine atom and a hydroxyl group, or a C_{1-6} alkoxy group optionally substituted with 1 to 3 substituents selected from a fluorine atom, a

C_{3-8} cycloalkyl group and a 4- to 6-membered heterocycloalkyl group,

R_3 is a hydrogen atom or a C_{1-6} alkyl group, and

R_4 is a C_{1-6} alkyl group optionally substituted with 1 to 3 substituents selected from a fluorine atom and a hydroxyl group, or a C_{1-6} alkoxy group.

[3] The compound or a pharmaceutically acceptable acid addition salt thereof according to [2], wherein R is a methyl group, an ethyl group, a fluoromethyl group or a difluoromethyl group.

[4] The compound or a pharmaceutically acceptable acid addition salt thereof according to [3],

wherein R_1 is a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, an ethyl group, a 1,1-difluoroethyl group, a methoxy group, a fluoromethoxy group, a difluoromethoxy group, a trifluoromethoxy group, an ethoxy group, a 2-fluoroethoxy group, a 2-propyloxy group, a cyclopropylmethoxy group, a cyclopropyloxy group or an (oxetan-3-yl)oxy group.

[5] The compound or a pharmaceutically acceptable acid addition salt thereof according to [4],

wherein R_2 is a hydrogen atom, a cyano group, a fluorine atom, a chlorine atom, a methyl group, a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a hydroxymethyl group, an ethyl group, a methoxy group, a fluoromethoxy group, a difluoromethoxy group, a trifluoromethoxy group, an ethoxy group, a 2-fluoroethoxy group, a 2-propyloxy group, a cyclopropylmethoxy group, a cyclobutylmethoxy group or a (tetrahydro-2H-pyran-4-

yl)methoxy group.

[6] The compound or a pharmaceutically acceptable acid addition salt thereof according to [5], wherein R_3 is a hydrogen atom or a methyl group.

[7] The compound or a pharmaceutically acceptable acid addition salt thereof according to [6], wherein R_4 is a methyl group, a fluoromethyl group, a difluoromethyl group, a hydroxymethyl group or a methoxy group.

[8] The compound or a pharmaceutically acceptable acid addition salt thereof according to [2], wherein

R is a methyl group optionally substituted with 1 to 2 fluorine atoms,

R_1 is a hydrogen atom, a chlorine atom, a methyl group optionally substituted with 1 to 3 fluorine atoms, an ethyl group, a C_{1-6} alkoxy group optionally substituted with 1 to 3 fluorine atoms, or a C_{3-6} cycloalkyloxy group,

R_2 is a cyano group, a chlorine atom, a C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms, or a C_{1-6} alkoxy group optionally substituted with 1 to 3 fluorine atoms,

R_3 is a hydrogen atom or a methyl group, and

R_4 is a methyl group optionally substituted with 1 to 3 fluorine atoms.

[9] The compound or a pharmaceutically acceptable acid addition salt thereof according to [2], wherein

R is a methyl group optionally substituted with 1 to 2 fluorine atoms,

R_1 is a hydrogen atom, a halogen atom, a C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms, a C_{1-6} alkoxy group optionally substituted with 1 to 3 fluorine atoms, or a C_{3-6} cycloalkyloxy group,

R_2 is a cyano group, a halogen atom, a C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms, or a C_{1-6} alkoxy group optionally substituted with 1 to 3 fluorine atoms,

R_3 is a methyl group, and

R_4 is a methyl group optionally substituted with 1 to 3 fluorine atoms,

with a proviso that

when R_1 is an unsubstituted methoxy group, R_2 is not a fluorine atom.

[10] A compound selected from the following compounds or a pharmaceutically acceptable acid addition salt thereof:

(R)-3-(4-chloro-3-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-1-(2,6-dimethylpyridin-4-yl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-6-methyl-3-(3-methyl-4-(trifluoromethoxy)phenyl)-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(4-(difluoromethoxy)-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(4-(difluoromethoxy)-3-methylphenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-3-(3-methoxy-4-(tr

ifluoromethoxy)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(3-chloro-4-cyclopropoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(4-cyclopropoxy-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(3-chloro-4-(difluoromethoxy)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-3-(4-cyclopropoxy-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-1-(2,6-dimethylpyridin-4-yl)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-3-(4-(difluoromethoxy)-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(3-chloro-4-(difluoromethoxy)phenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(3-chloro-4-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(3-chloro-4-ethoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(3-chloro-4-isopropoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-3-(3-chloro-4-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-3-(3-chloro-4-ethoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

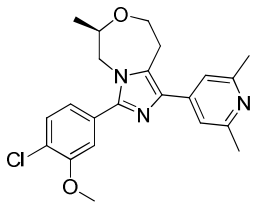
(S)-3-(3-chloro-4-isopropoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(3-(fluoromethyl)-4-(trifluoromethoxy)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-3-(4-(difluoromethoxy)-3-methylphenyl)-6-(fluoromethyl)-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine, and

(S)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine.

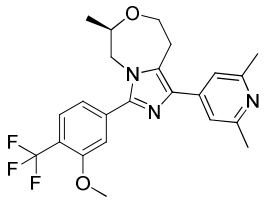
[11] (R)-3-(4-chloro-3-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



or a pharmaceutically acceptable acid addition salt thereof.

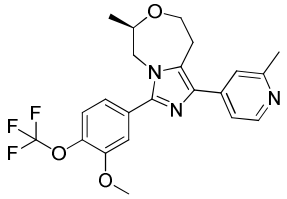
[12] (R)-1-(2,6-dimethylpyridin-4-yl)-3-(3-methoxy-4-(trifluorometh

yl)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



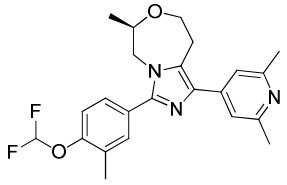
or a pharmaceutically acceptable acid addition salt thereof.

[13] (R)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



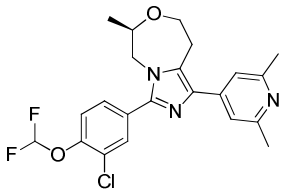
or a pharmaceutically acceptable acid addition salt thereof.

[14] (R)-3-(4-(difluoromethoxy)-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



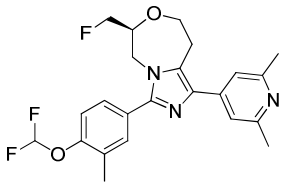
or a pharmaceutically acceptable acid addition salt thereof.

[15] (R)-3-(3-chloro-4-(difluoromethoxy)phenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



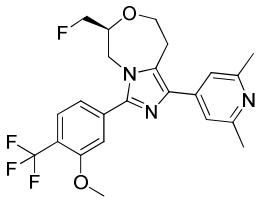
or a pharmaceutically acceptable acid addition salt thereof.

[16] (S)-3-(4-(difluoromethoxy)-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



or a pharmaceutically acceptable acid addition salt thereof.

[17] (S)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



or a pharmaceutically acceptable acid addition salt thereof.

[18] A pharmaceutical composition comprising the compounds or pharmaceutically acceptable acid addition salt according to any one of [1] to [17], and one or more pharmaceutically acceptable excipients.

[19] The pharmaceutical composition according to [18] for treatment of a disease or symptom in which an antagonistic action against a group II metabotropic glutamate receptor is effective.

[20] The pharmaceutical composition according to [19], wherein the disease or symptom is Alzheimer's disease.

[21] A method for treating a disease or symptom in which an antagonistic action against a group II metabotropic glutamate receptor is effective, comprising administrating the compound or pharmaceutically acceptable acid addition salt according to any one of [1] to [17] to a subject in need thereof.

[22] The method for treating according to [21], wherein the disease or symptom is Alzheimer’s disease.

[23] The compound or pharmaceutically acceptable acid addition salt according to any one of [1] to [17], for use in treatment of a disease or symptom in which an antagonistic action against a group II metabotropic glutamate receptor is effective.

[24] The compound or pharmaceutically acceptable acid addition salt according to [23], wherein the disease or symptom is Alzheimer’s disease.

[25] Use of the compound or pharmaceutically acceptable acid addition salt according to any one of [1] to [17], in the manufacture of a pharmaceutical composition for treating a disease or symptom in which an antagonistic action against a group II metabotropic glutamate receptor is effective

[26] Use according to [25], wherein the disease or symptom is Alzheimer’s disease.

[27] The compound or pharmaceutically acceptable acid addition salt according to any one of [1] to [17], for use as an active ingredient of a pharmaceutical composition.

[28] The compound or pharmaceutically acceptable acid addition salt according to [27], wherein the pharmaceutical composition is a pharmaceutical composition for treatment of a disease or symptom in which an antagonistic action against a group II metabotropic glutamate receptor is effective.

[29] The compound or pharmaceutically acceptable acid addition salt according to [28], wherein the disease or symptom is Alzheimer's disease.

ADVANTAGEOUS EFFECTS OF INVENTION

[0006] The compound of the present invention represented by formula (I) (hereinafter also referred to as the tetrahydroimidazo[1,5-d][1,4]oxazepine derivative) or a pharmaceutically acceptable acid addition salt thereof shows an antagonistic action against group II metabotropic glutamate receptors. Therefore, the tetrahydroimidazo[1,5-d][1,4]oxazepine derivative of the present invention or a pharmaceutically acceptable acid addition salt thereof has a potential use as a therapeutic agent for diseases or symptoms for which the antagonistic action against group II metabotropic glutamate receptors effectively works, such as Alzheimer's disease.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0007] Hereinafter, the meanings of signs, terms and the like used herein will be explained, and the present invention will be described in details.

[0008] Herein, a structural formula of a compound may represent a given isomer for convenience, but a compound of the present invention includes isomers, such as all geometric isomers structurally

formed from the compound, optical isomers based on asymmetric carbon, stereoisomers and tautomers, and the isomeric mixtures thereof. The compound is not limited to the formula given for convenience, and it may be any one of the isomers and mixtures. Accordingly, the compound of the present invention may have an asymmetric carbon atom in a molecule thereof and exist as an optically active substance and a racemic form. However, the present invention is not limited thereto, but it includes all cases. Incidentally, any one of isomers, racemic compounds and mixtures of isomers may show stronger activity than the other isomers. Furthermore, there may exist crystal polymorphisms, which also does not limit the present invention, and the compound may be any of single crystals or mixtures thereof, and may be a hydrate or a solvate as well as an anhydrate, all of which are included in the scope of the claims herein.

The present invention includes an isotopically-labeled compound of the compound of formula (I). The isotopically-labeled compound is equivalent to the compound of formula (I) except that one or more of atoms are replaced by atom(s) having an atomic mass or a mass number different from those usually found in nature. Examples of an isotope that can be incorporated into the compound of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine, chlorine, phosphorus, sulfur and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{14}C, ^{13}N, ^{15}O, ^{18}F, ^{32}P, ^{35}S, ^{123}I and ^{125}I.

The compound of the present invention containing any of the aforementioned isotopes and/or another isotope, and a

pharmaceutically acceptable derivative (such as a salt) thereof fall in the scope of the claims herein. The isotopically-labeled compound of the present invention, for example those into which radioactive isotopes such as ^{3}H and/or ^{14}C are incorporated, may be useful in drug and/or substrate tissue distribution assays. The isotopes ^{3}H and ^{14}C are regarded to be useful because these isotopes can be easily prepared and detected. The isotopes ^{11}C and ^{18}F are regarded to be useful in PET (positron emission tomography), the isotope ^{125}I is regarded to be useful in SPECT (single photon emission computed tomography), and these isotopes are all useful in brain imaging. Replacement by a heavier isotope such as ^{2}H causes, because of its higher metabolic stability, some types of advantages, in a treatment, of, for example, extension of half-life in vivo or reduction of a necessary dose, and therefore, is regarded useful under given circumstances. An isotopically-labeled compound of the compound of formula (I) of the present invention can be similarly prepared by using a readily available isotopically-labeled reagent instead of a nonisotopically-labeled reagent and by performing procedures disclosed in schemes and/or examples described below.

[0009] Herein, a "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom, an iodine atom and the like, and is preferably a fluorine atom or a chlorine atom.

[0010] A "C_{1-6} alkyl group" means a linear or branched alkyl group having 1 to 6 carbon atoms, and specific examples include a methyl group, an ethyl group, a n-propyl group, an isopropyl group, a n-butyl group, an isobutyl group, a tert-butyl group, a n-pentyl group,

an isopentyl group, a neopentyl group, a n-hexyl group, a 1-methylpropyl group, a 1,2-dimethylpropyl group, a 1-ethylpropyl group, a 1-methyl-2-ethylpropyl group, a 1-ethyl-2-methylpropyl group, a 1,1,2-trimethylpropyl group, a 1-methylbutyl group, a 2-methylbutyl group, a 1,1-dimethylbutyl group, a 2,2-dimethylbutyl group, a 2-ethylbutyl group, a 1,3-dimethylbutyl group, a 2-methylpentyl group and a 3-methylpentyl group, and more preferable examples include a methyl group, an ethyl group and a n-propyl group.

[0011] A "C_{1-6} alkoxy group" means an oxy group binding to the "C_{1-6} alkyl group", and specific examples include a methoxy group, an ethoxy group, a 1-propyloxy group, a 2-propyloxy group, a 2-methyl-1-propyloxy group, a 2-methyl-2-propyloxy group, a 1-butyloxy group, a 2-butyloxy group, a 1-pentyloxy group, a 2-pentyloxy group, a 3-pentyloxy group, a 2-methyl-1-butyloxy group, a 3-methyl-1-butyloxy group, a 2-methyl-2-butyloxy group, a 3-mehtyl-2-butyloxy group, a 2,2-dimethyl-1-propyloxy group, a 1-hexyloxy group, a 2-hexyloxy group, a 3-hexyloxy group, a 2-methyl-1-pentyloxy group, a 3-methyl-1-pentyloxy group, a 4-methyl-1-pentyloxy group, a 2-methyl-2-pentyloxy group, a 3-methyl-2-pentyloxy group, a 4-methyl-2-pentyloxy group, a 2-methyl-3-pentyloxy group, a 3-methyl-3-pentyloxy group, a 2,3-dimethyl-1-butyloxy group, a 3,3-dimethyl-1-butyloxy group, a 2,2-dimethyl-1-butyloxy group, a 2-ethyl-1-butyloxy group, a 3,3-dimethyl-2-butyloxy group, and a 2,3-dimethyl-2-butyloxy group, and preferable examples include a methoxy group, an ethoxy group and a 1-propyloxy group.

[0012] A "C_{3-8} cycloalkyl group" means a cyclic alkyl group having 3 to 8 carbon atoms, and specific examples include a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group and a cyclooctyl group.

[0013] A "C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms" means the "C_{1-6} alkyl group" unsubstituted or the "C_{1-6} alkyl group" in which 1 to 3 hydrogen atoms are substituted with a fluorine atom. Specific examples of the C_{1-6} alkyl group substituted with 1 to 3 fluorine atoms include a fluoromethyl group, a 1-fluoroethyl group, a 2-fluoroethyl group, a 3-fluoropropyl group, a difluoromethyl group, a 1,1-difluoroethyl group, a 2,2-difluoroethyl group, a trifluoromethyl group and a 2,2,2-trifluoroethyl group.

[0014] A "C_{1-6} alkoxy group optionally substituted with 1 to 3 substituents selected from a fluorine atom and a C_{3-8} cycloalkyl group" means the "C_{1-6} alkoxy group" unsubstituted or the "C_{1-6} alkoxy group" in which 1 to 3 hydrogen atoms are substituted with a fluorine atom or a C_{3-8} cycloalkyl group. Specific examples of the C_{1-6} alkoxy group substituted with one or more fluorine atoms include a fluoromethoxy group, a 1-fluoroethoxy group, a 2-fluoroethoxy group, a 3-fluoropropyloxy group, a difluoromethoxy group, a 1,1-difluoroethoxy group, a 2,2-difluoroethoxy group, a trifluoromethoxy group and a 2,2,2-trifluoroethoxy group. Specific examples of the C_{1-6} alkoxy group substituted with a C_{3-8} cycloalkyl group include a cyclopropylmethoxy group, a cyclobutylmethoxy group, a cyclopentylmethoxy group, a cyclohexylmethoxy group, a cyclopropylethoxy group, a cyclobutylethoxy group, a

cyclopentylethoxy group and a cyclohexylethoxy group.

[0015] A "C_{3-8} cycloalkyloxy group" means an oxy group binding to the "C_{3-8} cycloalkyl group", and specific examples include a cyclopropyloxy group, a cyclobutyloxy group, a cyclopentyloxy group, a cyclohexyloxy group, a cycloheptyloxy group and a cyclooctyloxy group.

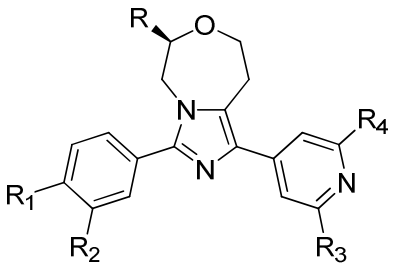
[0016] A "4- to 6-membered heterocycloalkyl group" means a 4- to 6-membered ring group containing one or more hetero atoms of nitrogen, oxygen, sulfur and the like, and specific examples include a 3-azetidinyl group, a 1-methyl-3-azetidinyl group, a 3-pyrrolidinyl group, a 1-methyl-3-pyrrolidinyl group, a 1-methyl-3-piperidinyl group, a 1-methyl-4-piperidinyl group, a 3-oxetanyl group, a 3-tetrahydrofuryl group, a 3-tetrahydropyranyl group, a 4-tetrahydropyranyl group, a 3-tetrahydrothienyl group and a 4-tetrahydrothiopyranyl group.

[0017] A "4- to 6-membered heterocycloalkyloxy group" means an oxy group binding to the "4- to 6-membered heterocycloalkyl group", and specific examples include a 3-azetidinyloxy group, a 1-methyl-3-azetidinyloxy group, a 3-pyrrolidinyloxy group, a 1-methyl-3-pyrrolidinyloxy group, a 1-methyl-3-piperidinyloxy group, a 1-methyl-4-piperidinyloxy group, a 3-oxetanyloxy group, a 3-tetrahydrofuryloxy group, a 3-tetrahydropyranyloxy group, a 4-tetrahydropyranyloxy group, a 3-tetrahydrothienyloxy group and a 4-tetrahydrothiopyranyloxy group.

[0018] The tetrahydroimidazo[1,5-d][1,4]oxazepine derivative of formula (I) of the present invention may be in the form of a

pharmaceutically acceptable acid addition salt. Specific examples of the pharmaceutically acceptable acid addition salt include inorganic acid salts (such as a sulfate, a nitrate, a perchlorate, a phosphate, a carbonate, a bicarbonate, a hydrofluoride, a hydrochloride, a hydrobromide and a hydroiodide), organic carboxylates (such as an acetate, an oxalate, a maleate, a tartrate, a fumarate and a citrate), organic sulfonates (such as a methanesulfonate, a trifluoromethanesulfonate, an ethanesulfonate, a benzene sulfonate, a toluene sulfonate and a camphorsulfonate), and amino acid salts (such as an aspartate and a glutamate).

[0019] An embodiment of the present invention includes a compound represented by the following formula (I) or a pharmaceutically acceptable acid addition salt thereof:



(I)

wherein R, R_1, R_2, R_3 and R_4 represent the same as defined in [1] above.

[0020] A preferred embodiment of the present invention provides a tetrahydroimidazo[1,5-d][1,4]oxazepine derivative or a pharmaceutically acceptable acid addition salt thereof, in which when R is a hydrogen atom in formula (I), R_1 is a chlorine atom, a bromine atom, a trifluoromethyl group, an ethyl group, a trifluoromethoxy group, a methyl group substituted with a phenyl group, a methoxy

group substituted with a C_{3-8} cycloalkyl group, an ethoxy group optionally substituted with 1 to 3 fluorine atoms, or a C_{3-8} cycloalkyloxy group; R_2 is a fluorine atom, a chlorine atom, a methyl group optionally substituted with 2 to 3 fluorine atoms, a methoxy group optionally substituted with 1 to 3 fluorine atoms, or an ethoxy group optionally substituted with 1 to 3 fluorine atoms; R_3 is a hydrogen atom or a methyl group; and R_4 is a fluorine atom or a methyl group optionally substituted with 1 to 3 fluorine atoms.

[0021] Another preferable embodiment of the present invention is a tetrahydroimidazo[1,5-d][1,4]oxazepine derivative or a pharmaceutically acceptable acid addition salt thereof, in which when R is a C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms in formula (I), R_1 is a hydrogen atom, a halogen atom, a C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms, a C_{1-6} alkoxy group optionally substituted with 1 to 3 substituents selected from a fluorine atom and a C_{3-8} cycloalkyl group, a C_{3-8} cycloalkyloxy group, or a 4- to 6-membered heterocycloalkyloxy group; R_2 is a hydrogen atom, a cyano group, a halogen atom, a C_{1-6} alkyl group optionally substituted with 1 to 3 substituents selected from a fluorine atom and a hydroxyl group, or a C_{1-6} alkoxy group optionally substituted with 1 to 3 substituents selected from a fluorine atom, a C_{3-8} cycloalkyl group and a 4- to 6-membered heterocycloalkyl group; R_3 is a hydrogen atom or a C_{1-6} alkyl group; and R_4 is a C_{1-6} alkyl group optionally substituted with 1 to 3 substituents selected from a fluorine atom and a hydroxyl group, or a C_{1-6} alkoxy group.

[0022] In formula (I), R preferably is a methyl group, an ethyl group, a fluoromethyl group or a difluoromethyl group; R_1 preferably is a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, an ethyl group, a 1,1-difluoroethyl group, a methoxy group, a fluoromethoxy group, a difluoromethoxy group, a trifluoromethoxy group, an ethoxy group, a 2-fluoroethoxy group, a 2-propyloxy group, a cyclopropylmethoxy group, a cyclopropyloxy group or an (oxetan-3-yl)oxy group; R_2 preferably is a hydrogen atom, a cyano group, a fluorine atom, a chlorine atom, a methyl group, a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a hydroxymethyl group, an ethyl group, a methoxy group, a fluoromethoxy group, a difluoromethoxy group, a trifluoromethoxy group, an ethoxy group, a 2-fluoroethoxy group, a 2-propyloxy group, a cyclopropylmethoxy group, a cyclobutylmethoxy group or a (tetrahydro-2H-pyran-4-yl)methoxy group; R_3 preferably is a hydrogen atom or a methyl group; and R_4 preferably is a methyl group, a fluoromethyl group, a difluoromethyl group, a hydroxymethyl group or a methoxy group.

[0023] In formula (I), a preferable combination of R, R_1, R_2, R_3 and R_4 is as follows: R is a methyl group optionally substituted with 1 to 2 fluorine atoms; R_1 is a hydrogen atom, a halogen atom, a C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms, a C_{1-6} alkoxy group optionally substituted with 1 to 3 fluorine atoms, or a C_{3-6} cycloalkyloxy group; R_2 is a cyano group, a halogen atom, a C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms, or a C_{1-6} alkoxy group optionally substituted with 1 to 3 fluorine atoms; R_3 is

a methyl group; R_4 is a methyl group optionally substituted with 1 to 3 fluorine atoms, provided that when R_1 is an unsubstituted methoxy group, R_2 is not a fluorine atom.

[0024] Specifically, the tetrahydroimidazo[1,5-d][1,4]oxazepine derivative or a pharmaceutically acceptable acid addition salt thereof according to the present invention is preferably selected from the following compounds:

(R)-3-(4-chloro-3-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-1-(2,6-dimethylpyridin-4-yl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-6-methyl-3-(3-methyl-4-(trifluoromethoxy)phenyl)-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(4-(difluoromethoxy)-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(4-(difluoromethoxy)-3-methylphenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(3-chloro-4-cyclopropoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(4-cyclopropoxy-3-methylphenyl)-1-(2,6-dimethylpyridin-4-

yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,
(R)-3-(3-chloro-4-(difluoromethoxy)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,
(S)-3-(4-cyclopropoxy-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,
(R)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,
(R)-1-(2,6-dimethylpyridin-4-yl)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,
(S)-3-(4-(difluoromethoxy)-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,
(S)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,
(R)-3-(3-chloro-4-(difluoromethoxy)phenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,
(R)-3-(3-chloro-4-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,
(R)-3-(3-chloro-4-ethoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,
(R)-3-(3-chloro-4-isopropoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,
(S)-3-(3-chloro-4-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-3-(3-chloro-4-ethoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

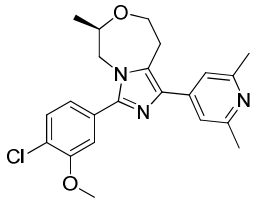
(S)-3-(3-chloro-4-isopropoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(3-(fluoromethyl)-4-(trifluoromethoxy)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-3-(4-(difluoromethoxy)-3-methylphenyl)-6-(fluoromethyl)-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine, or

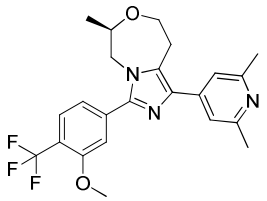
(S)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine.

[0025] More preferable examples of tetrahydroimidazo[1,5-d][1,4]oxazepine derivatives or a pharmaceutically acceptable acid addition salt thereof are (R)-3-(4-chloro-3-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



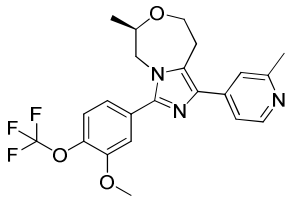
or a pharmaceutically acceptable acid addition salt thereof,

(R)-1-(2,6-dimethylpyridin-4-yl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



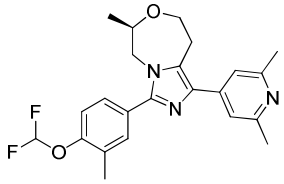
or a pharmaceutically acceptable acid addition salt thereof,

(R)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



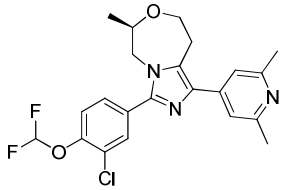
or a pharmaceutically acceptable acid addition salt thereof,

(R)-3-(4-(difluoromethoxy)-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



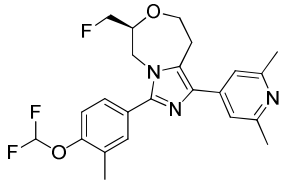
or a pharmaceutically acceptable acid addition salt thereof,

(R)-3-(3-chloro-4-(difluoromethoxy)phenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



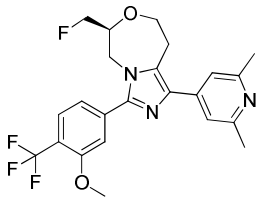
or a pharmaceutically acceptable acid addition salt thereof,

(S)-3-(4-(difluoromethoxy)-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



or a pharmaceutically acceptable acid addition salt thereof, and

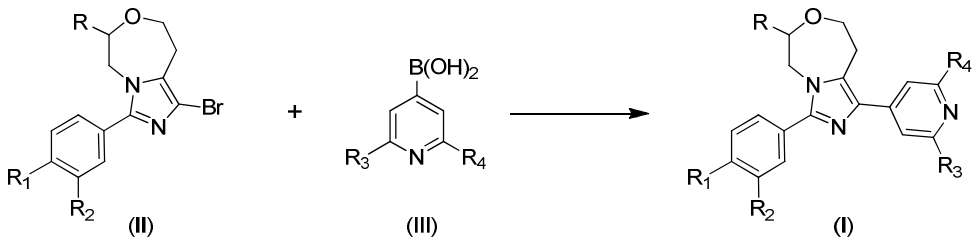
(S)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



or a pharmaceutically acceptable acid addition salt thereof.

[0026] Next, a method for producing the compound represented by formula (I) (hereinafter referred to as the compound (I), which expression is similarly used for other compounds represented by other formulas) of the present invention or a pharmaceutically acceptable acid addition salt thereof will be described.

[0027] Scheme 1



[0028] The compound (I) (wherein R, R_1, R_2, R_3 and R_4 represent the same as defined above) can be prepared in accordance with Scheme 1 by, for example, the Suzuki-Miyaura reaction of a compound (II) with a compound (III). The Suzuki-Miyaura reaction can be performed by heating the compound (II) and the compound (III) in a solvent in the presence of, for example, a palladium catalyst and a base, with a phosphorus ligand added if necessary. As the palladium catalyst, for example, tetrakis(triphenylphosphine)palladium (0), palladium (II) acetate, Pd_2DBA_3 or $(A\text{-}taPhos)_2PdCl_2$ can be used. As the base, for example, potassium phosphate, sodium hydroxide, potassium hydroxide, barium hydroxide, sodium carbonate or cesium carbonate can be used. Besides, as the phosphorus ligand, for example, triphenylphosphine, butyl di(1-adamantyl)phosphine or 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl can be used. The solvent used in the reaction is not especially limited as long as it is an inert solvent, and for example, THF, DME, DMF, 1,4-dioxane, water or a mixed solvent of these can be used. The reaction is accelerated by heating, but is generally performed at a temperature ranging from room temperature to the reflux temperature of the solution, and heating by microwaves can be employed as occasion demands.

When R_4 is, for example, a hydroxymethyl group, the compound can be also produced from a compound in which R_4 is methyl by oxidation with mCPBA or the like, rearrangement reaction with acetic anhydride or the like, and alkaline hydrolysis.

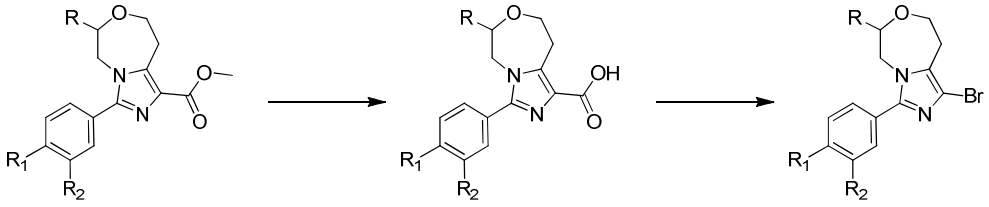
When R_2 is, for example, a hydroxymethyl group, the compound

can be also produced by deprotecting a corresponding compound in which a hydroxymethyl group is protected by MOM or the like.

When R_1 or R_2 is, for example, an alkoxy group, the compound can be also produced by alkylating a compound, which is obtained by deprotecting a corresponding alcohol compound protected by MOM, benzyl, methyl or the like, with alkyl bromide, alkyl iodide, alkyl triflate or the like, in a solvent such as DMF or THF in the presence of a base such as potassium carbonate or cesium carbonate. This reaction is generally performed at a temperature ranging from room temperature to the reflux temperature of the solution.

When R_4 or R_2 is, for example, a fluoromethyl group, the compound can be produced by fluorination of a hydroxymethyl group with DAST, BAST or the like.

[0029] Scheme 2

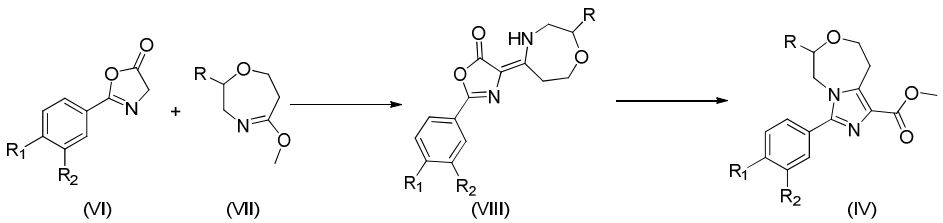


The compound (II) (wherein R, R_1 and R_2 represent the same as defined above) can be prepared in accordance with Scheme 2 by, for example, ester hydrolysis of a compound (IV) and decarboxylative bromination of a resulting compound (V). A solvent used in the ester hydrolysis of the compound (IV) is not especially limited as long as it is an inert solvent, and for example, methanol, ethanol, THF or a hydrous solvent thereof can be used. Besides, as a base, for example, sodium hydroxide or potassium hydroxide can be used.

This reaction is accelerated by heating, but is generally performed at a temperature ranging from room temperature to the reflux temperature of the solution. A solvent used in the decarboxylative bromination of the compound (V) is not especially limited, and for example, DMF, ethanol or a mixed solvent of DMF and ethanol can be used. Furthermore, a bromine source can be, for example, NBS. If potassium carbonate or the like is used as the base, the reaction is accelerated, and the reaction is generally performed at a temperature ranging from room temperature to the reflux temperature of the solution.

When R_1 or R_2 is, for example, an alkoxy group, the compound can be also produced by alkylating a compound, which is obtained by deprotecting a corresponding alcohol compound protected by MOM, benzyl, methyl or the like, with alkyl bromide, alkyl iodide, alkyl triflate or the like in a solvent such as DMF or THF in the presence of a base such as potassium carbonate or cesium carbonate. This reaction is generally performed at a temperature ranging from room temperature to the reflux temperature of the solution.

[0030] Scheme 3

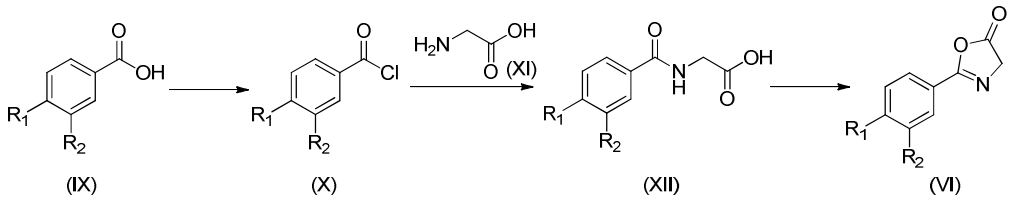


The compound (IV) (wherein R, R_1 and R_2 represent the same as defined above) can be prepared in accordance with Scheme 3 by, for example, condensing a compound (VI) with a compound (VII) and

treating a resulting compound (VIII) with a base. A solvent used in the condensation of the compounds (VI) and (VII) is not especially limited as long as it is an inert solvent, and for example, toluene, THF, DME or a mixed solvent of these can be used. The reaction is accelerated by heating, but is generally performed at a temperature ranging from room temperature to the reflux temperature of the solution, and heating with microwaves can be employed as occasion demands. A solvent used in the treatment of the compound (VIII) with a base is not especially limited as long as it is an inert solvent, and for example, methanol can be used. The base can be, for example, sodium methoxide. The reaction is accelerated by heating, but is generally performed at a temperature ranging from room temperature to the reflux temperature of the solution, and heating with microwaves can be employed as occasion demands.

When R_1 or R_2 is, for example, an alkoxy group, the compound can be also produced by alkylating a compound, which is obtained by deprotecting a corresponding alcohol compound protected by MOM, benzyl, methyl or the like, with alkyl bromide, alkyl iodide, alkyl triflate or the like in a solvent such as DMF or THF in the presence of a base such as potassium carbonate or cesium carbonate. This reaction is generally performed at a temperature ranging from room temperature to the reflux temperature of the solution.

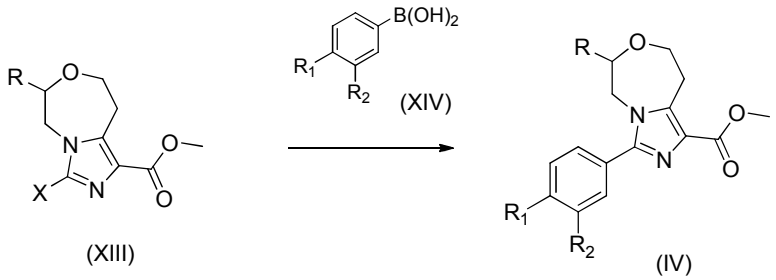
[0031] Scheme 4



The compound (VI) (wherein R_1 and R_2 represent the same as defined above) can be prepared in accordance with Scheme 4 by, for example, acid chloridization of a compound (IX), amidation of a resulting compound (X) and a compound (XI) under basic conditions, and cyclization of a resulting compound (XII). A solvent used in the acid chloridization of the compound (IX) is not especially limited as long as it is an inert solvent, and for example, toluene or DCM can be used. Furthermore, for example, oxalyl chloride or thionyl chloride can be used for the reaction, and the reaction is accelerated by addition of DMF. The reaction is accelerated by heating, but is generally performed at a temperature ranging from an ice cooling temperature to the reflux temperature of the solution. A solvent used in the amidation of the compounds (X) and (XI) is not especially limited as long as it is an inert solvent, and for example, toluene, THF, DCM, water or a mixed solvent of these can be used. Furthermore, as a base, for example, sodium hydroxide or potassium hydroxide can be used. This reaction is generally performed at a temperature ranging from an ice cooling temperature to the reflux temperature of the solution. A solvent used in the cyclization of the compound (XII) is not especially limited as long as it is an inert solvent, and for example, toluene or THF can be used. Besides, methyl chloroformate, isopropyl chloroformate, DCC or the like can

be used for the cyclization. This reaction is generally performed at a temperature ranging from −78°C to the reflux temperature of the solution.

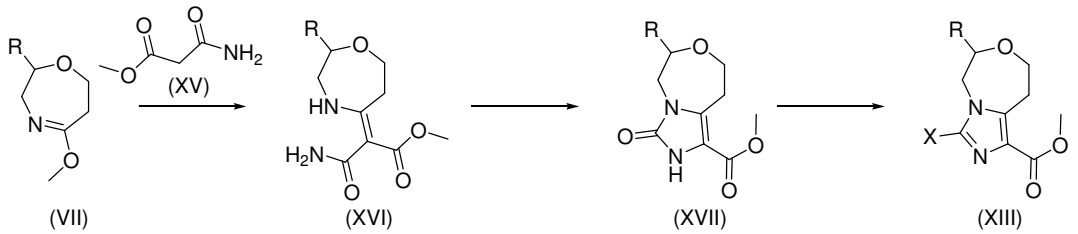
[0032] Scheme 5



The compound (IV) (wherein R, R_1 and R_2 represent the same as defined above) can be prepared also in accordance with Scheme 5 by, for example, the Suzuki-Miyaura reaction of a compound (XIII) (wherein X is halogen) and a compound (XIV). The Suzuki-Miyaura reaction can be performed by heating the compound (XIII) and the compound (XIV) in a solvent in the presence of, for example, a palladium catalyst and a base, with a phosphorus ligand added if necessary. As the palladium catalyst, for example, tetrakis(triphenylphosphine)palladium (0), palladium (II) acetate, Pd_2DBA_3 or $(A\text{-}taPhos)_2PdCl_2$ can be used. As the base, for example, potassium phosphate, sodium hydroxide, potassium hydroxide, barium hydroxide, sodium carbonate or cesium carbonate can be used. Besides, as the phosphorus ligand, for example, triphenylphosphine, butyl di(1-adamantyl)phosphine or 2-dicyclohexylphosphino-2',4',6'-triisopropyl biphenyl can be used. The solvent used in the reaction is not especially limited as long as it is an inert solvent, and for example, THF, DME, DMF, 1,4-dioxane or benzene can be used.

The reaction is accelerated by heating, but is generally performed at a temperature ranging from room temperature to the reflux temperature of the solution, and heating by microwaves can be employed as occasion demands.

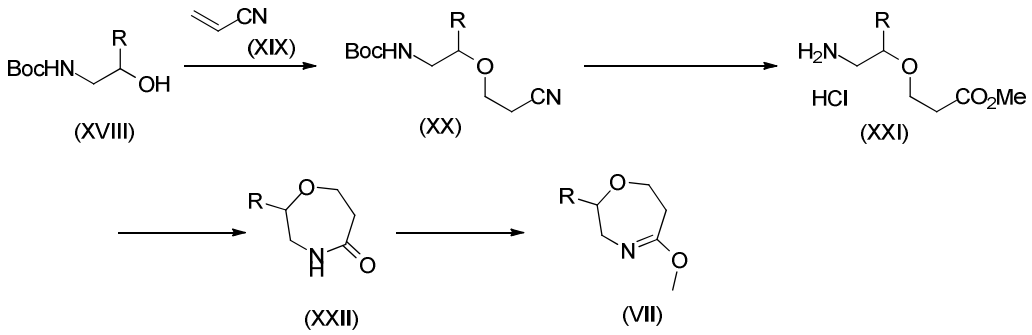
[0033] Scheme 6



The compound (XIII) (wherein R is the same as defined above and X is halogen) can be prepared in accordance with Scheme 6 by, for example, condensation of the compound (VII) with a compound (XV), a Hofmann rearrangement reaction of a resulting compound (XVI), and halogenation of a resulting compound (XVII). A solvent used in the condensation of the compounds (VII) and (XV) is not especially limited as long as it is an inert solvent, and for example, toluene, THF, DMF, DME or a mixed solvent of these can be used. The reaction is accelerated by heating, but is generally performed at a temperature ranging from room temperature to the reflux temperature of the solution, and heating with microwaves can be employed as occasion demands. A solvent used in the rearrangement reaction of the compound (XVI) is not especially limited as long as it is an inert solvent, and for example, toluene, THF, DME or a mixed solvent of these can be used. Furthermore, iodobenzene diacetate or the like can be used in the reaction. The reaction is generally performed at a temperature ranging from room temperature to the reflux temperature

of the solution. A solvent used in the halogenation of the compound (XVII) is not especially limited as long as it is an inert solvent, and for example, toluene can be used. Furthermore, phosphorus oxychloride or phosphorus oxybromide can be used in the reaction. The reaction is accelerated by heating, but is generally performed at a temperature ranging from room temperature to the reflux temperature of the solution.

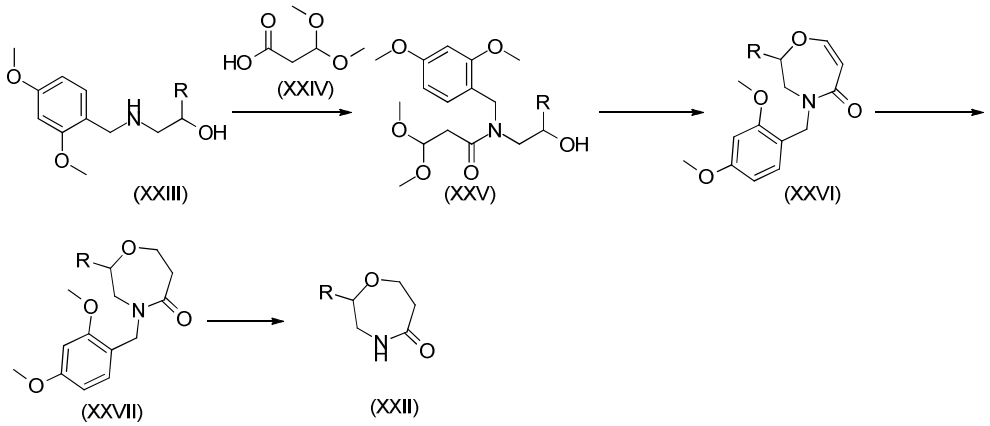
[0034] Scheme 7



The compound (VII) (wherein R is the same as defined above) can be prepared in accordance with Scheme 7 by, for example, four steps of a 1,4-addition reaction of a compound (XVIII) and a compound (XIX), alcoholysis of a resulting compound (XX) under acidic conditions, cyclization of a resulting compound (XXI) under basic conditions, and O-alkylation of a resulting compound (XXII). In the 1,4-addition reaction of the compound (XVIII), the compound(XIX) can be used as a solvent. As a base, DBU, TEA, DIPEA or the like can be used. This reaction is generally performed at a temperature ranging from an ice cooling temperature to the reflux temperature of the solution. A solvent used in the alcoholysis of the compound (XX) is not especially limited as long as it is an inert solvent, and for example, 1,4-dioxane can be used. As an acid,

hydrogen chloride or the like can be used. This reaction is accelerated by heating, but is generally performed at a temperature ranging from room temperature to the reflux temperature of the solution. A solvent used in the cyclization of the compound (XXI) is not especially limited as long as it is an inert solvent, and for example, methanol or the like can be used. As a base, DBU, TEA, potassium carbonate or cesium carbonate can be used. This reaction is accelerated by heating, but is generally performed at a temperature ranging from room temperature to the reflux temperature of the solution. A solvent used in the O-alkylation of the compound (XXII) is not especially limited as long as it is an inert solvent, and for example, DCM or toluene can be used. As an alkylating agent, trimethyloxonium tetrafluoroborate, dimethyl sulfate or the like can be used. This reaction is generally performed at a temperature ranging from an ice cooling temperature to the reflux temperature of the solution.

[0035] Scheme 8



The compound (XXII) (wherein R is the same as defined above) can also be prepared in accordance with Scheme 8 by, for example,

four steps of dehydrative condensation of a compound (XXIII) with a compound (XXIV), cyclization of a resulting compound (XXV) performed under acidic conditions, hydrogenation of a resulting compound (XXVI), and deprotection of a resulting compound (XXVII). A solvent used in the dehydrative condensation of the compound (XXIII) with the compound (XXIV) is not especially limited as long as it is an inert solvent, and for example, THF, DMF or DCM can be used. Besides, a condensation agent can be DCC, EDC, HOBt, HATU, HBTU or a combination of any of these. Furthermore, DIPEA, TEA or the like can be used as an additive in the reaction. This reaction is generally performed at a temperature ranging from an ice cooling temperature to the reflux temperature of the solution. A solvent used in the cyclization of the compound (XXV) is not especially limited as long as it is an inert solvent, and for example, THF, acetonitrile, toluene or xylene can be used. Besides, an acid can be, for example, PTS or PPTS. The reaction is accelerated by heating, but is generally performed at a temperature ranging from room temperature to the reflux temperature of the solution. A solvent used in the hydrogenation of the compound (XXVI) is not especially limited as long as it is an inert solvent, and for example, methanol, ethanol or THF can be used. As a catalyst, palladium/carbon, palladium hydroxide/carbon, platinum oxide or the like can be used. This reaction is generally performed at a temperature ranging from room temperature to the reflux temperature of the solution. The deprotection of the compound (XXVII) can be performed, for example, in a solvent such as TFA. As an additive,

for example, a scavenger such as a triethyl silane can be used. This reaction is accelerated by heating, but is generally performed at a temperature ranging from room temperature to the reflux temperature of the solution.

[0036] The compound (I) of the present invention thus obtained can be prepared into a pharmaceutically acceptable salt by a conventional method as occasion demands. The preparation method can be an appropriate combination of, for example, methods conventionally employed in the field of synthetic organic chemistry. A specific example of the method includes neutralization titration of a solution of the free form of the present compound with an acid solution. Furthermore, the compound (I) of the present invention can be changed into a solvate by a known solvate forming reaction as occasion demands.

[0037] Representative examples of the method for producing the compound (I) have been described so far, and material compounds and various reagents used in the production method for the compound (I) may be in the form of a salt or a hydrate, and are different depending upon starting materials, solvents to be used and the like, and hence are not especially limited as long as the reactions are not retarded. Also the solvents to be used differ depending upon the starting materials, reagents and the like, and needless to say, are not especially limited as long as they do not retard the reactions and they dissolve starting materials to some extent. When the compound (I) is obtained in the form of a free form, it can be changed, by a conventional method, into the form of a salt that can be formed by the

compound (I). Similarly, when the compound (I) is obtained in the form of a salt of the compound (I), it can be changed, by a conventional method, into a free form of the compound (I). Furthermore, various isomers (such as a geometric isomer, an optical isomer based on asymmetric carbon, a stereoisomer and a tautomer) obtained as the compound (I) can be purified and isolated by general separation means such as recrystallization, a diastereomeric salt formation method, enzymatic resolution, and various types of chromatography (including thin layer chromatography, column chromatography and gas chromatography).

[0038] A term "composition" used herein includes a product that contains a specific ingredient in a particular amount, and any product directly or indirectly prepared by a combination of particular ingredients in particular amounts. Such a term used in regard to a pharmaceutical composition is used to intend to include: a product containing an active ingredient and an inactive ingredient forming a carrier; and all products directly or indirectly prepared by combination, complexation or aggregation of any two or more ingredients, or dissociation, another type of reaction, or interaction of one or more ingredients. Accordingly, the pharmaceutical composition of the present invention includes all compositions prepared by mixing the tetrahydroimidazo[1,5-d][1,4]oxazepine derivative of the present invention with any of pharmaceutically acceptable carriers. The term "pharmaceutically acceptable" means that a carrier, a diluent or an excipient should be compatible with other ingredients of the formulation and should not be harmful to

those who take the composition.

[0039] The compounds of the present invention mostly have, as binding ability to the group II metabotropic glutamate receptors, an IC50 value of 100 nM or less, and have an IC50 value of preferably 30 nM or less and more preferably 10 nM or less.

[0040] The tetrahydroimidazo[1,5-d][1,4]oxazepine derivative of the present invention or a pharmaceutically acceptable acid addition salt thereof has an antagonistic action against the group II metabotropic glutamate receptors. Accordingly, it is applicable as a therapeutic agent for diseases in which the antagonistic action against the group II metabotropic glutamate receptors effectively works. Examples of the diseases in which the antagonistic action against the group II metabotropic glutamate receptors effectively works include Alzheimer's disease.

[0041] The tetrahydroimidazo[1,5-d][1,4]oxazepine derivative of the present invention or a pharmaceutically acceptable acid addition salt thereof can be formulated by a general method, and the dosage form can be, for example, an oral formulation (such as a tablet, a granule, a powder, a capsule or a syrup), an injection formulation (for intravenous administration, intramuscular administration, subcutaneous administration, intraperitoneal administration or the like), or an external formulation (such as a transdermal absorbable drug (including an ointment, a patch and the like), an eye dropper, nasal drops or a suppository).

[0042] For producing an oral solid formulation, an excipient, a binder, a disintegrator, a lubricant, a colorant and the like can be

added, if necessary, to the tetrahydroimidazo[1,5-d][1,4]oxazepine derivative of the present invention or a pharmaceutically acceptable acid addition salt thereof, and the resulting mixture can be prepared by a conventional method into tablets, granules, powders or capsules. Furthermore, the tablets, granules, powders or capsules can be coated with a film if necessary.

Examples of the excipient include lactose, corn starch and crystalline cellulose, examples of the binder include hydroxypropyl cellulose and hydroxypropylmethyl cellulose, examples of the disintegrator include carboxymethylcellulose calcium and croscarmellose sodium, examples of the lubricant include magnesium stearate and calcium stearate, an example of the colorant includes titanium oxide, and examples of a film-coating agent include hydroxypropyl cellulose, hydroxypropylmethyl cellulose and methyl cellulose, and it goes without saying that these ingredients are not limited to the aforementioned examples.

The solid formulation such as a tablet, a capsule, a granule or a powder may contain the tetrahydroimidazo[1,5-d][1,4]oxazepine derivative of the present invention, a pharmaceutically acceptable salt thereof, or a solvate thereof in a content of generally 0.001 to 99.5% by weight, preferably 0.001 to 90% by weight, and the like.

[0043] For producing an injection formulation (for intravenous administration, intramuscular administration, subcutaneous administration, intraperitoneal administration or the like), a pH adjuster, a buffer, a suspending agent, a solubilizing agent, an antioxidant, a preservative (an antiseptic agent), a tonicity adjusting

agent and the like are added, if necessary, to the tetrahydroimidazo[1,5-d][1,4]oxazepine derivative of the present invention or a pharmaceutically acceptable acid addition salt thereof, and the resulting mixture can be prepared into an injection formulation by a conventional method. Furthermore, the resultant can be freeze-dried to be used as a lyophilized product to be dissolved before use.

Examples of the pH adjuster and the buffer include organic acids, inorganic acids and/or salts thereof, examples of the suspending agent include methyl cellulose, Polysorbate 80 and carboxymethyl cellulose sodium, examples of the solubilizing agent include Polysorbate 80 and polyoxyethylene sorbitan monolaurate, an example of the antioxidant includes α-tocopherol, examples of the preservative include methyl paraoxybenzoate and ethyl paraoxybenzoate, and examples of the tonicity adjusting agent include glucose, sodium chloride and mannitol, and it goes without saying that these ingredients are not limited to the aforementioned examples.

Such an injection formulation can contain the tetrahydroimidazo[1,5-d][1,4]oxazepine derivative of the present invention, a pharmaceutically acceptable salt thereof or a solvate thereof in a content of generally 0.000001 to 99.5% by weight, preferably 0.000001 to 90% by weight, and the like.

[0044] For producing an external formulation, a base material is added to the tetrahydroimidazo[1,5-d][1,4]oxazepine derivative or a pharmaceutically acceptable acid addition salt thereof of the present invention, and if necessary, for example, a preservative, a stabilizer,

a pH adjuster, an antioxidant, a colorant and the like described above are further added thereto, and the resulting mixture is prepared by a conventional method into, for example, a transdermal absorbable drug (such as an ointment or a patch), an eye dropper, nasal drops or a suppository.

As the base material to be used, various materials usually used for, for example, medicines, quasi-drugs and cosmetics can be used. Specific examples of the material include animal and vegetable oils, mineral oils, ester oils, waxes, emulsifiers, higher alcohols, fatty acids, silicone oils, surfactants, phospholipids, alcohols, polyalcohols, water soluble polymers, clay minerals and purified water.

Such an external formulation can contain the tetrahydroimidazo[1,5-d][1,4]oxazepine derivative of the present invention, or a pharmaceutically acceptable salt thereof or a solvate thereof in a content of generally 0.000001 to 99.5% by weight, preferably 0.000001 to 90% by weight, and the like.

[0045] A dosage of the tetrahydroimidazo[1,5-d][1,4]oxazepine derivative of the present invention or a pharmaceutically acceptable acid addition salt thereof depends upon the level of symptom severity, the patient's age, sex and weight, the administration form and the kind of salt, a specific kind of disease and the like, and in an adult patient, it is administered, once or dividedly several times per day, at a dose for oral administration of generally approximately 30 μg to 10 g, preferably 100 μg to 5 g and more preferably 100 μg to 1 g, or a dose for injection administration of generally approximately 30 μg to 1 g, preferably 100 μg to 500 mg, and more preferably 100 μg to 300

mg.

[0046] The compound of the present invention can be used as a chemical probe for capturing a target protein of a biologically active low molecular weight compound. Specifically, the compound of the present invention can be transformed into an affinity chromatography probe, a photo-affinity probe or the like by introducing a labeling group, a linker or the like into a portion other than a structural portion indispensable to activity expression of the compound by a method described in J. Mass Spectrum. Soc. Jpn. Vol. 51, No. 5, 2003, p. 492-498, WO2007/139149 or the like.

Examples of the labeling group, the linker or the like used in such a chemical probe include groups belonging to the following groups (1) to (5):

(1) protein labeling groups such as photoaffinity labeling groups (such as a benzoyl group, a benzophenone group, an azido group, a carbonyl azide group, a diaziridine group, an enone group, a diazo group and a nitro group), and chemical affinity groups (such as a ketone group in which an alpha carbon atom is substituted with a halogen atom, a carbamoyl group, an ester group, an alkylthio group, a Michael receptor of α, β-unsaturated ketone, ester or the like, and an oxirane group);

(2) cleavable linkers such as −S−S−, −O−Si−O−, a monosaccharide (such as a glucose group or a galactose group) and a disaccharide (such as lactose), and oligopeptide linkers that can be cleaved by an enzyme reaction;

(3) fishing tag groups such as biotin and a 3-(4,4-difluoro-5,7-

dimethyl-4H-3a,4a-diaza-4-bora-s-indacen-3-yl)propionyl group;

(4) radioactive labeling groups such as ^{125}I, ^{32}P, ^{3}H and ^{14}C; fluorescence labeling groups such as fluorescein, rhodamine, dansyl, umbelliferone, 7-nitrofurazanyl, and a 3-(4,4-difluoro-5,7-dimethyl-4H-3a,4a-diaza-4-bora-s-indacen-3-yl) propionyl group; chemiluminescent groups such as lumiferin and luminol; and detectable markers such as heavy metal ions such as lanthanoid metal ions and radium ions; and

(5) groups to be bonded to a solid phase carrier such as glass beads, a glass bed, a microtiter plate, agarose beads, an agarose bed, polystyrene beads, a polystyrene bed, nylon beads and a nylon bed.

A probe prepared by introducing, into the compound of the present invention, a labeling group or the like selected from the above-described groups (1) to (5) by the method described in any of the aforementioned literatures or the like can be used as a chemical probe for identifying a marker protein useful for research of a novel potential drug target or the like.

[0047] Hereinafter, the present invention will be described in detail with reference to Examples, Production Examples, and Test Examples. However, the present invention is not limited to them. In addition, abbreviations used in Examples are commonly used abbreviations well known to the person skilled in the art, and some of the abbreviations will be described below.

$(A\text{-}taPhos)_2PdCl_2$: bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II)

BAST: bis(2-methoxyethyl)aminosulfurtrifluoride

Bn: benzyl

Boc: tert-butoxycarbonyl

CSA: camphorsulfonic acid

DAST: diethylaminosulfurtrifluoride

DBN: 1,5-diazabicyclo[4.3.0]non-5-ene

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DCC: 1,3-dicyclohexylcarbodiimide

DCE: 1,2-dichloroethane

DCM: dichloromethane

DIPEA: diisopropylethylamine

DME: dimethoxyethane

DMF: N,N-dimethylformamide

DMPI: Dess-Martin Periodinane

DMSO: dimethylsulfoxide

EDC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

HATU: O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

HBTU: O-benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate

HFIP: 1,1,1,3,3,3-hexafluoro-2-propanol

HOBT: 1-hydroxybenzotriazole

mCPBA: 3-chloroperbenzoic acid

MOM: methoxymethyl

n-: normal

NBS: N-bromosuccinimide

NMM: N-methylmorpholine

$Pd(dppf)Cl_2 \cdot CH_2Cl_2$: (1,1'-bis(diphenylphosphino)ferrocene-dichloropalladium-dichloromethane complex

Pd_2DBA_3: tris(dibenzylideneacetone)dipalladium

PPTS: pyridinium paratoluenesulfonate

PTS: paratoluenesulfonic acid

tert-: tertiary

TBAF: tetrabutylammonium fluoride

TBS: tert-butyldimethylsilyl

TBSCl: tert-butyldimethylsilyl chloride

TBME: tert-butyl methyl ether

TEA: triethylamine

TFA: trifluoroacetic acid

THF: tetrahydrofuran

Ts: paratoluenesulfonyl

^{1}H-NMR: proton nuclear magnetic resonance spectrometry

Chemical shifts of proton nuclear magnetic resonance spectra are recorded in the unit of δ (ppm) with respect to tetramethylsilane and coupling constants are recorded in the unit of Herz (Hz). Patterns include: s; singlet, d; doublet, t; triplet, q; quartet, br; broad, and sep; septet.

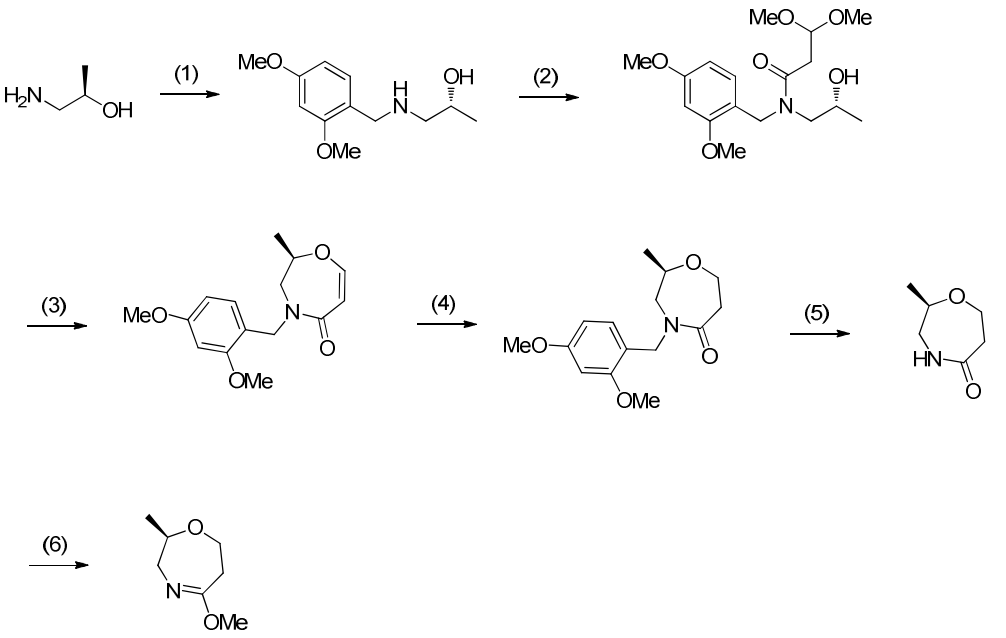
[0048] The term "room temperature" in Examples and Production Examples described below usually stands for a temperature in the range of about 10°C to 35°C. The symbol "%" denotes % by weight, unless otherwise described.

The chemical names of compounds in Examples and Production Examples were determined based on their chemical structures with

reference to "E-Notebook", version 12 (PerkinElmer Inc.).

[0049] Production Example 1

Synthesis of (R)-5-methoxy-2-methyl-2,3,6,7-tetrahydro-1,4-oxazepine



[0050] (1) Synthesis of (R)-1-((2,4-dimethoxybenzyl)amino)propan-2-ol

2,4-Dimethoxybenzaldehyde (CAS No. 613-45-65; 55.8 g, 336 mmol) was added to a solution of (R)-(-)-1-amino-2-propanol (CAS No. 2799-16-8; 24.0 g, 320 mmol) and acetic acid (40.2 mL, 703 mmol) in THF (440 mL) at room temperature, and the mixture was stirred at room temperature for 1 hour. Sodium triacetoxyborohydride (102 g, 479 mmol) was added to the reaction liquid at room temperature, and the mixture was stirred for 18 hours. The solvent was concentrated under reduced pressure after the reaction. A 5 N aqueous sodium hydroxide solution (100 mL) and ethyl acetate (500 mL) were added to the resultant residue to separate

the organic layer. Chloroform (300 mL) was added to the resultant water layer to separate the organic layer. The resultant organic layers were combined, and the resultant was washed with a saturated aqueous sodium chloride solution and then dried over anhydrous magnesium sulfate. The drying agent was filtered off, and then the solvent was evaporated under reduced pressure. The resultant residue was filtered through NH silica gel (ethyl acetate) for purification to obtain a crude title compound (72 g).

^{1}H-NMR(400MHz,$CDCl_3$) δ (ppm):1.13(d,J=6.3Hz,3H),2.34(dd,J=9.4,12.1Hz,1H),2.68(dd,J=3.1,12.1Hz,1H),3.72(d,J=2.0Hz,2H),3.75-3.79(m,1H),3.80(s,3H),3.82(s,3H),6.39-6.48(m,2H),7.10(d,J=8.2Hz,1H).

[0051] (2) Synthesis of (R)-N-(2,4-dimethoxybenzyl)-N-(2-hydroxypropyl)-3,3-dimethoxypropanamide

DIPEA (173 mL, 995 mmol) was added to a solution of the compound obtained in Production Example 1-(1) (74.7 g, 332 mmol), 3,3-dimethoxypropionic acid (CAS No. 6191-98-6; 38.5 g, 287 mmol), EDC (95 g, 497 mmol), and HOBT (67.2 g, 497 mmol) in DMF (500 mL) at room temperature, and the mixture was stirred for 14 hours. Water (1 L) and ethyl acetate (1 L) were added to the reaction mixture to separate the organic layer. The resultant organic layer was washed with water (1 L) and a saturated aqueous sodium chloride solution, then dried over anhydrous magnesium sulfate, the drying agent was filtered off, and the solvent was evaporated under reduced pressure. The resultant residue was purified by NH-silica gel

column chromatography (n-heptane/ethyl acetate) to obtain a title compound (61 g, 179 mmol).

ESI-MS m/z 342 $[M+H]^+$

[0052] (3) Synthesis of (R)-4-(2,4-dimethoxybenzyl)-2-methyl-3,4-dihydro-1,4-oxazepin-5(2H)-one

PPTS (19.7 g, 78.4 mmol) was added to a solution of the compound obtained in Production Example 1-(2) (53.5 g, 157 mmol) in toluene (900 mL) at room temperature, and then the mixture was heated under reflux for 7 hours. The reaction mixture was cooled to room temperature and then a saturated aqueous sodium bicarbonate solution and ethyl acetate were added to separate the organic layer. The resultant organic layer was washed with a saturated aqueous sodium chloride solution and then dried over anhydrous magnesium sulfate, the drying agent was filtered off, and then the solvent was evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (30.5 g, 110 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.19(d,J=6.6Hz,3H),3.39-3.44(m,2H),3.80(s,3H),3.82(s,3H),4.03-4.11(m,1H),4.44(d,J=14.5Hz,1H),4.73(d,J=14.5Hz,1H),5.08(d,J=8.2Hz,1H),6.43-6.48(m,3H),7.24(d,J=9.0Hz,1H).

[0053] (4) Synthesis of (R)-4-(2,4-dimethoxybenzyl)-2-methyl-1,4-oxazepan-5-one

20% Palladium hydroxide/carbon (3 g, including 50% water content) was added to a solution of the compound obtained in Production Example 1-(3) (30.5 g, 110 mmol) in methanol (500 mL)

at room temperature, and the mixture was stirred under hydrogen atmosphere at 40°C for 18 hours. The reaction mixture was cooled to room temperature and then was filtered through Celite (trademark), and the filtrate was concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (ethyl acetate) to obtain a title compound (29.1 g, 104 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.05(d,J=6.6Hz,3H),2.60(dd,J=5.1,15.6Hz,1H),2.92(ddd,J=2.2,11.0,15.4Hz,1H),3.20(d,J=15.2Hz,1H),3.29-3.38(m,1H),3.40-3.50(m,1H),3.56-3.66(m,1H),3.81(s,3H),3.82(s,3H),3.96(ddd,J=2.3,5.5,12.5Hz,1H),4.37(d,J=14.5Hz,1H),4.70(d,J=14.5Hz,1H),6.43-6.48(m,2H),7.21(d,J=8.6Hz,1H).

[0054] (5) Synthesis of (R)-2-methyl-1,4-oxazepan-5-one

Triethylsilane (26.2 mL, 164 mmol) was added to a solution of the compound obtained in Production Example 1-(4) (30.5 g, 110 mmol) in TFA (150 mL) at room temperature, and the mixture was stirred at 60°C for 3 hours. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (ethyl acetate/methanol) to obtain a title compound (12.3 g, 95 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.19(d,J=6.3Hz,3H),2.48-2.58(m,1H),2.89(ddd,J=2.5,10.9,15.4Hz,1H),3.03(ddd,J=0.9,7.6,15.3Hz,1H),3.35(ddd,J=3.9,8.4,15.4Hz,1H),3.57-3.76(m,2H),4.01(ddd,J=2.5,5.3,12.7Hz,1H),5.85-6.07(m,1H).

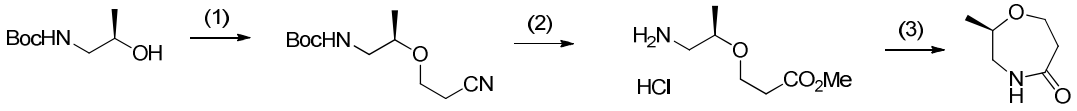
[0055] (6) Synthesis of (R)-5-methoxy-2-methyl-2,3,6,7-tetrahydro-1,4-oxazepine

Trimethyloxonium tetrafluoroborate (16.8 g, 114 mmol) was added to a solution of the compound obtained in Production Example 1-(5) (13.4 g, 103 mmol) in DCM (500 mL) at room temperature, and the mixture was stirred for 18 hours. A saturated aqueous sodium bicarbonate solution was added to the reaction mixture, and the organic layer was separated. DCM was added to the resultant water layer, and the organic layer was separated. The resultant organic layers were combined, the resultant was washed with a saturated aqueous sodium chloride solution, then the resultant was dried over anhydrous magnesium sulfate, and then the drying agent was filtered off and the solvent was evaporated under reduced pressure to obtain a title compound (13.7 g, 96 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.19(d,J=6.4Hz,3H),2.42(ddd,J=1.2,4.5,15.6Hz,1H),2.81-2.92(m,1H),3.33-3.42(m,1H),3.47-3.59(m,3H),3.61(s,3H),3.85-3.93(m,1H).

[0056] Production Example 2

Synthesis of (R)-2-methyl-1,4-oxazepan-5-one



[0057] (1) Synthesis of (R)-tert-butyl(2-(2-cyanoethoxy)propyl)carbamate

DBU (27.3 mL, 182 mmol) was added to a solution of (R)-tert-butyl(2-hydroxypropyl)carbamate (CAS No. 119768-44-4; 71.0 g, 405

mmol) in acrylonitrile (400 mL) at room temperature, and the mixture was stirred at the same temperature for 5 hours. Acetic acid (10.4 mL, 182 mmol) was added to the reaction mixture, and the mixture was concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (63.1 g, 276 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.10-1.20(m,3H),1.45(s,9H),2.59(dd,J=6.3,6.3Hz,2H),2.96-3.11(m,1H),3.23-3.41(m,1H),3.52-3.66(m,1H),3.61(td,J=6.3,9.2Hz,1H),3.75(td,J=6.3,9.2Hz,1H),4.88(brs,1H).

[0058] (2) Synthesis of (R)-methyl 3-((1-aminopropan-2-yl)oxy)propanoate hydrochloride

The compound obtained in Production Example 2-(1) (63.1 g, 276 mmol) was dissolved in a 4 M hydrogen chloride/1,4-dioxane solution (691 mL) and a 5 to 10% hydrogen chloride/methanol solution (140 mL), and the mixture was stirred at 50°C for 3 hours. A 4 M hydrogen chloride/1,4-dioxane solution (311 mL) was further added to the reaction mixture, the mixture was stirred at 50°C for 3 hours, and then the resultant was concentrated under reduced pressure. Diethyl ether was added to the residue and the resultant was concentrated under reduced pressure to obtain a crude title compound (76.9 g).

ESI-MS m/z 162 [M+H]+

[0059] (3) Synthesis of (R)-2-methyl-1,4-oxazepan-5-one

DBU (132 mL, 884 mmol) was added to a solution of the

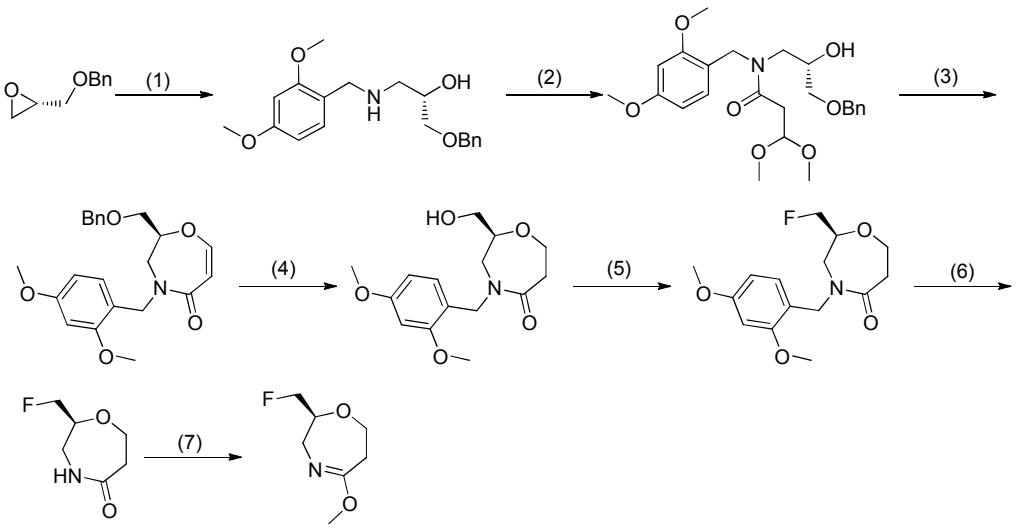
compound obtained in Production Example 2-(2) (76.9 g) in methanol (693 mL) at room temperature, and the mixture was heated under reflux for 16 hours. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (ethyl acetate/methanol) twice to obtain a title compound (21.5 g, 166 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.19(d,J=6.3Hz,3H),2.48-2.58(m,1H),2.89(ddd,J=2.5,10.9,15.4Hz,1H),3.03(ddd,J=0.9,7.6,15.3 Hz,1H),3.35(ddd,J=3.9,8.4,15.4Hz,1H),3.57-3.76(m,2H),4.01(ddd,J=2.5,5.3,12.7Hz,1H),5.85-6.07(m,1H).

ESI-MS m/z 130 [M+H]+

[0060] Production Example 3

Synthesis of (S)-2-(fluoromethyl)-5-methoxy-2,3,6,7-tetrahydro-1,4-oxazepine



[0061] (1) Synthesis of (S)-1-(benzyloxy)-3-((2,4-dimethoxybenzyl)amino)propan-2-ol

Lithium bis(trifluoromethanesulfonyl)imide (87 g, 304.5 mmol)

was added to a solution of 2,4-dimethoxybenzylamine (CAS No. 20781-20-8; 46.7 mL, 310.6 mmol) and (S)-(+)-benzyl glycidyl ether (CAS No. 16495-13-9; 50.0 g, 304.5 mmol) in DCM (1.0 L) under water-cooling. The reaction mixture was stirred at room temperature for 20 hours. Water was added to the reaction mixture to separate the organic layer. The organic layers were dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to obtain a crude title compound (119.4 g).

ESI-MS m/z 332 [M+H]+

[0062] (2) Synthesis of (S)-N-(3-(benzyloxy)-2-hydroxypropyl)-N-(2,4-dimethoxybenzyl)-3,3-dimethoxypropanamide

EDC (88 g, 456.7 mmol) and HOBT (456.7 mmol) were added to a solution of the compound obtained in Production Example 3-(1) (119.4 g), 3,3-dimethoxypropionic acid (47.0 g, 350.1 mmol), and DIPEA (159 mL) in DMF (800 mL) at room temperature. The reaction mixture was stirred for 16 hours, and then ethyl acetate and a saturated aqueous sodium chloride solution were added. The organic layer was separated and washed with a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate. The organic layer was filtered through a silica gel pad (NH silica gel + silica gel, ethyl acetate). The resultant filtrate was concentrated under reduced pressure to obtain a crude title compound (125.5 g).

ESI-MS m/z 470 [M+Na]+

[0063] (3) Synthesis of (S)-2-((benzyloxy)methyl)-4-(2,4-dimethoxybenzyl)-3,4-dihydro-1,4-oxazepin-5(2H)-one

A solution of the compound obtained in Production Example 3-(2) (125.5 g) and PPTS (35.2 g, 140.2 mmol) in xylene (1 L) was heated under reflux for 6 hours. The reaction mixture was cooled to room temperature, and ethyl acetate and a saturated aqueous sodium bicarbonate solution were added to the reaction mixture to separate the organic layer. The organic layer was washed with a saturated aqueous sodium chloride solution and then dried over anhydrous magnesium sulfate. The organic layer was concentrated under reduced pressure and the resultant residue was purified by column chromatography (n-heptane/ethyl acetate) to obtain a title compound (57.7 g, 150 mmol).

ESI-MS m/z 384 [M+H]+, 406 [M+Na]+

[0064] (4) Synthesis of (S)-4-(2,4-dimethoxybenzyl)-2-(hydroxymethyl)-1,4-oxazepan-5-one

A mixture of the compound obtained in Production Example 3-(3) (57.7 g, 150.5 mmol), 20% palladium hydroxide/carbon (6 g, including 50% water content), acetic acid (20 mL), and ethanol (600 mL) was stirred under hydrogen atmosphere at 4 to 5 MPa and 70°C for 50 hours. The reaction mixture was cooled to room temperature. The insolubles were filtered off through Celite (trademark) and the resultant was washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate → ethyl acetate/methanol) to obtain a title compound (33.7 g).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.83(dd,J=5.1,7.0Hz,1H),2.63(dd,J=5.

1,15.2Hz,1H),2.95(ddd,J=2.7,11.3,15.6Hz,1H),3.22-3.30(m,2H),3.40-3.45(m,2H),3.51(dd,J=8.2,16.0Hz,1H),3.62-3.67(m,1H),3.80(s,3H),3.81(s,3H),4.04(ddd,J=2.3,5.1,12.5Hz,1H),4.36(d,J=14.5Hz,1H),4.73(d,J=14.5Hz,1H),6.43-6.47(m,2H),7.22(d,J=8.6Hz,1H).

ESI-MS m/z 296 [M+H]+, 318 [M+Na]+

[0065] (5) Synthesis of (S)-4-(2,4-dimethoxybenzyl)-2-(fluoromethyl)-1,4-oxazepan-5-one

Perfluorobutanesulfonyl fluoride (45.1 mL, 251.0 mmol) was added to a solution of the compound obtained in Production Example 3-(4) (33.7 g, 114.1 mmol), DIPEA (49.2 mL, 285.3 mmol), and tetrabutylammonium difluorotriphenyl silicate (73.9 g, 136.9 mmol) in THF (600 mL) at room temperature. The reaction mixture was stirred at room temperature for 64 hours. The reaction mixture was concentrated under reduced pressure. A mixed solvent of toluene/ethyl acetate (5/1) and a saturated aqueous sodium chloride solution were added to the resultant residue to separate the organic layer. The organic layer was further washed with a saturated aqueous sodium chloride solution twice. The organic layer was concentrated under reduced pressure and the resultant residue was purified serially by silica gel column chromatography (n-heptane/ethyl acetate) and NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain a crude title compound (41 g).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.62(dd,J=5.5,15.2Hz,1H),2.96(ddd,J=2.3,11.3,15.2Hz,1H),3.35-

3.68(m,4H),3.80(s,3H),3.81(s,3H),4.00(ddd,J=2.3,5.1,12.5Hz,1H),4.09-4.36(m,2H),4.40(d,J=14.5Hz,1H),4.74(d,J=14.5Hz,1H),6.44-6.47(m,2H),7.24(d,J=8.2Hz,1H).

ESI-MS m/z 298 [M+H]+

[0066] (6) Synthesis of (S)-2-(fluoromethyl)-1,4-oxazepan-5-one

Triethylsilane (27.4 mL, 171.7 mmol) was added to a solution of the compound obtained in Production Example 3-(5) (41 g) in TFA (300 mL) at room temperature. The reaction mixture was stirred at 60°C for 3 hours. The reaction mixture was concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate → ethyl acetate/methanol) to obtain a title compound (15 g, 101.94 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.54(ddd,J=2.0,5.1,15.6Hz,1H),2.93(ddd,J=2.7,11.3,15.6Hz,1H),3.23-3.31(m,1H),3.46(ddd,J=3.5,8.6,15.2Hz,1H),3.66-3.78(m,2H),4.07(ddd,J=2.7,5.1,12.5Hz,1H),4.24-4.53(m,2H),6.50(brs,1H).

[0067] (7) Synthesis of (S)-2-(fluoromethyl)-5-methoxy-2,3,6,7-tetrahydro-1,4-oxazepine

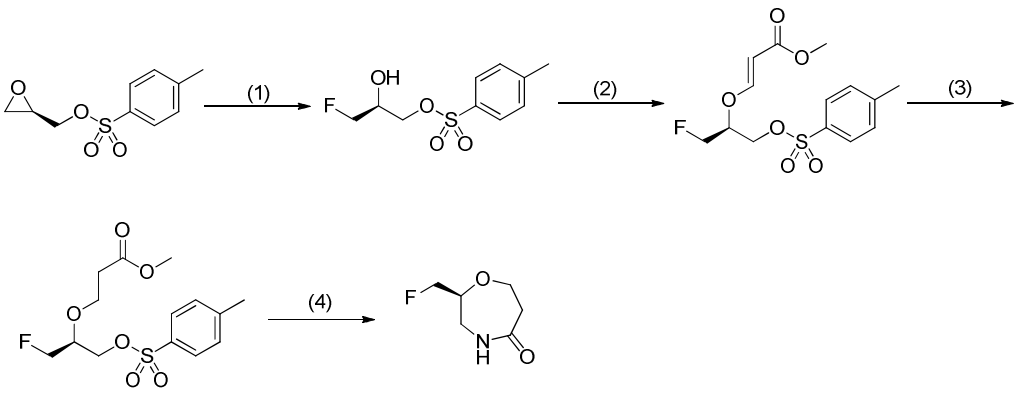
Trimethyloxonium tetrafluoroborate (17.34 g, 117.2 mmol) was added to a solution of the compound obtained in Production Example 3-(6) (15 g, 101.94 mmol) in DCM (400 mL) at room temperature. The reaction solution was stirred at room temperature for 14 hours. A saturated aqueous sodium bicarbonate solution was added to the reaction mixture, and the mixture was stirred at room temperature for

30 minutes. Chloroform was added to the mixture to separate the organic layer. The organic layer was dried over anhydrous magnesium sulfate. The organic layer was concentrated under reduced pressure to obtain a title compound (14.9 g, 93 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.47(ddd,J=1.2,4.3,15.6Hz,1H),2.87-2.96(m,1H),3.45-3.70(m,4H),3.63(s,3H),3.98(ddd,J=3.1,4.3,12.1Hz,1H),4.30-4.50(m,2H).

[0068] Production Example 4

Synthesis of (S)-2-(fluoromethyl)-1,4-oxazepan-5-one



[0069] (1) Synthesis of (S)-3-fluoro-2-hydroxypropyl-4-methylbenzene sulfonate

Diethyl ether (1.00 L), (2R)-(-)-glycidyl tosylate (CAS No. 113826-06-5; 50.0 g, 219 mmol), and benzoyl fluoride (33.4 mL, 307 mmol) were added to a mixture of (R,R)-(-)-N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (9.26 g, 15.3 mmol), HFIP (64.4 mL, 613 mmol), and DBN (1.51 mL, 12.3 mmol). The reaction mixture was stirred at room temperature overnight and then a 7 M ammonia/methanol solution (150 mL) was added. The

mixture was stirred at room temperature for 2 hours and the solvent was evaporated under reduced pressure. Ethyl acetate (300 mL) was added to the resultant residue, and the resultant was washed serially with water and a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (45.5 g, 183 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.28-2.42(m,1H),2.46(s,3H),4.03-4.18(m,3H),4.34-4.54(m,2H),7.37(d,J=8.2Hz,2H),7.81(d,J=8.2Hz,2H).

ESI-MS m/z 271 [M+Na]+

[0070] (2) Synthesis of (S,E)-methyl 3-((1-fluoro-3-(tosyloxy)propan-2-yl)oxy)acrylate

A solution of the compound obtained in Production Example 4-(1) (45.5 g, 183 mmol), NMM (12.1 mL, 110 mmol), and methyl propionate (CAS No. 922-67-8; 19.8 mL, 238 mmol) in THF (315 mL) was stirred under ice-cooling for 3 hours. Acetic acid (6.29 mL, 110 mmol) was added to the reaction mixture, and then water and ethyl acetate were added. The organic layer was separated and washed serially with water and a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (49.2 g, 148 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.46(s,3H),3.70 (s,3H),4.11-4.37(m,3H),4.42-4.66(m,2H),5.26(d,J=12.5Hz,1H),7.33-7.42(m,

3H),7.76-7.83(m,2H).

ESI-MS m/z 355 [M+Na]+

[0071] (3) Synthesis of (S)-methyl 3-((1-fluoro-3-(tosyloxy)propan-2-yl)oxy)propanoate

A suspension of the compound obtained in Production Example 4-(2) (48.8 g, 147 mmol) and 5% palladium/carbon (6.25 g, including 50% water content) in ethanol (279 mL) was stirred under hydrogen atmosphere at room temperature for 2 hours. The insolubles were removed, and then the filtrate was concentrated under reduced pressure to obtain a crude title compound (45.8 g).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.46(s,3H),2.53(t,J=6.3Hz,2H),3.68(s,3H),3.27-3.87(m,3H),4.08(dt,J=1.6,5.5Hz,2H),4.29-4.53(m,2H),7.36(d,J=8.2Hz,2H),7.80(d,J=8.2Hz,2H).

ESI-MS m/z 357 [M+Na]+

[0072] (4) Synthesis of (S)-2-(fluoromethyl)-1,4-oxazepan-5-one

A mixture of the compound obtained in Production Example 4-(3) (45.8 g, 137 mmol) and a 7 M ammonia/methanol solution (391 mL, 2.74 mol) was stirred in an autoclave at 130°C for 2 hours. The reaction mixture was cooled to room temperature, and then the mixture was concentrated under reduced pressure. Methanol (300 mL) and DBU (41.0 mL, 274 mmol) were added to the residue at room temperature. The reaction mixture was stirred at 100°C for 3 hours. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate

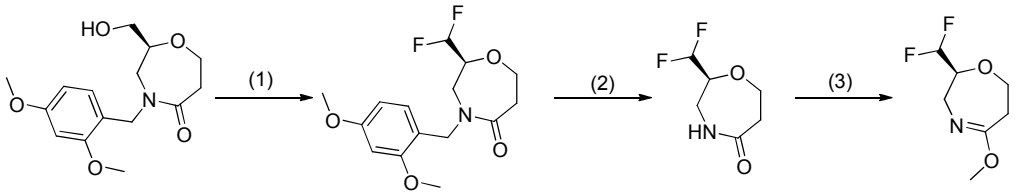
→ ethyl acetate/methanol) to obtain a title compound (10.4 g, 70.7 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.54(ddd,J=2.0,5.1,15.6Hz,1H),2.93(ddd,J=2.7,11.3,15.6Hz,1H),3.23-3.31(m,1H),3.46(ddd,J=3.5,8.6,15.2Hz,1H),3.66-3.78(m,2H),4.07(ddd,J=2.7,5.1,12.5Hz,1H),4.24-4.53(m,2H),6.50(brs,1H).

ESI-MS m/z 295 [M+M+H]+

[0073] Production Example 5

Synthesis of (S)-2-(difluoromethyl)-5-methoxy-2,3,6,7-tetrahydro-1,4-oxazepine



[0074] (1) Synthesis of (S)-2-(difluoromethyl)-4-(2,4-dimethoxybenzyl)-1,4-oxazepan-5-one

Oxalyl chloride (1.18 mL, 14.0 mmol) was added to a solution of DMSO (1.03 mL, 14.5 mmol) in THF (60 mL) under nitrogen atmosphere at -78°C. The mixture was stirred at -78°C for 10 minutes and a solution of the compound obtained in Production Example 3-(4) (3.30 g, 11.2 mmol) in THF (40 mL) was added dropwise at the same temperature. After the mixture was stirred at the same temperature for 1 hour, DIPEA (7.79 mL, 44.7 mmol) was added dropwise. After 10 minutes, the reaction mixture was warmed to room temperature and further stirred for 1 hour. An aqueous

ammonium chloride solution and ethyl acetate were added to the mixture to separate the organic layer. The organic layer was washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The organic layer was concentrated under reduced pressure. The resultant residue was dissolved in DCM (66 mL) and the resultant was cooled to -78°C. BAST (6.18 mL, 33.5 mmol) was added to the mixture at the same temperature, then the resultant was slowly warmed to room temperature and stirred for 15 hours. A saturated aqueous sodium chloride solution and ethyl acetate were added to the reaction mixture to separate the organic layer. The organic layer was washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The organic layer was concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (1.13 g, 3.58 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.63(dd,J=5.1,15.6Hz,1H),2.97(ddd,J=2.4,11.4,15.6Hz,1H),3.26-3.36(m,1H),3.60(d,J=4.7Hz,2H),3.77-3.84(m,1H),3.80(s,3H),3.81(s,3H),4.04-4.10(m,1H),4.36(d,J=14.1Hz,1H),4.75(d,J=14.1Hz,1H),5.47-5.76(m,1H),6.44-6.47(m,2H),7.24-7.27(m,1H).

ESI-MS m/z 316 [M+H]+

[0075] (2) Synthesis of (S)-2-(difluoromethyl)-1,4-oxazepan-5-one

Triethylsilane (0.881 mL, 5.52 mmol) was added to a solution

of the compound obtained in Production Example 5-(1) (1.16 g, 3.68 mmol) in TFA (10 mL) at room temperature. The reaction mixture was stirred at 60°C for 3 hours. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate → ethyl acetate/methanol) to obtain a title compound (472 mg, 2.86 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.57(ddd,J=1.9,4.8,15.7Hz,1H),2.95(ddd,J=2.7,11.3,15.6Hz,1H),3.35(dd,J=7.8,15.4Hz,1H),3.54(ddd,J=3.7,8.8,15.5Hz,1H),3.63-3.78(m,2H),4.14(ddd,J=2.7,5.0,12.8Hz,1H),5.63-5.92(m,1H),6.00(brs,1H).

[0076] (3) Synthesis of (S)-2-(difluoromethyl)-5-methoxy-2,3,6,7-tetrahydro-1,4-oxazepine

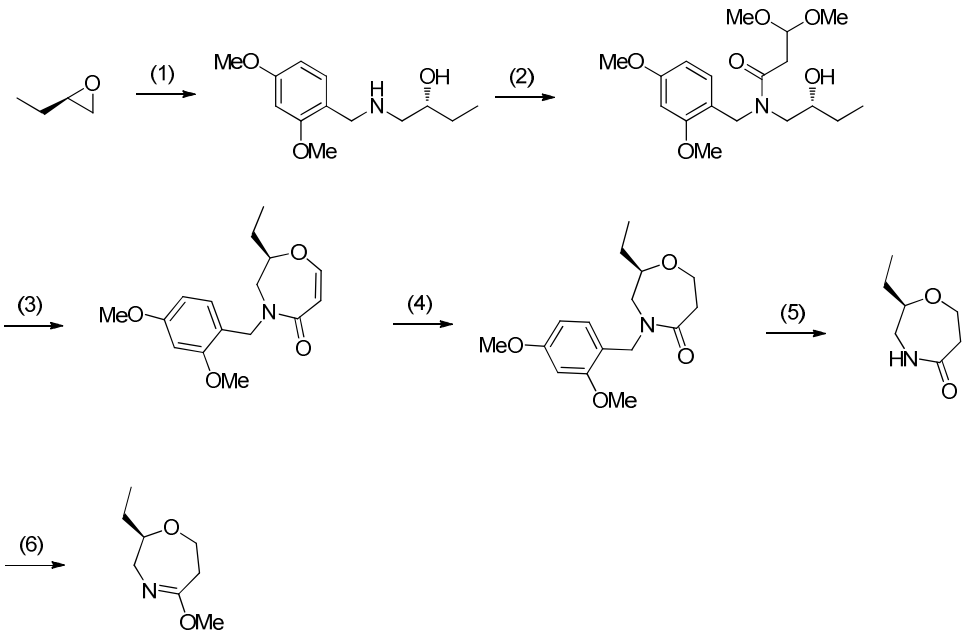
Trimethyloxonium tetrafluoroborate (597 mg, 4.04 mmol) was added to a solution of the compound obtained in Production Example 5-(2) (580 mg, 3.51 mmol) in DCM (100 mL) under ice-cooling. The reaction mixture was stirred under ice-cooling for 20 minutes, then warmed to room temperature, and further stirred for 14 hours. A saturated aqueous sodium bicarbonate solution was added to the reaction mixture, and the mixture was stirred at room temperature for 30 minutes. Chloroform was added to the mixture to separate the organic layer. The organic layer was dried over anhydrous magnesium sulfate. The organic layer was concentrated under reduced pressure to obtain a title compound (450 mg, 2.51 mmol).

^{1}H-

NMR(400MHz,CDCl3) δ(ppm):2.47(ddd,J=1.2,4.2,15.6Hz,1H),2.89-2.97(m,1H),3.46-3.61(m,3H),3.64(s,3H),3.77(d,J=14.5Hz,1H),3.98-4.05(m,1H),5.57-5.86(m,1H).

[0077] Production Example 6

Synthesis of (R)-2-ethyl-5-methoxy-2,3,6,7-tetrahydro-1,4-oxazepine



[0078] (1) Synthesis of (R)-1-((2,4-dimethoxybenzyl)amino)butan-2-ol

According to the method of Production Example 3-(1), a crude title compound (15.7 g) was obtained from (R)-(+)-1,2-epoxybutane (CAS No. 3760-95-0; 5.0 g, 69 mmol) and 2,4-dimethoxybenzylamine (15.7 g, 65.8 mmol).

ESI-MS m/z 240 [M+H]+

[0079] (2) Synthesis of (R)-N-(2,4-dimethoxybenzyl)-N-(2-hydroxybutyl)-3,3-dimethoxypropanamide

According to the method of Production Example 1-(2), a title

compound (16.3 g, 45.9 mmol) was obtained from the compound obtained in Production Example 6-(1) (15.7 g) and 3,3-dimethoxypropionic acid (8.80 g, 65.6 mmol).

ESI-MS m/z 378 [M+Na]+

[0080] (3) Synthesis of (R)-4-(2,4-dimethoxybenzyl)-2-ethyl-3,4-dihydro-1,4-oxazepin-5(2H)-one

According to the method of Production Example 1-(3), a title compound (5.88 g, 20.2 mmol) was obtained from the compound obtained in Production Example 6-(2) (16.3 g, 45.9 mmol).

ESI-MS m/z 292 [M+H]+

[0081] (4) Synthesis of (R)-4-(2,4-dimethoxybenzyl)-2-ethyl-1,4-oxazepan-5-one

According to the method of Production Example 1-(4), a title compound (5.92 g, 20.2 mmol) was obtained from the compound obtained in Production Example 6-(3) (5.88 g, 20.2 mmol).

ESI-MS m/z 316 [M+Na]+

[0082] (5) Synthesis of (R)-2-ethyl-1,4-oxazepan-5-one

According to the method of Production Example 1-(5), a title compound (2.78 g, 19.4 mmol) was obtained from the compound obtained in Production Example 6-(4) (5.92 g, 20.2 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.96(t,J=7.6Hz,3H),1.38-1.50(m,1H),1.52-1.62(m,1H),2.54(dd,J=4.5,15.4Hz,1H),2.82-2.94(m,1H),3.08(dd,J=7.4,14.1Hz,1H),3.27-3.41(m,2H),3.63-3.74(m,1H),4.04(ddd,J=2.3,5.3,12.7Hz,1H),6.02-6.22(m,1H).

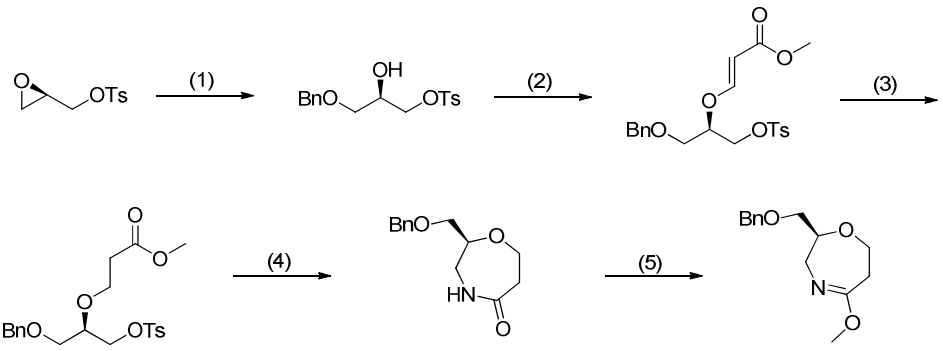
[0083] (6) Synthesis of (R)-2-ethyl-5-methoxy-2,3,6,7-tetrahydro-1,4-oxazepine

According to the method of Production Example 1-(6), a title compound (2.51 g, 16.0 mmol) was obtained from the compound obtained in Production Example 6-(5) (2.78 g, 19.4 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.95(t,J=8.0Hz,3H),1.44-1.57(m,2H),2.43(ddd,J=1.2,4.5,15.4Hz,1H),2.87(ddd,J=3.1,11.5,15.0Hz,1H),3.24-3.32(m,1H),3.33-3.41(m,1H),3.47-3.57(m,2H),3.62(s,3H),3.87-3.95(m,1H).

[0084] Production Example 7

Synthesis of (S)-2-((benzyloxy)methyl)-5-methoxy-2,3,6,7-tetrahydro-1,4-oxazepine



[0085] (1) Synthesis of (R)-3-(benzyloxy)-2-hydroxypropyl 4-methylbenzene sulfonate

A boron trifluoride-ethyl ether complex (0.694 mL, 5.48 mmol) was added to a mixture of (2R)-(-)-glycidyl tosylate (25.0 g, 109 mmol), benzyl alcohol (22.7 mL, 219 mmol) and toluene (200 mL) under ice-cooling. The reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with a saturated aqueous sodium bicarbonate solution (50.0 mL) twice and further with water (50.0 mL) twice. Ethanol was added to the organic layer until the suspension became clear. The solvent was

evaporated under reduced pressure and the residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (28.0 g, 83.0 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.40(d,J=5.5Hz,1H),2.44(s,3H),3.46-3.57(m,2H),3.96-4.15(m,3H),4.50(s,2H),7.26-7.39(m,7H),7.75-7.82(m,2H).

[0086] (2) Synthesis of (R,E)-methyl 3-((1-(benzyloxy)-3-(tosyloxy)propan-2-yl)oxy)acrylate

A mixture of the compound obtained in Production Example 7-(1) (28.0 g, 83.2 mmol), methyl propiolate (15.3 mL, 183 mmol), NMM (9.15 mL, 83.2 mmol) and THF (280 mL) was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (34.7 g, 82.5 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.44(s,3H),3.57(dd,J=1.8,4.9Hz,2H),3.69(s,3H),4.14-4.30(m,3H),4.44-4.55(m,2H),5.20(d,J=12.5Hz,1H),7.24-7.40(m,8H),7.75-7.78(m,2H).

[0087] (3) Synthesis of (R)-methyl 3-((1-(benzyloxy)-3-(tosyloxy)propan-2-yl)oxy)propanoate

10% Palladium/carbon (4.39 g, including 50% water content) was added to a solution of the compound obtained in Production Example 7-(2) (34.7 g, 82.5 mmol) in ethanol (347 mL). The reaction mixture was stirred under hydrogen atmosphere for 7 hours.

The insolubles were filtered off through Celite (trademark). The solvent was evaporated under reduced pressure to obtain a title compound (34.5 g, 82.0 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.44(s,3H),2.51(t,J=6.3Hz,2H),3.43-3.52(m,2H),3.66(s,3H),3.68-3.72(m,1H),3.74-3.85(m,2H),4.02-4.08(m,1H),4.11-4.18(m,1H),4.46(s,2H),7.21-7.26(m,2H),7.28-7.40(m,5H),7.74-7.82(m,2H).

[0088] (4) Synthesis of (S)-2-((benzyloxy)methyl)-1,4-oxazepan-5-one

The compound obtained in Production Example 7-(3) (22.0 g, 52.1 mmol) was dissolved in a 7 M ammonia/methanol solution (100 mL, 700 mmol). The reaction mixture was stirred in a sealed tube at 100°C overnight. The reaction mixture was transferred into an eggplant shaped flask and DBU (24.9 mL, 167 mmol) was added. The reaction mixture was stirred at 80°C for 6 hours. The resultant was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (5.56 g, 23.6 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.48-2.56(m,1H),2.91(ddd,J=2.7,11.0,15.5Hz,1H),3.24-3.33(m,1H),3.35-3.44(m,2H),3.53(dd,J=4.7,9.8Hz,1H),3.61-3.76(m,2H),4.04(ddd,J=2.7,5.2,12.8Hz,1H),4.49-4.60(m,2H),5.92(brs,1H),7.27-7.41(m,5H).

[0089] (5) Synthesis of (S)-2-((benzyloxy)methyl)-5-methoxy-

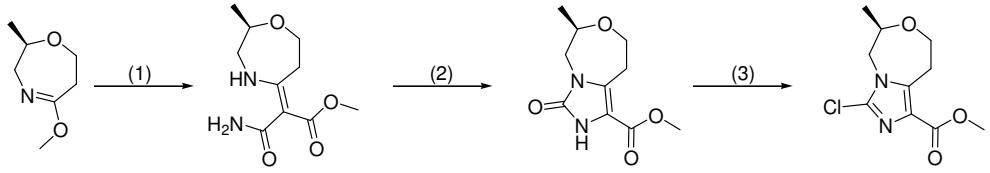
2,3,6,7-tetrahydro-1,4-oxazepine

Trimethyloxonium tetrafluoroborate (1.51 g, 10.2 mmol) was added to a solution of the compound obtained in Production Example 7-(4) (2.00 g, 8.50 mmol) in DCM (40.0 mL) at room temperature, and the mixture was stirred at room temperature for 15 hours. A saturated aqueous sodium bicarbonate solution was added to the reaction mixture, and the mixture was stirred at room temperature for 20 minutes. The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to obtain a title compound (2.12 g, 8.50 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.44(ddd,1.2,4.4,15.5Hz,1H),2.90(ddd, J=3.1,11.6,15.3Hz,1H),3.41-3.65(m,9H),3.97(ddd,J=3.1,4.6,12.2Hz,1H),4.53-4.60(m,2H),7.27-7.42(m,5H).

[0090] Production Example 8

Synthesis of (R)-methyl 3-chloro-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate



[0091] (1) Synthesis of (R)-methyl 3-amino-2-(2-methyl-1,4-oxazepan-5-ylidene)-3-oxopropanoate

A solution of the compound obtained in Production Example 1-(6) (16.0 g, 156 mmol) and methyl carbamoyl acetate (CAS No. 51513-29-2; 18.3 g, 156 mmol) in THF (40 mL)/DMF (10 mL) was

stirred at 90°C for 15 hours. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The resultant residue was purified by silica gel chromatography (n-heptane/ethyl acetate → ethyl acetate/methanol) to obtain a title compound (14.2 g, 62.2 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.20(d,J=6.3Hz,3H),2.73-2.81(m,1H),3.33-3.66(m,5H),3.77(s,3H),4.04-4.10(m,1H).

[0092] (2) Synthesis of (R)-methyl 6-methyl-3-oxo-2,3,5,6,8,9-hexahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

Iodobenzene diacetate (24.1 g, 74.7 mmol) was added to a solution of the compound obtained in Production Example 8-(1) (14.2 g, 62.2 mmol) in THF (100 mL)/toluene (100 mL), and the mixture was stirred at room temperature for 60 hours. A saturated aqueous sodium bicarbonate solution (60 mL) and a saturated aqueous sodium sulfite solution (60 mL) were added to the reaction mixture, and the mixture was stirred at room temperature for 1 hour. The mixture was extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate → ethyl acetate/methanol) to obtain a title compound (9.97 g, 44.1 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.27(d,J=6.3Hz,3H),2.86(ddd,J=2.4,11.0,16.3Hz,1H),3.45(dd,J=9.0,14.7Hz,1H),3.53-3.70(m,3H),3.83(s,3H),4.13-4.19(m,1H),4.29(d,J=14.7Hz,1H),8.03(brs,1H).

ESI-MS m/z 227 [M+H]+

[0093] (3) Synthesis of (R)-methyl 3-chloro-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

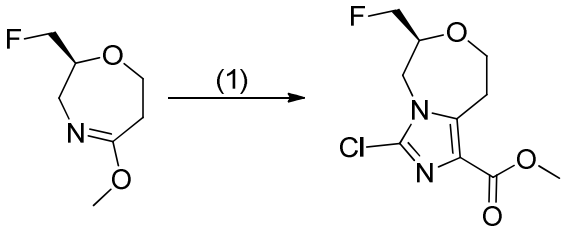
A mixture of the compound obtained in Production Example 8-(2) (9.97 g, 44.1 mmol) and phosphorus oxychloride (60 mL) was stirred at 110°C for 4 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resultant residue was purified by NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (5.94 g, 24.3 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.30(d,J=6.5Hz,3H),3.02(ddd,J=2.7,10.8,16.4Hz,1H),3.55-3.62(m,1H),3.66-3.74(m,1H),3.87(s,3H),3.88-3.98(m,2H),4.13-4.19(m,1H),4.26-4.31(m,1H).

ESI-MS m/z 245 [M+H]+

[0094] Production Example 9

Synthesis of (S)-methyl 3-chloro-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate



[0095] According to Production Examples 8-(1), 8-(2), and 8-(3), a title compound (1.77 g, 6.74 mmol) was obtained from the compound obtained in Production Example 3-(7) (9.39 g, 58.3 mmol).

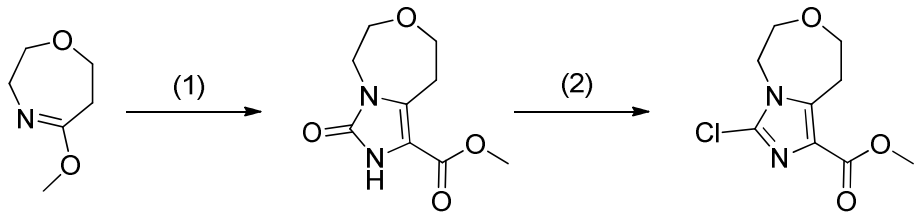
^{1}H-

NMR(400MHz,CDCl3) δ(ppm):3.02(ddd,J=2.7,11.4,16.4Hz,1H),3.58-3.65(m,1H),3.71-3.80(m,1H),3.88(s,3H),3.98-4.09(m,2H),4.23-4.28(m,1H),4.33-4.65(m,3H).

ESI-MS m/z 263 [M+H]+

[0096] Production Example 10

Synthesis of methyl 3-chloro-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate



[0097] (1) Synthesis of methyl 3-oxo-2,3,5,6,8,9-hexahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

According to the methods of Production Examples 8-(1) and 8-(2), a title compound (13.0 g, 6.74 mmol) was obtained from 5-methoxy-2,3,6,7-tetrahydro-1,4-oxazepine (CAS No. 384330-36-3; 25.0 g, 194 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):3.26-3.30(m,2H),3.76-3.85(m,4H),3.83(s,3H),4.00-4.03(m,2H),8.20(brs,1H).

ESI-MS m/z 213 [M+H]+

[0098] (2) Synthesis of methyl 3-chloro-5,6,8,9-hexahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

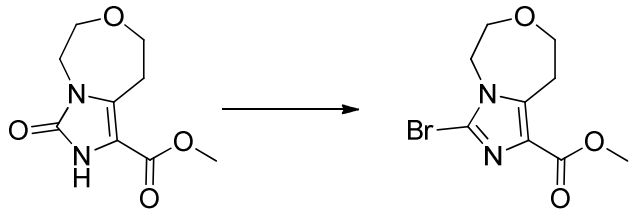
According to the method of Production Example 8-(3), a title compound (7.58 g, 32.9 mmol) was obtained from the compound obtained in Production Example 10-(1) (11 g, 51.8 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):3.51-3.55(m,2H),3.85-

3.89(m,4H),3.89(s,3H),4.25-4.28(m,2H).

[0099] Production Example 11

Synthesis of methyl 3-bromo-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

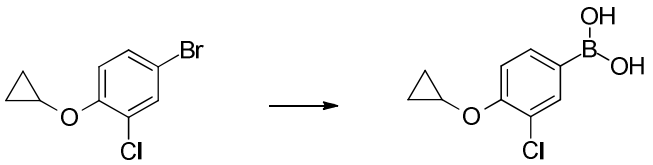


[0100] Phosphorus oxybromide (25.0 g, 87.2 mmol) was added to a solution of the compound obtained in Production Example 10-(1) (7.64 g, 36.0 mmol) in toluene (140 mL), and the mixture was stirred and heated under reflux for 24 hours. The reaction mixture was cooled to room temperature, ice and a saturated aqueous sodium bicarbonate solution were added, and the mixture was stirred for 3 hours. The solid was filtered off and the filtrate was extracted with chloroform three times. The resultant organic layer was dried over anhydrous sodium sulfate and then the resultant was concentrated under reduced pressure. The resultant residue was washed with ethyl acetate three times to obtain a title compound (3.18 g, 11.6 mmol). The filtrate was concentrated and the resultant residue was purified by NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (0.84 g, 3.1 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):3.42-3.61(m,2H),3.80-3.89(m,4H),3.86(s,3H),4.25(t,J=3.5Hz,2H).

[0101] Production Example 12

Synthesis of (3-chloro-4-cyclopropoxyphenyl)boronic acid

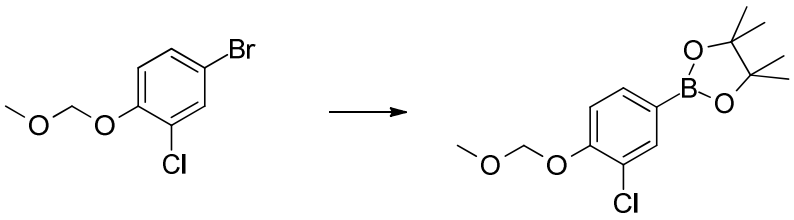


[0102] An n-butyl lithium/n-hexane solution (2.69 mol/L, 1.70 mL) was added dropwise into a solution of 4-bromo-2-chloro-1-cyclopropoxybenzene (CAS 869569-68-6; 1.10 g, 4.44 mmol) in THF (8.5 mL) at -78°C, and the mixture was stirred at the same temperature for 30 minutes. Triethyl borate (0.980 mL, 5.79 mmol) was slowly added to the reaction mixture, then the dry ice was removed from the cooling bath, and then the mixture was stirred until the internal temperature rose to 0°C. A saturated aqueous ammonium chloride solution and ethyl acetate were added to the mixture to separate the organic layer. The resultant was washed with a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Ether was added to the resultant residue, and the resultant solid was collected by filtration to obtain a title compound (520 mg, 2.45 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.85-0.98(m,4H),3.87-3.98(m,1H),7.43(d,J=8.2Hz,1H),8.09(dd,J=1.6,8.2Hz,1H),8.14(d,J=1.6Hz,1H).

[0103] Production Example 13

Synthesis of 2-(3-chloro-4-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

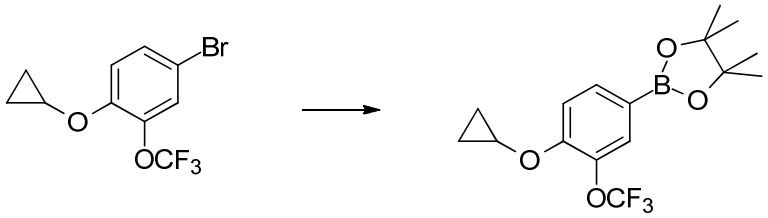


[0104] A mixture of 4-bromo-2-chloro-1-(methoxymethoxy)benzene (CAS 1301146-84-8; 4.85 g, 19.3 mmol), bis(pinacolate)diboron (6.87 g, 27.1 mmol), potassium acetate (5.73 g, 58.4 mmol), and Pd(dppf)Cl2·CH2Cl2 (0.788 g, 0.964 mmol) was stirred in DMSO (76 mL) at 80°C for 5 hours. Water and diethyl ether were added to the reaction mixture to separate the organic layer. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (4.50 g, 15.1 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.33(s,12H),3.51(s,3H),5.28(s,2H),7.15(d,J=8.2Hz,1H),7.64(dd,J=1.6,8.2Hz,1H),7.82(d,J=1.6Hz,1H).

[0105] Production Example 14

Synthesis of 2-(4-cyclopropoxy-3-(trifluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



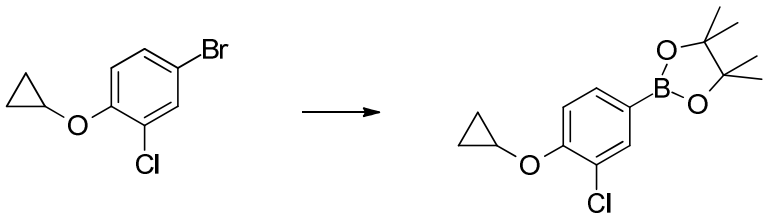
[0106] According to the method of Production Example 13, a

title compound (1.05 g, 3.05 mmol) was obtained from 4-bromo-1-cyclopropoxy-2-(trifluoromethoxy)benzene (CAS 1337606-89-9; 1.30 g, 4.38 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.76-0.84(m,4H),1.33(s,12H),3.76-3.90(m,1H),7.31(d,J=8.2Hz,1H),7.63(qd,J=1.3,1.5Hz,1H),7.70(dd,J=1.5,8.2Hz,1H).

[0107] Production Example 15

Synthesis of 2-(3-chloro-4-cyclopropoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

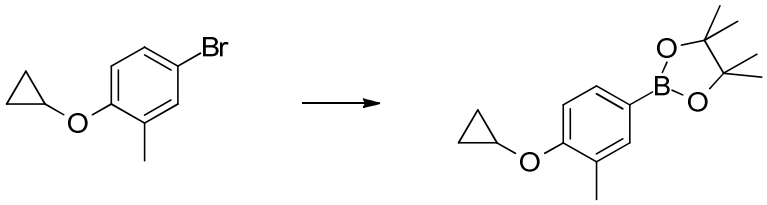


[0108] According to the method of Production Example 13, a title compound (1.10 g, 3.73 mmol) was obtained from 4-bromo-2-chloro-1-cyclopropoxybenzene (CAS 869569-68-6; 1.10 g, 4.44 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.74-0.96(m,4H),1.33(s,12H),3.71-3.94(m,1H),7.28(d,J=8.2Hz,1H),7.67(dd,J=1.6,8.2Hz,1H),7.78(d,J=1.6Hz,1H).

[0109] Production Example 16

Synthesis of 2-(4-cyclopropoxy-3-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

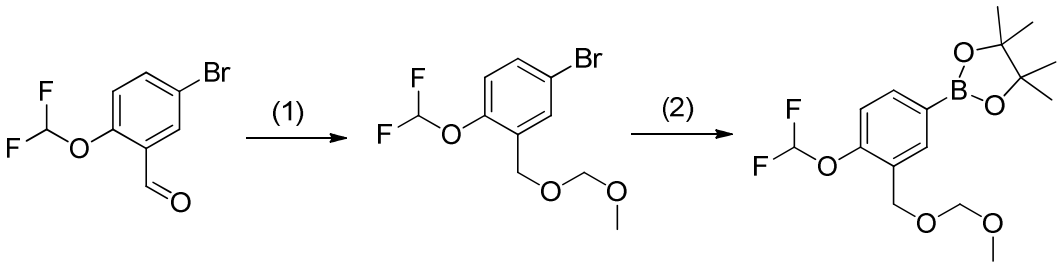


[0110] According to the method of Production Example 13, a title compound (1.20 g, 4.38 mmol) was obtained from 4-bromo-1-cyclopropoxy-2-methylbenzene (CAS 1243345-41-6; 2.00 g, 8.81 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.62-0.85(m,4H),1.33(s,12H),2.16(s,3H),3.71-3.81(m,1H),7.19(d,J=8.2Hz,1H),7.58(brs,1H),7.65(brd,J=8.2Hz,1H).

[0111] Production Example 17

Synthesis of 2-(4-(difluoromethoxy)-3-((methoxymethoxy)methyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[0112] (1) Synthesis of 4-bromo-1-(difluoromethoxy)-2-((methoxymethoxy)methyl)benzene

Sodium borohydride (113 mg, 2.99 mmol) was added to a solution of 5-bromo-2-(difluoromethoxy)benzaldehyde (CAS No. 329269-64-9; 750 mg, 2.99 mmol) in methanol (15 mL) under ice-cooling. The reaction mixture was stirred under ice-cooling for 30 minutes. Acetic acid was added to the reaction mixture, the mixture

was warmed to room temperature, and then the solvent was evaporated under reduced pressure. The residue was mixed with methanol for azeotropically evaporation three times and further mixed with chloroform for azeotropically evaporation. The resultant residue was dissolved in DCM. Dimethoxymethane (5.29 mL, 59.8 mmol) was added to the resultant solution. Diphosphorus pentaoxide (4.24 g, 29.9 mmol) was added to the reaction mixture under ice-cooling. The reaction mixture was stirred under ice-cooling for 30 minutes. Potassium carbonate (20 g, 145 mmol) was added to the reaction solution, and then the mixture was warmed to room temperature. The reaction solution was filtered and then the filtrate was concentrated under reduced pressure. The resultant residue was purified by silica gel chromatography (n-heptane/ethyl acetate) to obtain a title compound (622 mg, 2.09 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):3.42(s,3H),4.62(s,2H),4.74(s,2H),6.50(t,J=73.8Hz,1H)7.03(d,J=8.6Hz,1H)7.43(dd,J=2.3,8.6Hz,1H)7.65(d,J=2.3Hz,1H).

[0113] (2) Synthesis of 2-(4-(difluoromethoxy)-3-((methoxymethoxy)methyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

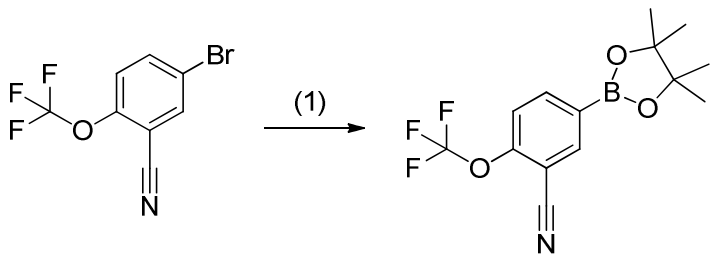
Pd(dppf)Cl2·CH2Cl2 (171 mg, 209 μmol) was added to a solution of the compound obtained in Production Example 17-(1) (622 mg, 2.09 mmol), potassium acetate (616 mg, 6.28 mmol), and bis(pinacolate)diboron (1.06 g, 4.19 mmol) in DMF (10 mL) at room temperature. The reaction mixture was stirred at 110°C for 2 hours

and then cooled to room temperature. The reaction solution was diluted with ethyl acetate, then the resultant was washed with water five times and then with a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a crude title compound (726 mg).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.34(s,12H),3.42(s,3H),4.64(s,2H),4.73,(s,2H),6.55(dt,J=1.2,74.2Hz,1H),7.11(d,J=8.2Hz,1H),7.77(dd,J=1.6,8.2Hz,1H),7.90(d,J=1.2Hz,1H).

[0114] Production Example 18

Synthesis of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethoxy)benzonitrile

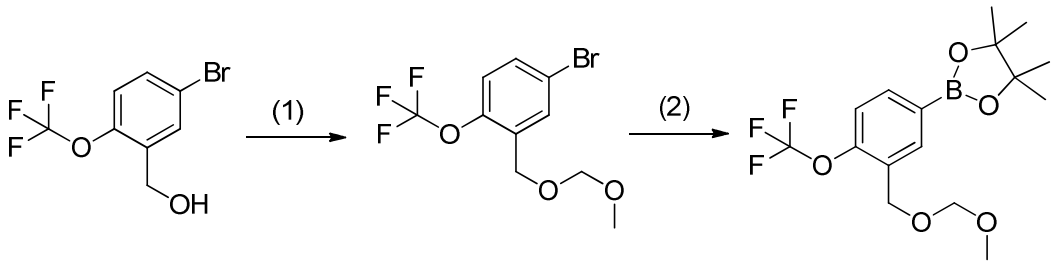


[0115] According to the method of Production Example 17-(2), a crude title compound (744 mg) was obtained from 5-bromo-2-(trifluoromethoxy)benzonitrile (CAS No. 1210906-15-2; 500 mg, 1.88 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.35(s,12H),7.37,(qd,J=1.6,8.6Hz,1H),8.04(dd,J=1.4,8.4Hz,1H),8.14(d,J=1.6Hz,1H).

[0116] Production Example 19

Synthesis of 2-(3-((methoxymethoxy)methyl)-4-(trifluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[0117] (1) Synthesis of 4-bromo-2-((methoxymethoxy)methyl)-1-(trifluoromethoxy)benzene

Chloromethyl methyl ether (2.80 mL, 36.9 mmol) was added to a solution of (5-bromo-2-(trifluoromethoxy)phenyl)methanol (CAS No. 685126-86-7; 5.00 g, 18.4 mmol) and DIPEA (9.64 mL, 55.3 mmol) in DCM (50 mL) under ice-cooling. The reaction mixture was stirred under ice-cooling for 30 minutes, then warmed to room temperature, and stirred for 13 hours. Water was added to the reaction mixture to separate the organic layer. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (5.60 g, 17.8 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):3.42(s,3H),4.63(s,2H),4.74(s,2H),7.12(dd,J=1.6,9.0Hz,1H)7.44(dd,J=2.5,8.8Hz,1H)7.70(d,J=2.0Hz,1H).

[0118] (2) Synthesis of 2-(3-((methoxymethoxy)methyl)-4-(trifluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

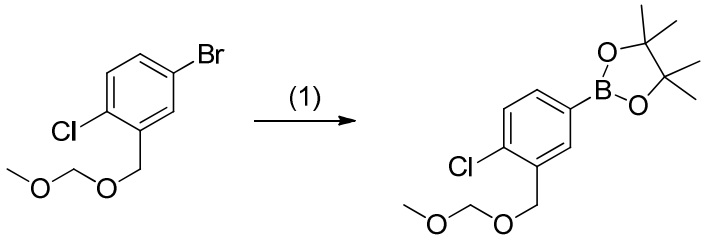
According to the method of Production Example 17-(2), a crude title compound (1.66 g) was obtained from the compound obtained in

Production Example 19-(1) (1.12 g, 3.56 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.34(s,12H),3.43(s,3H),4.66(s,2H),4.74,(s,2H),7.24(qd,J=2.0,8.2Hz,1H),7.78(dd,J=1.6,8.2Hz,1H),7.95(d,1.6 Hz,1H).

[0119] Production Example 20

Synthesis of 2-(4-chloro-3-((methoxymethoxy)methyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

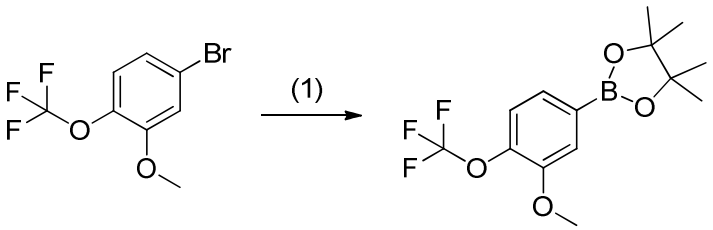


[0120] According to the method of Production Example 17-(2), a title compound (3.36 g, 10.8 mmol) was obtained from 4-bromo-1-chloro-2-((methoxymethoxy)methyl)benzene (CAS No. 790228-98-7; 3.95 g, 14.9 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.34(s,12H),3.48(s,3H),4.69(s,2H),4.76(s,2H),7.37(d,J=7.8Hz,1H),7.67(dd,J=1.6,7.8Hz,1H),7.89(d,J=1.5Hz,1H).

[0121] Production Example 21

Synthesis of 2-(3-methoxy-4-(trifluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

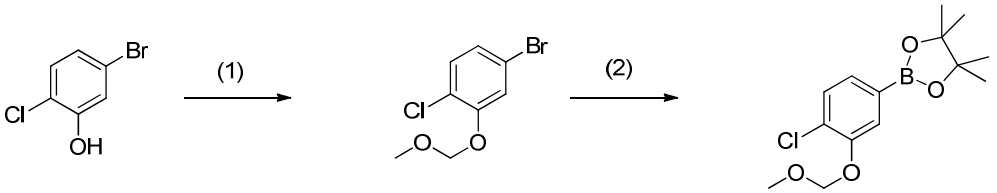


[0122] According to the method of Production Example 17-(2), a title compound (4.58 g, 14.4 mmol) was obtained from 4-bromo-2-methoxy-1-(trifluoromethoxy)benzene (CAS No. 672948-65-1; 5.23 g, 19.7 mmol).

^{1}H-NMR(400MHz,CDCl3) δ (ppm):1.35(s,12H),3.92,(s,3H),7.23(qd,J=1.2,8.2Hz,1H),7.40(m,2H).

[0123] Production Example 22

Synthesis of 2-(4-chloro-3-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[0124] (1) Synthesis of 4-bromo-1-chloro-2-(methoxymethoxy)benzene

Chloromethyl methyl ether (0.44 mL, 5.78 mmol) was added to a mixture of 5-bromo-2-chlorophenol (CAS No. 183802-98-4; 1.00 g, 4.82 mmol), potassium carbonate (2.00 g, 14.5 mmol) and acetone (15.0 mL). The reaction mixture was stirred at room temperature for 2 hours. Water and ethyl acetate were added to the reaction mixture to separate the organic layer. The organic layer was washed serially with water and a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The filtrate was

concentrated under reduced pressure and the resultant residue was purified by silica gel chromatography (n-heptane/ethyl acetate) to obtain a title compound (1.20 g, 4.77 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):3.52(s,3H),5.23(s,2H),7.08(dd,J=2.2,8.4Hz,1H),7.25(d,J=9.8Hz,1H),7.34-7.38(m,2H),7.53(s,1H).

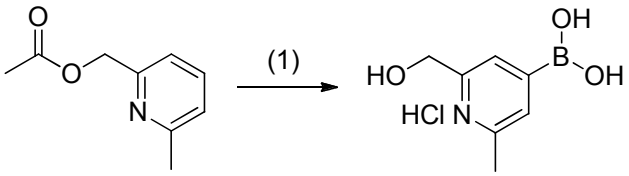
[0125] (2) Synthesis of 2-(4-chloro-3-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

According to the method of Production Example 17-(2), a title compound (688 mg, 2.30 mmol) was obtained from the compound obtained in Production Example 22-(1) (1.20 g, 4.77 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.34(s,12H),3.54(s,3H),5.29(s,2H),7.34-7.38(m,2H),7.53(s,1H)

[0126] Production Example 23

Synthesis of (2-(hydroxymethyl)-6-methylpyridin-4-yl)boronic acid hydrochloride



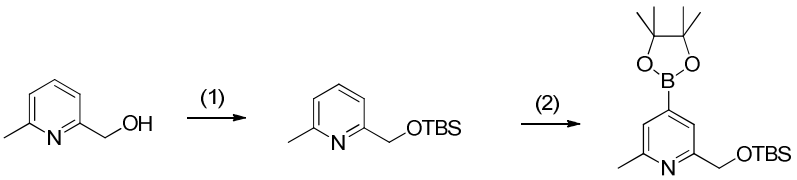
[0127] A solution comprising (6-methylpyridin-2-yl)methyl acetate (CAS No. 13287-64-4; 839 mg, 5.08 mmol), bis(pinacolate)diboron (1.29 g, 5.08 mmol), bis(1,5-cyclooctadiene)di-μ-methoxydiiridium(I) (337 mg, 0.508 mmol) and 4,4'-di-tert-butyl-2,2'-dipyridyl (136 mg, 0.508 mmol) in TBME (9.08 mL) was stirred under microwave irradiation at 80°C for 30 minutes.

The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was dissolved in THF (15.1 mL), and a 5 N hydrochloric acid (5.08 mL) was added to the mixture. The resultant solution was stirred for 48 hours, and THF was evaporated under reduced pressure. The resultant solution was washed with diethyl ether four times and then concentrated under reduced pressure. The resultant solid was washed with DCM to obtain a title compound (514 mg, 2.53 mmol).

^{1}H-NMR(400MHz,MeOH-d4) δ(ppm):2.78(brs,3H),4.93(brs,2H),7.95(brs,1H),8.03(brs,1H).

[0128] Production Example 24

Synthesis of 2-(((tert-butyldimethylsilyl)oxy)methyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine



[0129] (1) Synthesis of 2-(((tert-butyldimethylsilyl)oxy)methyl)-6-methylpyridine

Imidazole (2.16 g, 31.7 mmol) and TBSCl (4.04 g, 26.8 mmol) were serially added to a solution of 6-methyl-2-pyridinemethanol (CAS No. 1122-71-0; 3.00 g, 24.4 mmol) in DMF (50 mL) under ice-cooling, and the mixture was stirred at room temperature for 30 minutes. Water and n-heptane were added to the reaction mixture to separate the organic layer. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The

resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (4.70 g, 19.8 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.12(s,6H),0.96(s,9H),2.52(s,3H),4.81(s,2H),7.00(d,J=7.7Hz,1H),7.32(d,J=7.7Hz,1H),7.59(t,J=7.7Hz,1H).

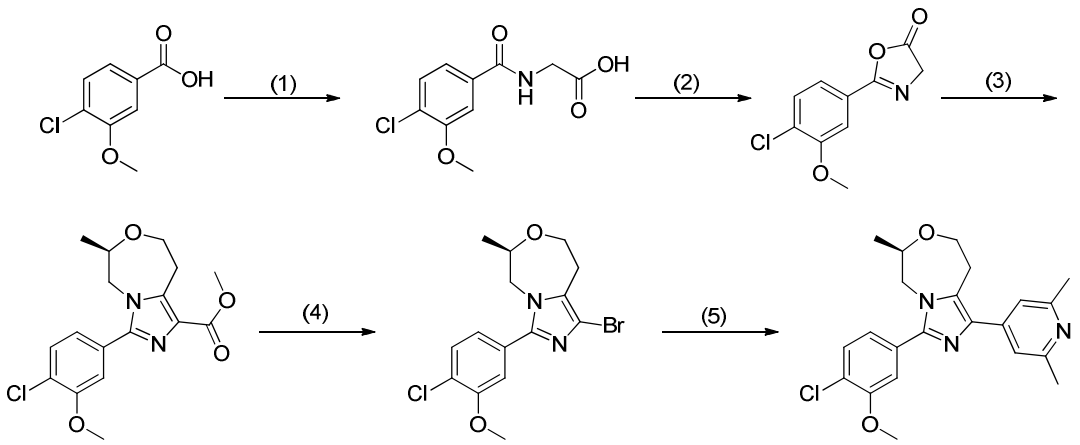
[0130] (2) Synthesis of 2-(((tert-butyldimethylsilyl)oxy)methyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

A mixture of the compound obtained in Production Example 24-(1) (2.00 g, 8.42 mmol), bis(pinacolate)diboron (2.14 g, 8.42 mmol), bis(1,5-cyclooctadiene)di-μ-methoxydiiridium(I) (168 mg, 0.253 mmol) and 4,4-di-tert-butyl-2,2-dipyridyl (68 mg, 0.253 mmol) in TBME (20 mL) was stirred at 85°C for 1.5 hours. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate → ethyl acetate/methanol) twice to obtain a title compound (450 mg, 1.24 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.12(s,6H),0.96(s,9H),1.35(s,12H),2.52(s,3H),4.82(s,2H),7.37(s,1H),7.63(s,1H).

[0131] Example 1

Synthesis of (R)-3-(4-chloro-3-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0132] (1) Synthesis of 2-(4-chloro-3-methoxybenzamido)acetic acid

A mixture of 4-chloro-3-methoxybenzoic acid (CAS No. 85740-98-3; 25.0 g, 134 mmol), thionyl chloride (19.6 mL, 268 mmol), and DMF (1.04 mL) was stirred in toluene (428 mL) at 110°C for 2 hours. The reaction mixture was cooled to room temperature, and then the solvent was evaporated under reduced pressure to obtain crude acid chloride. The resultant crude acid chloride was dissolved in an adequate amount of THF, and glycine (CAS No. 56-40-6; 17.93 g, 161 mmol) was added to the mixture. A 3 N aqueous sodium hydroxide solution (134 mL) was slowly added to the mixture at room temperature, and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was acidified with hydrochloric acid, and ethyl acetate was added. The organic layer was separated and the resultant organic layers were washed serially with water and a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate. The organic layers were concentrated under reduced pressure to obtain a title compound (31.1 g, 128 mmol).

^{1}H-NMR(400MHz,MeOH-d4) δ(ppm):3.94-3.97(m,3H),4.07-4.12(m,2H),7.40-7.49(m,2H),7.54-7.56(m,1H),8.81(brs,1H).

[0133] (2) Synthesis of 2-(4-chloro-3-methoxyphenyl)oxazol-5(4H)-one

A solution of the compound obtained in Example 1-(1) (30.5 g, 125 mmol) and NMM (14.5 mL, 131 mmol) in THF (300 mL) was cooled to -10°C. Methyl chloroformate (10.2 mL, 131 mmol) was added dropwise into the reaction solution at the same temperature. After the addition was complete, the reaction mixture was slowly warmed to room temperature and further stirred for 1 hour at room temperature. The generated insolubles were filtered off and the filtrate was concentrated under reduced pressure. The resultant solid was washed with n-heptane to obtain a title compound (24.3 g, 108 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):3.97(s,3H),4.43(s,2H),7.45-7.55(m,3H).

[0134] (3) Synthesis of (R)-methyl 3-(4-chloro-3-methoxyphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

A solution of the compound obtained in Production Example 1-(6) (1.90 g, 13.3 mmol) and the compound obtained in Example 1-(2) (3.0 g, 13.3 mmol) in THF (24 mL) was heated and stirred under microwave irradiation at 150°C for 2 hours. The mixture was concentrated under reduced pressure, and the resultant residue was dissolved in methanol (30 mL). Sodium methoxide (718 mg, 13.3 mmol) was added to the mixture and the resultant was stirred at

100°C for 1 hour. The reaction mixture was cooled to room temperature, and water and ethyl acetate were added. The organic layer was separated and washed serially with water and a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (3.47 g, 9.89 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.22(d,J=6.3Hz,3H),3.06-3.14(m,1H),3.60-3.75(m,2H),3.90(s,3H),3.94(s,3H),3.93-3.99(m,1H),4.06(dd,J=4.7,16.4Hz,1H),4.17-4.24(m,2H),6.87(dd,J=2.0,8.2Hz,1H),7.16(d,J=2.0Hz,1H),7.43(d,J=8.2Hz,1H).

[0135] (4) (R)-1-bromo-3-(4-chloro-3-methoxyphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

A solution of the compound obtained in Example 1-(3) (3.47 g, 9.89 mmol) and a 5 N aqueous sodium hydroxide solution (9.9 mL, 49.5 mmol) in methanol (20 mL) was stirred at 100°C for 2 hours. The reaction mixture was cooled to room temperature and acidified with a 5 N hydrochloric acid. The mixture was concentrated under reduced pressure. DMF (20 mL), potassium carbonate (2.32 g, 16.8 mmol), and NBS (1.99 g, 11.2 mmol) were added to the residue, and the mixture was stirred at room temperature for 8 hours. An aqueous sodium thiosulfate solution and ethyl acetate were added to the reaction mixture. The organic layer was separated and washed serially with water and a saturated aqueous sodium chloride solution.

The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The resultant residue was purified by NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (2.42 g, 6.51 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.23(d,J=6.6Hz,3H),2.93-3.11(m,2H),3.57-3.74(m,2H),3.89-3.97(m,1H),3.94(s,3H),4.14-4.26(m,2H),6.85(dd,J=2.0,8.2Hz,1H),7.15(d,J=2.0Hz,1H),7.43(d,J=8.2Hz,1H).

[0136] (5) Synthesis of (R)-3-(4-chloro-3-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

A mixture of the compound obtained in Example 1-(4) (570 mg, 1.53 mmol), 2,6-dimethyl-pyridine-4-boronic acid (CAS No. 846548-44-5; 463 mg, 3.07 mmol), tetrakis(triphenylphosphine)palladium(0) (89 mg, 0.077 mg), an aqueous sodium carbonate solution (2 M, 2.3 mL) and DME (8 mL) was stirred under microwave irradiation at 150°C for 1 hour. Water and ethyl acetate were added to the mixture. The organic layer was separated, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate → ethyl acetate/methanol) to obtain a title compound (388 mg, 0.975 mmol).

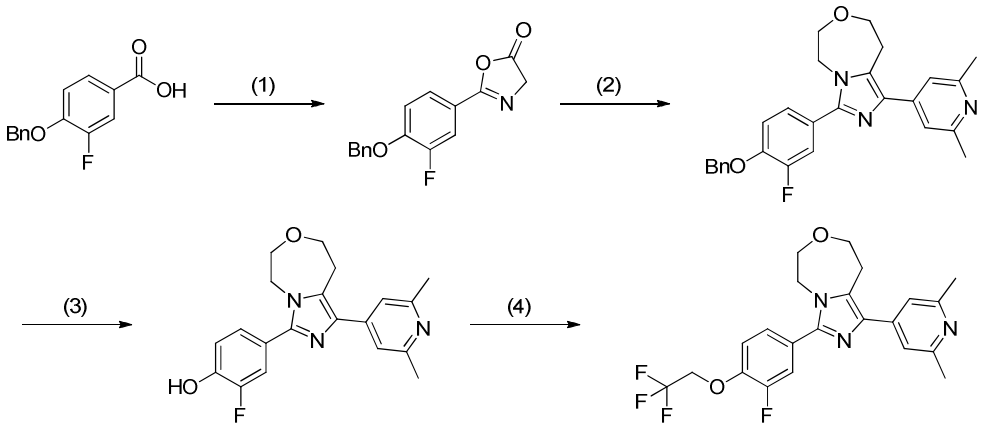
^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.27(d,J=6.6Hz,3H),2.56(s,6H),3.19(ddd,J=2.4,10.6,16.0Hz,1H),3.37(dd,J=3.9,16.0Hz,1H),3.63-3.70(m,1H),3.75-3.82(m,1H),3.94-4.01(m,1H),3.97(s,3H),4.19-

4.28(m,2H),6.93(dd,J=2.0,8.2Hz,1H),7.18(d,J=2.0Hz,1H),7.21(s,2H), 7.46(d,J=8.2Hz,1H).

ESI-MS m/z 398 [M+H]+

[0137] Example 2

Synthesis of 1-(2,6-dimethylpyridin-4-yl)-3-(3-fluoro-4-(2,2,2-trifluoroethoxy)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0138] (1) Synthesis of 2-(4-benzyloxy-3-fluorophenyl)oxazol-5(4H)-one

According to the methods of Examples 1-(1) and 1-(2), a title compound (1.58 g, 5.54 mmol) was obtained from 4-benzyloxy-3-fluorobenzoate (CAS No. 152552-64-2; 2.00 g, 8.12 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):4.39(s,2H),5.22(s,2H),7.03-7.09(m,1H),7.33-7.48(m,5H),7.67-7.78(m,2H).

[0139] (2) Synthesis of 3-(4-(benzyloxy)-3-fluorophenyl)-1-(2,6-dimethylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the methods of Examples 1-(3), 1-(4), and 1-(5), a title compound (0.112 g, 0.253 mmol) was obtained from the compound obtained in Example 2-(1) (1.10 g, 3.87 mmol) and 5-

methoxy-2,3,6,7-tetrahydro-1,4-oxazepine (0.500 g, 3.87 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.55(s,6H),3.27(dd,J=3.7,5.7Hz,2H),3.89(td,J=4.3,9.0Hz,4H),4.22-4.29(m,2H),5.20(s,2H),7.04-7.10(m,1H),7.15-7.22(m,3H),7.27-7.46(m,6H).

[0140] (3) Synthesis of 4-(1-(2,6-dimethylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepin-3-yl)-2-fluorophenol

A suspension of the compound obtained in Example 2-(2) (105 mg, 0.237 mmol), 5% palladium/carbon (25.2 mg, including 50% water content), and acetic acid (0.014 mL, 0.237 mmol) in ethanol (2.00 mL) was stirred under hydrogen atmosphere at room temperature for 4 hours. The insolubles were removed, then the filtrate was concentrated under reduced pressure and the resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (71.0 mg, 0.201 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.55(s,6H),3.26(dd,J=3.9,5.5Hz,2H),3.86-3.91(m,4H),4.22-4.29(m,2H),6.90-6.97(m,1H),7.05(d,J=8.6Hz,1H),7.14-7.23(m,1H),7.21(s,2H).

ESI-MS m/z 354 [M+H]+

[0141] (4) Synthesis of 1-(2,6-dimethylpyridin-4-yl)-3-(3-fluoro-4-(2,2,2-trifluoroethoxy)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

2-Iodo-1,1,1-trifluoroethane (16.6 mg, 0.079 mmol) was added to a mixture of the compound obtained in Example 2-(3) (14.0 mg,

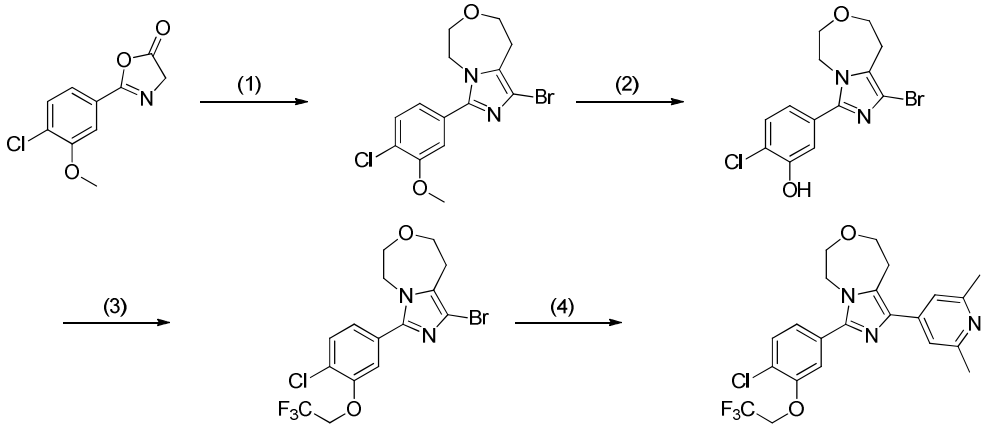
0.040 mmol), potassium carbonate (16.4 mg, 0.119 mmol) and DMF (500 μL). The reaction mixture was stirred at 100°C for 3 hours. The reaction mixture was cooled to room temperature and water and ethyl acetate were added. The organic layer was separated, washed serially with water and a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate → ethyl acetate/methanol) to obtain a title compound (4.88 mg, 0.011 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.56(s,6H),3.28(dd,J=3.7,5.7Hz,2H),3.84-3.95(m,4H),4.23-4.31(m,2H),4.45-4.52(m,2H),7.09-7.16(m,1H),7.19(s,2H),7.26-7.29(m,1H),7.35(dd,J=2.2,11.5Hz,1H).

ESI-MS m/z 436 [M+H]+

[0142] Example 3

Synthesis of 3-(4-chloro-3-(2,2,2-trifluoroethoxy)phenyl)-1-(2,6-dimethylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0143] (1) Synthesis of 1-bromo-3-(4-chloro-3-methoxyphenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the methods of Examples 1-(3) and 1-(4), a title compound (73.0 mg, 0.204 mmol) was obtained from the compound obtained in Example 1-(2) (873 mg, 3.87 mmol) and 5-methoxy-2,3,6,7-tetrahydro-1,4-oxazepine (0.500 g, 3.87 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):3.00-3.08(m,2H),3.79-3.90(m,4H),3.94(s,3H),4.22-4.28(m,2H),6.87(dd,J=1.8,8.0Hz,1H),7.17(d,J=1.6Hz,1H),7.41(d,J=8.2Hz,1H).

[0144] (2) Synthesis of 5-(1-bromo-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepin-3-yl)-2-chlorophenol

A solution of the compound obtained in Example 3-(1) (68.0 mg, 0.190 mmol) in DCM (3.00 mL) was cooled to -78°C, and a 1 M boron tribromide solution (0.951 mL, 0.951 mmol) in DCM was added dropwise. The reaction mixture was slowly warmed to room temperature and an aqueous ammonia solution was added. Chloroform was added to the mixture to separate the organic layer. The organic layer was washed serially with water and a saturated aqueous sodium chloride solution and then dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (41.2 mg, 0.120 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):3.00-3.07(m,2H),3.78-3.90(m,4H),4.20-

4.27(m,2H),6.88(dd,J=2.0,8.2Hz,1H),7.24(d,J=2.0Hz,1H),7.36(d,J=8.2Hz,1H).

[0145] (3) Synthesis of 1-bromo-3-(4-chloro-3-(2,2,2-trifluoroethoxy)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

2-Iodo-1,1,1-trifluoroethane (69.8 mg, 0.333 mmol) was added to a mixture of the compound obtained in Example 3-(2) (38.1 mg, 0.111 mmol), potassium carbonate (61.3 mg, 0.444 mmol) and DMF (1.00 mL), and the mixture was stirred at 120°C for 4 hours. The reaction mixture was cooled to room temperature and water and ethyl acetate were added. The organic layer was separated, washed serially with water and a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (31.1 mg, 0.073 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):3.01-3.10(m,2H),3.80-3.92(m,4H),4.22-4.30(m,2H),4.44-4.50(m,2H),7.02(dd,J=2.0,8.2Hz,1H),7.21(d,J=1.8Hz,1H),7.47(d,J=8.2Hz,1H).

[0146] (4) Synthesis of 3-(4-chloro-3-(2,2,2-trifluoroethoxy)phenyl)-1-(2,6-dimethylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 1-(5), a title compound (7.20 mg, 0.016 mmol) was obtained from the compound obtained in Example 3-(3) (31.0 mg, 0.073 mmol) and 2,6-dimethyl-pyridine-4-

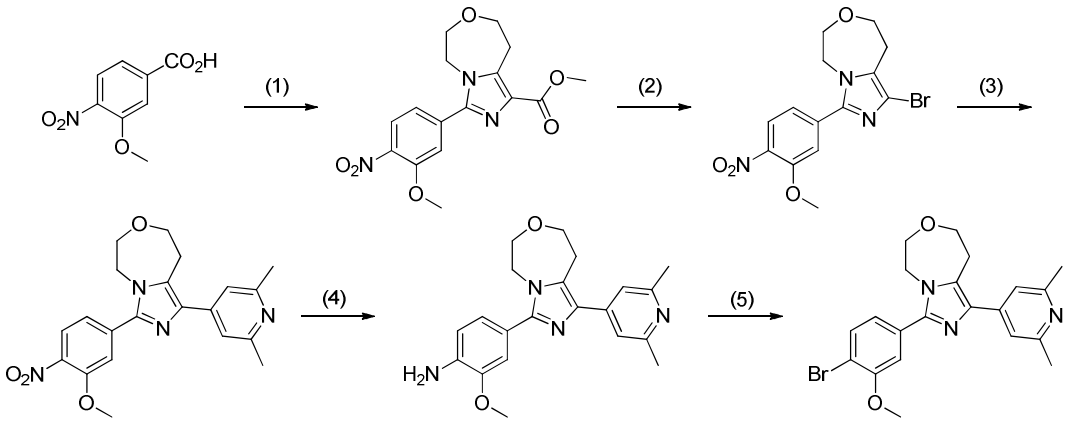
boronic acid (22.0 mg, 0.146 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.56(s,6H),3.28(dd,J=3.9,5.5Hz,2H),3.84-3.95(m,4H),4.24-4.31(m,2H),4.45-4.52(m,2H),7.09(dd,J=1.8,8.4Hz,1H),7.19(s,2H),7.25(d,J=1.6Hz,1H),7.50(d,J=8.2Hz,1H).

ESI-MS m/z 452 [M+H]+

[0147] Example 4

Synthesis of 3-(4-bromo-3-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0148] (1) Synthesis of methyl 3-(3-methoxy-4-nitrophenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

According to the methods of Examples 1-(1) and 1-(2), an oxazolone compound was obtained from 3-methoxy-4-nitrobenzoic acid (CAS No. 5081-36-7; 3.88 g, 19.7 mmol). According to the method of Example 1-(3), a title compound (1.20 g, 3.46 mmol) was obtained from the oxazolone compound (3.36 g, 14.2 mmol) and 5-methoxy-2,3,6,7-tetrahydro-1,4-oxazepine (1.82 g, 14.2 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):3.60-3.66(m,2H),3.82-

3.86(m,2H),3.87-3.93(m,2H),3.92(s,3H),4.02(s,3H),4.26-4.31(m,2H),7.02(dd,1.4,8.0Hz,1H),7.39(d,J=1.6Hz,1H),7.93(d,J=8.2Hz,1H).

[0149] (2) Synthesis of 1-bromo-3-(3-methoxy-4-nitrophenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 1-(4), a title compound (83.4 mg, 0.227 mmol) was obtained from the compound obtained in Example 4-(1) (111 mg, 0.320 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):3.08(dd,J=4.3,5.9Hz,2H),3.86(td,J=4.2,8.0Hz,4H),4.02(s,3H),4.27-4.32(m,2H),7.00(dd,J=1.6,8.6Hz,1H),7.38(d,J=1.6Hz,1H),7.92(d,J=8.6Hz,1H).

ESI-MS m/z 368, 370 [M+H]+ 390, 392 [M+Na]+

[0150] (3) Synthesis of 1-(2,6-dimethylpyridin-4-yl)-3-(3-methoxy-4-nitrophenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 1-(5), a crude title compound (101 mg) was obtained from the compound obtained in Example 4-(2) (83 mg, 0.23 mmol) and 2,6-dimethyl-pyridine-4-boronic acid (68 mg, 0.45 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.57(s,6H),3.30(dd,J=3.9,5.5Hz,2H),3.88-3.95(m,4H),4.04(s,3H),4.30-4.36(m,2H),7.07(dd,1.6,8.2Hz,1H),7.20(s,2H),7.42(d,J=1.6Hz,1H),7.96(d,J=8.6Hz,1H).

ESI-MS m/z 395 [M+H]+

[0151] (4) Synthesis of 4-(1-(2,6-dimethylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepin-3-yl)-2-methoxyaniline

A solution of the compound obtained in Example 4-(3) (101 mg) and 10% palladium/carbon (20 mg, including 50% water content) in ethanol (1.0 mL) was stirred under hydrogen atmosphere for 6 hours. The reaction solution was filtered through Celite (trademark), and then the filtrate was concentrated under reduced pressure. The resultant residue was purified by NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (39.8 mg, 0.109 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.53(s,6H),3.22-3.32(m,2H),3.80-3.94(m,4H),3.89(s,3H),3.99(brs,2H),4.23-4.34(m,2H),6.73(d,J=7.8Hz,1H),6.82(dd,J=1.8,8.0Hz,1H),7.02(d,J=2.1Hz,1H),7.21(s,2H).

ESI-MS m/z 365 [M+H]+

[0152] (5) Synthesis of 3-(4-bromo-3-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

An aqueous sodium nitrite solution (1.0 M, 0.11 mL) was added to a solution of the compound obtained in Example 4-(4) (20 mg, 0.055 mmol), water (0.10 mL), and concentrated sulfuric acid (0.10 mL) in acetonitrile (0.40 mL) under ice-cooling. The mixture was stirred at the same temperature for 10 minutes, then an aqueous copper(I) bromide solution (2.0 M, 0.22 mL) was added, and the mixture was stirred for 1 hour. The reaction mixture was heated to 50°C and stirred for 5 hours, and then cooled to room temperature.

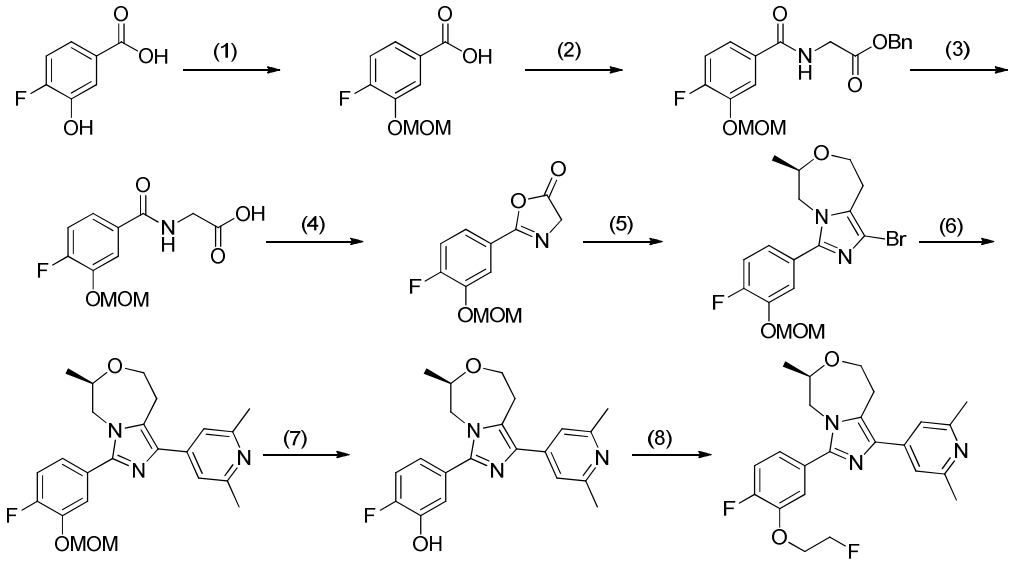
Ethyl acetate was added to the reaction mixture, washed with aqueous ammonia twice, and washed with a saturated aqueous sodium chloride solution. The resultant organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resultant residue was purified by silica gel thin layer chromatography (ethyl acetate) to obtain a title compound (16 mg, 0.037 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.55(s,6H),3.27(dd,J=3.9,5.5Hz,2H),3.84-3.93(m,4H),3.95(s,3H),4.25-4.30(m,2H),6.87(dd,J=2.0,8.2Hz,1H),7.16(d,J=2.0Hz,1H),7.20(s,2H),7.62(d,J=7.8Hz,1H).

ESI-MS m/z 428, 430 [M+H]+

[0153] Example 5

Synthesis of (R)-1-(2,6-dimethylpyridin-4-yl)-3-(4-fluoro-3-(2-fluoroethoxy)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0154] (1) Synthesis of 4-fluoro-3-(methoxymethoxy)benzoic

acid

Chloromethyl methyl ether (14.5 mL, 192 mmol) was added to a solution of 4-fluoro-3-hydroxybenzoic acid (CAS No. 51446-31-2; 10.0 g, 64.1 mmol) and TEA (35.7 mL, 256 mmol) in THF (150 mL) under ice-cooling. The reaction mixture was stirred at room temperature for 2 hours. A 1 N hydrochloric acid and ethyl acetate were added to the reaction mixture, the organic layer was separated, and the separated organic layer was filtered through a silica gel pad (silica gel, ethyl acetate/n-heptane). The resultant filtrate was evaporated under reduced pressure. The resultant residue was dissolved in methanol (100 mL), a 5 N aqueous sodium hydroxide solution (38.4 mL) was added, and the mixture was stirred at 80°C for 1 hour. The reaction mixture was cooled to room temperature, and a 5 N hydrochloric acid and ethyl acetate were added to the reaction mixture to separate the organic layer. The organic layer was washed serially with water and a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to obtain a crude title compound (10.1 g).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):3.54(s,3H),5.28(s,2H),7.13-7.22(m,1H),7.78(ddd,J=2.0,4.5,8.4Hz,1H),7.93(dd,J=2.0,7.8Hz,1H).

[0155] (2) Synthesis of benzyl 2-(4-fluoro-3-(methoxymethoxy))benzamido)acetate

EDC (11.1 g, 57.8 mmol) was added to a solution of the compound obtained in Example 5-(1) (8.90 g), glycine benzyl ester p-toluenesulfonate (CAS No. 28607-46-7; 19.5 g; 57.8 mmol), HOBT

(7.81 g, 57.8 mmol), and TEA (16.1 mL, 116 mmol) in DCM (100 mL) under ice-cooling. The reaction mixture was stirred overnight, and then a 1 N hydrochloric acid and chloroform were added. The organic layer was separated, washed serially with water and a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The filtrate was concentrated under reduced pressure and the resultant residue was purified by silica gel chromatography (n-heptane/ethyl acetate) to obtain a title compound (14.2 g, 40.9 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):3.52(s,3H),4.27(d,J=5.1Hz,2H),5.23(s,2H),5.26(s,2H),6.61(brs,1H),7.14(dd,J=8.4,10.4Hz,1H),7.30-7.51(m,6H),7.68(dd,J=2.2,8.0 Hz,1H).

[0156] (3) Synthesis of 2-(4-fluoro-3-(methoxymethoxy)benzamide)acetic acid

A suspension of the compound obtained in Example 5-(2) (14.2 g, 40.9 mmol) and 5% palladium/carbon (0.44 g, including 50% water content) in ethanol (100 mL) was stirred under hydrogen atmosphere at room temperature for 30 minutes. The palladium catalyst was removed and the solvent was evaporated under reduced pressure to obtain a crude title compound (10.3 g).

^{1}H-NMR(400MHz,MeOH-d4) δ(ppm):3.51(s,3H),4.02-4.12(m,2H),5.27(s,2H),7.21(dd,J=8.4,10.7Hz,1H),7.51-7.54(m,1H),7.75(dd,J=2.2,8.0Hz,1H).

[0157] (4) Synthesis of 2-(4-fluoro-3-(methoxymethoxy)phenyl)oxazol-5(4H)-one

According to the method of Example 1-(2), a title compound (9.11 g, 26.7 mmol) was obtained from the compound obtained in Example 5-(3) (10.3 g).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):3.54(s,3H),4.42(s,2H),5.28(s,2H),7.20(dd,J=8.5,10.5Hz,1H),7.63(ddd,J=2.1,4.4,8.5Hz,1H),7.84(dd,J=2.1,7.9Hz,1H).

[0158] (5) Synthesis of (R)-1-bromo-3-(4-fluoro-3-(methoxymethoxy)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the methods of Examples 1-(3) and 1-(4), a title compound (388.0 mg, 1.01 mmol) was obtained from the compound obtained in Example 5-(4) (1.50 g, 6.27 mmol) and the compound obtained in Production Example 1-(6) (0.898 g, 6.27 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.23(d,J=6.6Hz,3H),2.93-3.10(m,2H),3.52(s,3H),3.58-3.65(m,1H),3.68-3.76(m,1H),3.90(dd,J=8.4,14.7Hz,1H),4.14-4.24(m,2H),5.22-5.28(m,2H),7.03-7.07(m,1H),7.16(dd,J=8.4,10.6Hz,1H),7.32(dd,J=2.1,7.8Hz,1H).

[0159] (6) Synthesis of (R)-1-(2,6-dimethylpyridin-4-yl)-3-(4-fluoro-3-(methoxymethoxy)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 1-(5), a title compound (78 mg, 0.190 mmol) was obtained from the compound obtained in Example 5-(5) (330 mg, 0.857 mmol).

^{1}H-

NMR(400MHz,CDCl3) δ(ppm):1.27(d,J=6.4Hz,3H),2.55(s,6H),3.12-3.22(m,1H),3.32-3.38(m,1H),3.53(s,3H),3.63-3.68(m,1H),3.76-3.83(m,1H),3.92-3.98(m,1H),4.18-4.27(m,2H),5.24-5.30(m,2H),7.09-7.13(m,1H),7.17-7.22(m,3H),7.36(dd,J=2.0,7.8Hz,1H).

[0160] (7) Synthesis of (R)-5-(1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepin-3-yl)-2-fluorophenol hydrochloride

A 4 N hydrochloric acid (0.474 mL, 1.90 mmol) was added to a solution of the compound obtained in Example 5-(6) (78 mg, 190 μmol) in methanol, and the mixture was stirred at 80°C for 4 hours. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure to obtain a crude title compound (68 mg).

^{1}H-NMR(400MHz,MeOH-d4) δ(ppm):1.26(d,J=6.3Hz,3H),2.84(s,6H),3.35-3.39(m,1H),3.46-3.51(m,1H),3.74-3.86(m,1H),4.00(t=6.8Hz,1H),4.22-4.25(m,1H),4.35-4.45(m,2H),7.21(ddd,J=2.3,4.1,8.4Hz,1H),7.29-7.48(m,2H),7.95(s,2H).

[0161] (8) Synthesis of (R)-1-(2,6-dimethylpyridin-4-yl)-3-(4-fluoro-3-(2-fluoroethoxy)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

2-Fluoroethyl tosylate (24.3 mg, 0.111 mmol) was added to a mixture of the compound obtained in Example 5-(7) (30.0 mg, 0.074 mmol), potassium carbonate (30.8 mg, 0.223 mmol), and DMF (300 μL). The reaction mixture was stirred at 80°C for 3 hours. The reaction mixture was cooled to room temperature and water and ethyl

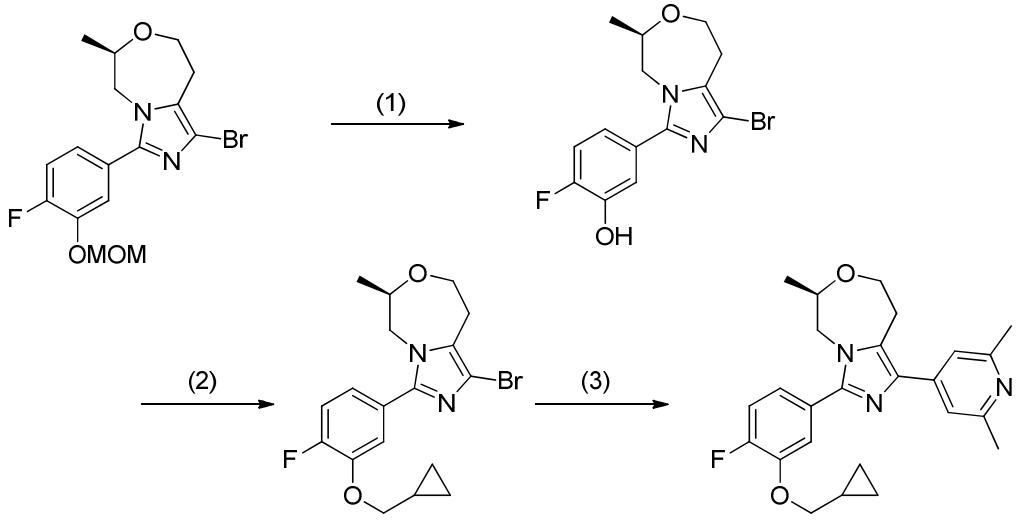
acetate were added. The organic layer was separated, washed serially with water and a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the resultant residue was purified by NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (24.3 mg, 0.059 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.24-1.27(m,3H),2.55(s,6H),3.11-3.23(m,1H),3.36(dd,J=4.3,16.0Hz,1H),3.60-3.82(m,2H),3.96(dd,J=8.4,15.0Hz,1H),4.17-4.27(m,2H),4.29-4.44(m,2H),4.69-4.89(m,2H),7.00-7.02(m,1H),7.14-7.25(m,4H).

ESI-MS m/z 414[M+H]+

[0162] Example 6

Synthesis of (R)-3-(3-cyclopropylmethoxy-4-fluorophenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0163] (1) Synthesis of (R)-5-(1-bromo-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepin-3-yl)-2-fluorophenol hydrochloride

A solution of the compound obtained in Example 5-(5) (170 mg, 0.441 mmol) in a 4 M hydrogen chloride/methanol (1.10 mL, 4.41 mmol) was stirred at 80°C for 2 hours. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure to obtain a crude title compound (166 mg).

^{1}H-NMR(400MHz,MeOH-d4) δ(ppm):1.21(d,J=6.6Hz,3H),3.07-3.16(m,2H),3.62-3.69(m,1H),3.83-3.89(m,1H),4.13-4.20(m,2H),4.25-4.36(m,1H),7.05-7.10(m,1H),7.19(d,J=8.2Hz,1H),7.31-7.39(m,1H).

[0164] (2) Synthesis of (R)-1-bromo-3-(3-(cyclopropylmethoxy)-4-fluorophenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

Cyclopropylmethyl bromide (64.2 μL, 0.662 mmol) was added to a mixture of the compound obtained in Example 6-(1) (50.0 mg, 0.132 mmol), potassium carbonate (110 mg, 0.794 mmol) and DMF (400 μL), and the mixture was stirred at 120°C for 5 hours. The reaction mixture was cooled to room temperature, and water and ethyl acetate were added. The organic layer was separated, washed serially with water and a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (20.8 mg, 0.053 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.28-0.42(m,2H),0.59-0.75(m、2H),1.13-1.25(m,3H),1.26-1.40(m,1H),2.87-3.13(m,2H),3.51-3.74(m,2H),3.84-3.96(m,3H),4.10-4.27(m,2H),6.85(ddd,J=2.0,4.2,8.3Hz,1H),7.07-7.20(m,2H).

[0165] (3) Synthesis of (R)-3-(3-cyclopropylmethoxy-4-fluorophenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

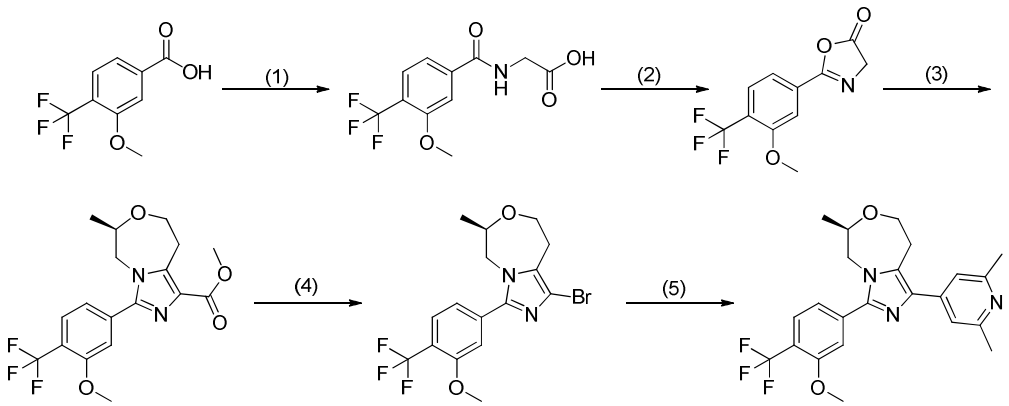
According to the method of Example 1-(5), a title compound (6.80 mg, 0.016 mmol) was obtained from the compound obtained in Example 6-(2) (19.5 mg, 0.049 mmol) and 2,6-dimethyl-pyridine-4-boronic acid (8.94 mg, 0.059 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.29-0.42(m,2H),0.62-0.73(m,2H),1.25(d,J=6.3Hz,3H),1.28-1.38(m,1H),2.55(s,6H),3.19(dd,J=2.3,10.5Hz,1H),3.35(dd,J=3.9,16.0Hz,1H),3.60-3.82(m,2H),3.88-4.01(m,3H),4.17-4.28(m,2H),6.93(ddd,J=2.3,4.1,8.4Hz,1H),7.11-7.23(m,4H).

ESI-MS m/z 422 [M+H]+

[0166] Example 7

Synthesis of (R)-1-(2,6-dimethylpyridin-4-yl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0167] (1) Synthesis of 2-(3-methoxy-4-(trifluoromethyl)benzamido)acetic acid

Oxalyl chloride (9.59 mL, 112 mmol) was added dropwise into a suspension of 3-methoxy-4-(trifluoromethyl)benzoic acid (CAS No. 276861-63-3; 20.5 g, 93.1 mmol) and DMF (0.205 mL, 2.65 mmol) in THF (41 mL)/DCM (164 mL) under ice-cooling. The reaction mixture was warmed to room temperature and further stirred for 2 hours. The solvent was evaporated under reduced pressure to obtain corresponding crude acid chloride. A solution of crude acid chloride in THF (40 mL) was added dropwise into a mixture of glycine (8.39 g, 112 mmol), a 2 N aqueous sodium hydroxide solution (93 mL) and THF (200 mL) over a period of 15 minutes under ice-cooling. The reaction mixture was stirred at room temperature for 3 days. The reaction mixture was acidified with a 5 N hydrochloric acid under ice-cooling. Ethyl acetate was added to the mixture to separate the organic layer. The resultant organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to obtain a title compound (25.6 g, 92.0 mmol).

^{1}H-NMR(400MHz,DMSO-d6) δ(ppm):3.94(s,2H),3.96(s,3H),7.57(d,J=8.2Hz,1H),7.67(s,1H),7.75(d,J=8.2Hz,1H),9.05(brs,1H).

[0168] (2) Synthesis of 2-(3-methoxy-4-(trifluoromethyl)phenyl)oxazol-5(4H)-one

Methyl chloroformate (2.34 mL, 30.3 mmol) was added into a solution of the compound obtained in Example 7-(1) (8.00 g, 28.9 mmol) and NMM (3.33 mL, 30.3 mmol) in THF (150 mL) at -10°C. The reaction mixture was stirred at -10°C for 1 hour and then stirred for 2 hours while slowly warming it to room temperature. The

resultant solid was separated by filtration through Celite (trademark). The filtrate was concentrated under reduced pressure to obtain a title compound (7.48 g, 28.9 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):3.95(s,3H),4.44(s,2H),7.32-7.39(m,1H),7.58-7.63(m,3H).

[0169] (3) Synthesis of (R)-methyl 3-(3-methoxy-4-(trifluoromethyl)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

A solution of the compound obtained in Example 7-(2) (4.16 g, 16.1 mmol) and the compound obtained in Production Example 1-(6) (2.00 g, 14.0 mmol) in toluene (25 mL) was heated under reflux for 6 hours. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The resultant residue was dissolved in methanol (30 mL). Sodium methoxide (755 mg, 14.0 mmol) was added to the mixture, then the resultant was heated under reflux. After 3 hours, the reaction mixture was cooled to room temperature and ethyl acetate and a saturated aqueous ammonium chloride solution were added. The organic layer was separated, washed with a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The insolubles were separated through filtration, and the filtrate was concentrated under reduced pressure. The resultant residue was purified by NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (3.18 g, 8.27 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.24(d,J=6.6Hz,3H),3.11(ddd,J=2.4,10

.9,16.4Hz,1H),3.61-3.74(m,2H),3.91(s,3H),3.96(s,3H),3.96-4.03(m,1H),4.07(dd,J=4.7,16.4Hz,1H),4.17-4.25(m,2H),6.97(d,J=8.2Hz,1H),7.25(s,1H),7.64(d,J=8.2Hz,1H).
ESI-MS m/z 385 [M+H]+

[0170] (4) Synthesis of (R)-1-bromo-3-(3-methoxy-4-(trifluoromethyl)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

A 2 N aqueous sodium hydroxide solution (3.31 mL) was added to a solution of the compound obtained in Example 7-(3) (3.18 g, 8.23 mmol) in ethanol (40 mL). The reaction mixture was heated under reflux for 2 hours. The reaction mixture was cooled to room temperature and acidified with a 5 N hydrochloric acid. The mixture was concentrated under reduced pressure. Ethanol (50 mL) was added to the resultant residue and the insolubles were separated through filtration. The resultant filtrate was concentrated under reduced pressure and dissolved in ethanol (5 mL) and DMF (50 mL). Potassium carbonate (2.86 g, 20.7 mmol) and NBS (2.21 g, 12.4 mmol) were added to the reaction mixture, and the mixture was stirred at room temperature for 14 hours. Water and ethyl acetate were added to the mixture to separate the organic layer. The resultant organic layer was washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The insolubles were separated through filtration and the filtrate was concentrated. The residue was purified by NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (2.73 g, 6.74 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.24(d,J=6.3Hz,3H),2.95-3.12(m,2H),3.57-3.65(m,1H),3.67-3.75(m,1H),3.92-4.00(m,1H),3.95(s,3H),4.16-4.28(m,2H),6.95(d,J=8.2Hz,1H),7.24(s,1H),7.63(d,J=8.2Hz,1H).

ESI-MS m/z 405, 407 [M+H]+

[0171] (5) Synthesis of (R)-1-(2,6-dimethylpyridin-4-yl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

A mixture of the compound obtained in Example 7-(4) (900 mg, 2.22 mmol), 2,6-dimethyl-pyridine-4-boronic acid (402 mg, 2.67 mmol), (A-taPhos)$_2$PdCl$_2$ (79 mg, 0.111 mmol), an aqueous sodium carbonate solution (1 M, 5.55 mL) and DMF (20 mL) was stirred at 130°C for 2.5 hours. The reaction mixture was cooled to room temperature, and then ethyl acetate and water were added to the mixture to separate the organic layer. The organic layer was washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The organic layer was concentrated under reduced pressure. The resultant residue was purified serially by silica gel column chromatography (n-heptane/ethyl acetate → ethyl acetate/methanol) and NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (750 mg, 1.74 mmol).

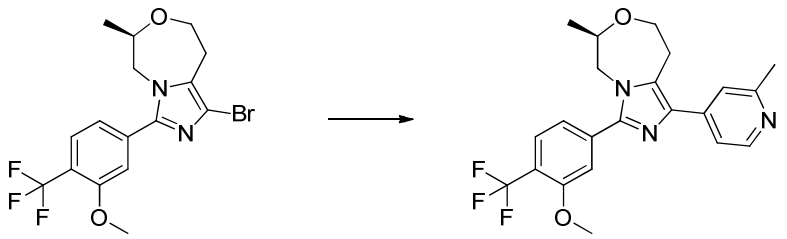
^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.28(d,J=6.6Hz,3H),2.56(s,6H),3.20(ddd,J=2.4,10.5,16.0Hz,1H),3.38(dd,J=4.3,16.0Hz,1H),3.64-3.71(m,1H),3.76-3.84(m,1H),3.96-4.05(m,1H),3.97(s,3H),4.20-

4.31(m,2H),7.03(d,J=8.2Hz,1H),7.21(s,2H),7.28(s,1H),7.67(d,J=8.2H z,1H).

ESI-MS m/z 432 [M+H]+

[0172] Example 8

Synthesis of (R)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0173] According to the method of Example 7-(5), a title compound (8.0 mg, 0.019 mmol) was obtained from the compound obtained in Example 7-(4) (18 mg, 0.044 mmol) and 2-picoline-4-boronic acid (CAS No. 579476-63-4; 18 mg, 0.13 mmol).

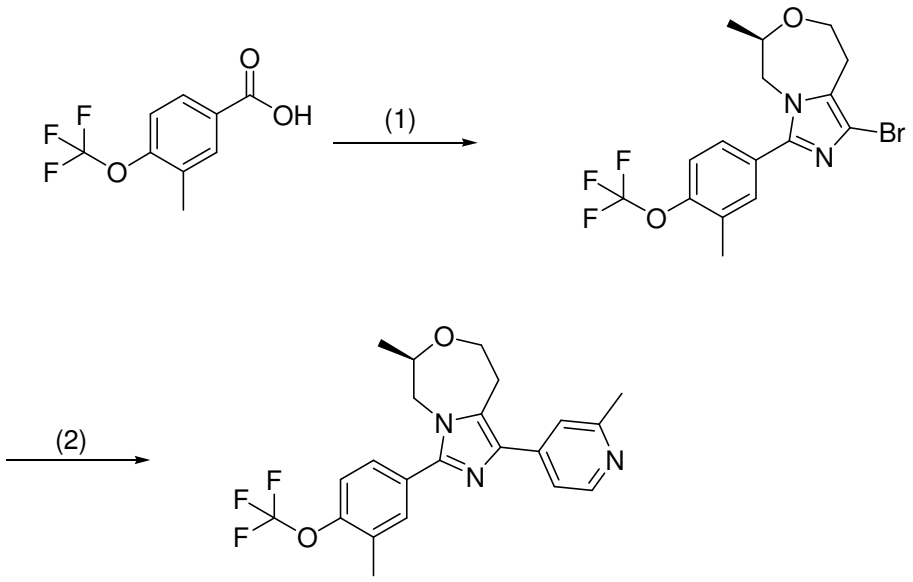
^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.28(d,J=6.6Hz,3H),2.60(s,3H),3.21(d dd,J=2.3,10.5,16.4Hz,1H),3.38(dd,J=3.9,15.6Hz,1H)3.64-3.72(m,1H),3.76-3.85(m,1H),3.98(s,3H),4.02(dd,J=8.6,14.8Hz,1H),4.23(ddd,J=2.3,4.7, 12.1Hz,1H),4.28(d,J=14.8Hz,1H),7.04(d,J=7.8Hz,1H)7.28(s,1H),7.30(dd,J=1.6,5.1Hz,1H),7.46(s,1H),7.67(d,J=7.8Hz,1H),8.50(d,J=5.1Hz,1 H).

ESI-MS m/z 418 [M+H]+

[0174] Example 9

Synthesis of (R)-6-methyl-3-(3-methyl-4-

(trifluoromethoxy)phenyl)-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-*d*][1,4]oxazepine



[0175] (1) Synthesis of (R)-1-bromo-6-methyl-3-(3-methyl-4-(trifluoromethoxy)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-*d*][1,4]oxazepine

According to the methods of Examples 7-(1) and 7-(2), an oxazolone compound was obtained from 3-methyl-4-(trifluoromethoxy)benzoic acid. According to the methods of Examples 7-(3) and 7-(4), a title compound (44.0 mg, 0.151 mmol) was obtained from the oxazolone compound (300 mg, 1.16 mmol) and the compound obtained in Production Example 1-(6) (166 mg, 1.16 mmol).

ESI-MS m/z 407 [M+H]+

[0176] (2) Synthesis of (R)-6-methyl-3-(3-methyl-4-(trifluoromethoxy)phenyl)-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-*d*][1,4]oxazepine

According to the method of Example 7-(5), a title compound

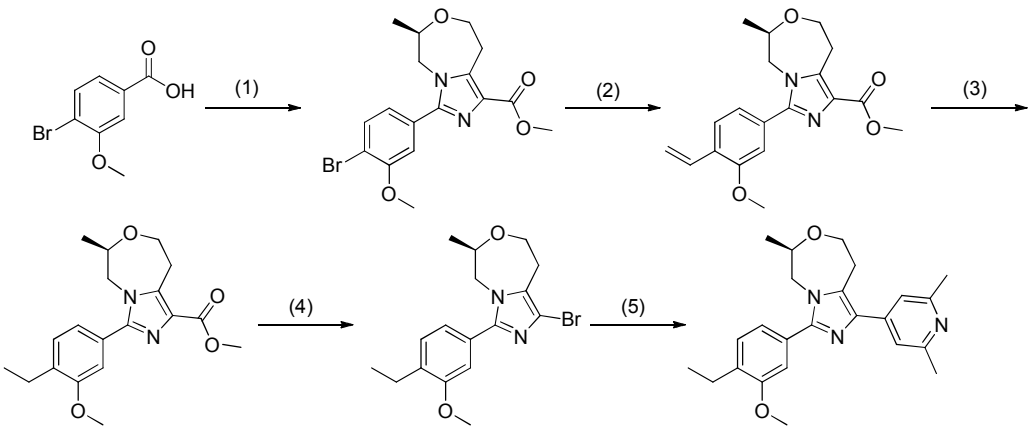
(7.20 mg, 0.017 mmol) was obtained from the compound obtained in Example 9-(1) (14.0 mg, 0.0350 mmol) and 2-picoline-4-boronic acid (9.46 mg, 0.069 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.28(d,J=6.3Hz,3H),2.38(s,3H),2.59(s,3H),3.13-3.25(m,1H),3.31-3.42(m,1H),3.62-3.72(m,1H),3.75-3.84(m,1H),3.95-4.04(m,1H),4.18-4.28(m,2H),7.28-7.34(m,3H),7.44-7.52(m,2H),8.47-8.52(m,1H).

ESI-MS m/z 418 [M+H]+

[0177] Example 10

Synthesis of (R)-1-(2,6-dimethylpyridin-4-yl)-3-(4-ethyl-3-methoxyphenyl)-6-methyl-5,6,8,9,-tetrahydroimidazo[1,5-*d*][1,4]oxazepine



[0178] (1) Synthesis of (R)-methyl 3-(4-bromo-3-methoxyphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-*d*][1,4]oxazepine-1-carboxylate

According to the methods of Examples 7-(1), 7-(2), and 7-(3), a title compound (224 mg, 0.567 mmol) was synthesized from 4-bromo-3-methoxybenzoic acid (CAS No. 56256-14-5).

ESI-MS m/z 395 [M+H]+

[0179] (2) Synthesis of (R)-methyl 3-(3-methoxy-4-vinylphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-*d*][1,4]oxazepine-1-carboxylate

A mixture of the compound obtained in Example 10-(1) (214 mg, 0.541 mmol), tributyl vinyl tin (0.190 mL, 0.65 mmol), tetrakis(triphenylphosphine)palladium(0) (25.0 mg, 0.022 mmol), and DMF (3.00 mL) was stirred at 130°C for 3 hours. The reaction mixture was cooled to room temperature, then the solvent was concentrated by nitrogen blowing and the residue was purified by silica gel column chromatography (n-heptane/ethyl acetate 1/1 to 0/1) to obtain a crude title compound (190 mg).

ESI-MS m/z 343 [M+H]+

[0180] (3) Synthesis of (R)-methyl 3-(4-ethyl-3-methoxyphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-*d*][1,4]oxazepine-1-carboxylate

A mixture of a crude product of the compound obtained in Example 10-(2) (182 mg), 10% palladium/carbon (30 mg, including 50% water content), and methanol (3.00 mL) was stirred under hydrogen atmosphere. 10% Palladium/carbon (100 mg, including 50% water content) was further added, and the mixture was stirred under hydrogen atmosphere for 3 days. After the completion of the reaction, the insolubles were filtered off through Celite (trademark). The solvent was evaporated under reduced pressure to obtain a title compound (157 mg, 0.456 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.18-

1.24(m,6H),2.67(q,J=7.4Hz,2H),3.05-3.15(m,1H),3.61-3.68(m,1H),3.69-3.74(m,1H),3.86(s,3H),3.90(s,3H),3.94(dd,J=8.4,15.0Hz,1H),4.06(dd,J=4.7,16.4Hz,1H),4.16-4.24(m,1H),4.29(d,J=15.2Hz,1H),6.87(dd,J=1.6,7.4,1H),7.04(d,J=1.6Hz,1H),7.19(d,J=7.4Hz,1H).

ESI-MS m/z 345 [M+H]+

[0181] (4) Synthesis of (R)-1-bromo-3-(4-ethyl-3-methoxyphenyl)-6-methyl-5,6,8,9,-tetrahydroimidazo[1,5-*d*][1,4]oxazepine

According to the method of Example 7-(4), a title compound (90.0 mg, 0.246 mmol) was obtained from the compound obtained in Example 10-(3) (157 mg, 0.456 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.18-1.24(m,6H),2.67(q,J=7.3Hz,2H),2.99(dd,J=2.6,10.6Hz,1H),3.03-3.11(m,1H),3.62(ddd,J=1.5,10.6,12.1Hz,1H),3.66-3.76(m,1H),3.82-3.97(m,4H),4.13-4.23(m,1H),4.31(d,J=14.6Hz,1H),6.85(dd,J=1.7,7.5Hz,1H),7.03(d,J=1.5Hz,1H),7.19(d,J=7.7Hz,1H).

ESI-MS m/z 367 [M+H]+

[0182] (5) Synthesis of (R)-1-(2,6-dimethylpyridin-4-yl)-3-(4-ethyl-3-methoxyphenyl)-6-methyl-5,6,8,9,-tetrahydroimidazo[1,5-*d*][1,4]oxazepine

According to the method of Example 7-(5) (DME was used as the solvent), a title compound (22.8 mg, 0.058 mmol) was obtained from the compound obtained in Example 10-(4) (30 mg, 0.082 mmol).

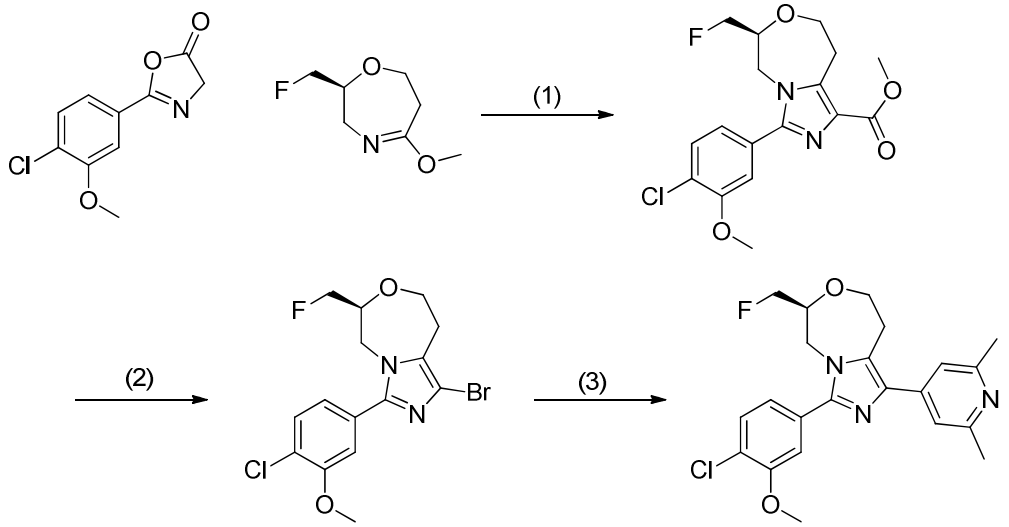
^{1}H-

NMR(400MHz,CDCl3) δ(ppm):1.22(t,J=7.6Hz,3H),1.27(d,J=6.6Hz,3H),2.55(s,6H),2.69(q,J=7.6Hz,2H),3.14-3.23(m,1H),3.33-3.40(m,1H),3.64-3.71(m,1H),3.76-3.82(m,1H),3.88(s,3H),3.92-4.00(m,1H),4.19-4.25(m,1H),4.33(d,J=14.7Hz,1H),6.92(dd,J=1.6,7.6Hz,1H),7.06(d,J=1.6Hz,1H),7.22(d,J=7.6Hz,1H),7.24(s,2H).

ESI-MS m/z 392 [M+H]+

[0183] Example 11

Synthesis of (S)-3-(4-chloro-3-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-fluoromethyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0184] (1) Synthesis of (S)-methyl 3-(4-chloro-3-methoxyphenyl)-6-fluoromethyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

According to the method of Example 1-(3), a title compound (1.10 g, 2.98 mmol) was obtained from the compound obtained in

Example 1-(2) (1.39 g, 6.18 mmol) and the compound obtained in Production Example 3-(7) (830 mg, 5.15 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):3.04-3.14(m,1H),3.68(t,J=11.9Hz,1H),3.76-3.86(m,1H),3.91(s,3H),3.94(s,3H),4.03(dd,J=8.6,14.8Hz,1H),4.17(dd,J=4.3,16.4Hz,1H),4.23-4.57(m,4H),6.94(dd,J=1.8,8.0Hz,1H),7.14(d,J=2.0Hz,1H),7.44(d,J=8.2Hz,1H).

[0185] (2) Synthesis of (S)-1-bromo-3-(4-chloro-3-methoxyphenyl)-6-fluoromethyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 1-(4), a title compound (858 mg, 2.20 mmol) was obtained from the compound obtained in Example 11-(1) (1.10 g, 2.98 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.94-3.06(m,1H),3.08-3.16(m,1H),3.65(ddd,J=1.4,10.9,12.3Hz,1H),3.74-3.87(m,1H),3.94(s,3H),3.99(dd,J=8.4,14.6Hz,1H),4.23-4.40(m,2H),4.43-4.60(m,2H),6.91(dd,J=2.0,8.2Hz,1H),7.13(d,J=2.0Hz,1H),7.43(d,J=8.2Hz,1H).

[0186] (3) Synthesis of (S)-3-(4-chloro-3-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-fluoromethyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 1-(5), a title compound (364 mg, 1.28 mmol) was obtained from the compound obtained in Example 11-(2) (500 mg, 1.28 mmol) and 2,6-dimethyl-pyridine-4-

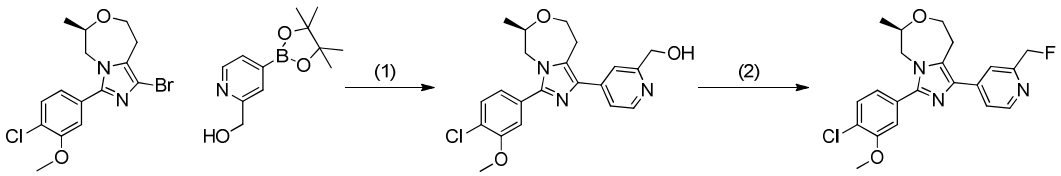
boronic acid (232 mg, 1.54 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.56(s,6H),3.15-3.26(m,1H),3.38(d,J=3.9Hz,1H),3.69(t,J=11.7Hz,1H),3.89(d,J=7.0Hz,1H),3.95(s,3H),4.03(d,J=15.2Hz,1H),4.27-4.42(m,2H),4.47-4.65(m,2H),6.99(dd,J=1.8,8.0Hz,1H),7.16(d,J=2.0Hz,1H),7.21(s,2H),7.46(d,J=7.8Hz,1H).

ESI-MS m/z 416 [M+H]+

[0187] Example 12

Synthesis of (R)-3-(4-chloro-3-methoxyphenyl)-1-(2-(fluoromethyl)pyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0188] (1) Synthesis of (R)-(4-(3-(4-chloro-3-methoxyphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepin-1-yl)pyridin-2-yl)methanol

According to the method of Example 1-(5), a title compound (53.0 mg, 0.133 mmol) was obtained from the compound obtained in Example 1-(4) (100 mg, 0.269 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)methanol (CAS No. 1314135-84-6; 76.0 mg, 0.323 mmol).

ESI-MS m/z 400 [M+H]+

[0189] (2) Synthesis of (R)-3-(4-chloro-3-methoxyphenyl)-1-(2-(fluoromethyl)pyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

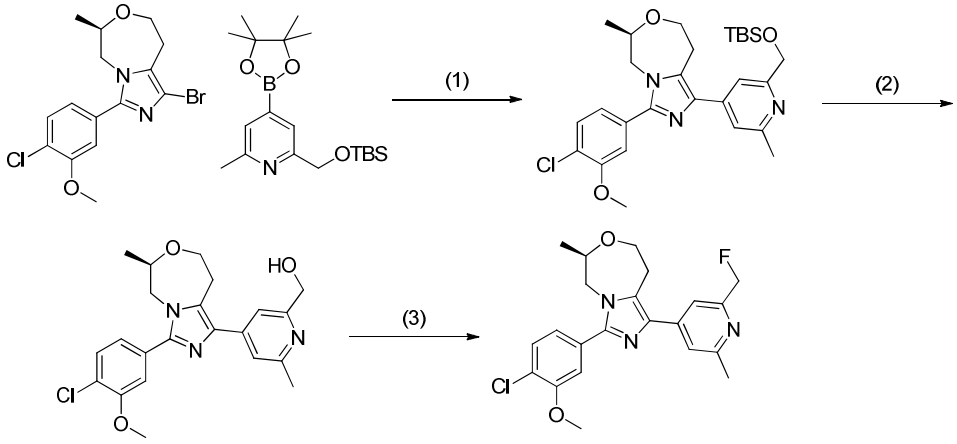
BAST (32.0 μL, 175 μmol) was added to a solution of the compound obtained in Example 12-(1) (50.0 mg, 125 μmol) in DCM (2 mL) under ice-cooling. The reaction mixture was warmed to room temperature and further stirred for 13 hours. A saturated aqueous sodium bicarbonate solution and DCM were added to the reaction mixture to separate the organic layer. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (9.5 mg, 24 μmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.27(d,J=6.2Hz,3H),3.17-3.26(m,1H),3.34-3.41(m,1H),3.63-3.71(m,1H),3.75-3.83(m,1H),3.95-4.03(m,1H),3.97(s,3H),4.20-4.30(m,2H),5.52(d,J=46.9Hz,2H),6.94(dd,J=2.0,8.0Hz,1H),7.19(d,J=2.0Hz,1H),7.45-7.52(m,2H),7.70(s,1H),8.58(d,J=5.2Hz,1H).

ESI-MS m/z 402 [M+H]+

[0190] Example 13

Synthesis of (R)-3-(4-chloro-3-methoxyphenyl)-1-(2-(fluoromethyl)-6-methylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0191] (1) Synthesis of (R)-1-(2-(((tert-butyldimethylsilyl)oxy)methyl)-6-methylpyridin-4-yl)-3-(4-chloro-3-methoxyphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 1-(5), a title compound (283 mg, 0.536 mmol) was obtained from the compound obtained in Example 1-(4) (300 mg, 0.807 mmol) and the compound obtained in Production Example 24 (440 mg, 1.21 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.10-0.16(m,6H),0.92-1.02(m,9H),1.26(d,J=6.6Hz,3H),2.54(s,3H),3.10-3.24(m,1H),3.42(dd,J=4.7,16.4Hz,1H),3.61-3.72(m,1H),3.74-3.84(m,1H),3.92-4.04(m,1H),3.96(s,3H),4.15-4.30(m,2H),4.83(s,2H),6.91-6.97(m,1H),7.20(d,J=1.6Hz,1H),7.41-7.50(m,3H).

[0192] (2) Synthesis of (R)-(4-(3-(4-chloro-3-methoxyphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepin-1-yl)-6-methylpyridin-2-yl)methanol

TBAF (a 1 M THF solution, 0.818 mL, 0.818 mmol) was slowly added to a solution of the compound obtained in Example 13-(1) (360

mg, 0.682 mmol) in THF (5.00 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 hour and an aqueous ammonium chloride solution was added. Ethyl acetate was added to the mixture to separate the organic layer. The organic layer was washed serially with water and a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate → ethyl acetate/methanol) to obtain a title compound (228 mg, 0.551 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.26(d,J=6.3Hz,3H),2.58(s,3H),3.19(ddd,J=2.3,10.6,16.3Hz,1H),3.30-3.40(m,1H),3.60-3.71(m,1H),3.73-3.82(m,1H),3.88(s,3H),3.88-4.03(m,1H),4.15-4.30(m,2H),4.74(s,2H),6.92(dd,J=1.8,8.0Hz,1H),7.17(d,J=1.6Hz,1H),7.26(s,1H),7.33(s,1H),7.46(d,J=8.2Hz,1H).

ESI-MS m/z 414 [M+H]+

[0193] (3) Synthesis of (R)-3-(4-chloro-3-methoxyphenyl)-1-(2-(fluoromethyl)-6-methylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

BAST (97.0 μL, 0.524 mmol) was added to a solution of the compound obtained in Example 13-(2) (31 mg, 75 μmol) in DCM (2 mL) at room temperature. The reaction mixture was stirred for 13 hours and a saturated aqueous sodium bicarbonate solution and DCM were added to the reaction mixture. The organic layer was separated and dried over anhydrous magnesium sulfate. The organic layer was

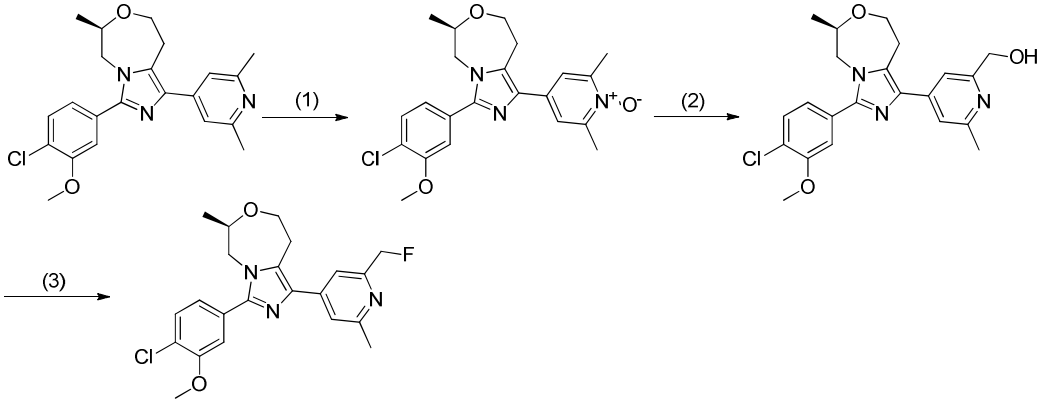
concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate → ethyl acetate/methanol) and NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (3.5 mg, 8.4 μmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.27(d,J=6.2Hz,3H),2.58(s,3H),3.16-3.25(m,1H),3.34-3.41(m,1H),3.63-3.71(m,1H),3.75-3.83(m,1H),3.95-4.02(m,1H),3.97(s,3H),4.20-4.29(m,2H),5.50(d,J=47.1Hz,2H),6.94(dd,J=1.8,7.9Hz,1H),7.19(d,J=1.8Hz,1H),7.42-7.48(m,3H).

ESI-MS m/z 416 [M+H]+

[0194] Example 13-A (an alternative method of Example 13)

Synthesis of (R)-3-(4-chloro-3-methoxyphenyl)-1-(2-(fluoromethyl)-6-methylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine (Example 13)



[0195] (1) Synthesis of (R)-4-(3-(4-chloro-3-methoxyphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepin-1-yl)-2,6-dimethylpyridine 1-oxide

mCPBA (75% by weight, 24.0 mg, 0.138 mmol) was added to a solution of the compound obtained in Example 1-(5) (50.0 mg, 0.126 mmol) in DCM (2 mL), and the mixture was stirred at room temperature for 15 hours. The mixture was purified by NH silica gel column chromatography (n-heptane/ethyl acetate → ethyl acetate/methanol) to obtain a title compound (45.0 mg, 0.109 mmol).
ESI-MS m/z 414 [M+H]+

[0196] (2) Synthesis of (R)-(4-(3-(4-chloro-3-methoxyphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepin-1-yl)-6-methylpyridin-2-yl)methanol

A solution of the compound obtained in Example 13-A-(1) (45.0 mg, 109 μmol) in acetic anhydride (2 mL) was stirred at 100°C for 3 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Chloroform and a saturated aqueous sodium bicarbonate solution were added to the resultant residue to separate the organic layer. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The resultant residue was dissolved in methanol (3 mL) and potassium carbonate (45.1 mg, 326 μmol) was added. The reaction mixture was stirred at 80°C for 3 hours and then cooled to room temperature. Ethyl acetate and a saturated aqueous sodium bicarbonate solution were added to the reaction mixture to separate the organic layer. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The resultant residue was purified serially by NH silica gel column chromatography (n-heptane/ethyl acetate →

ethyl acetate/methanol) and NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (3.5 mg, 8.4 μmol).
ESI-MS m/z 414 [M+H]+

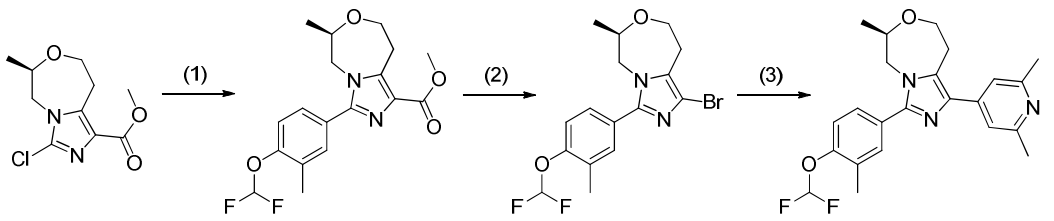
[0197] (3) Synthesis of (R)-3-(4-chloro-3-methoxyphenyl)-1-(2-(fluoromethyl)-6-methylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

BAST (97.0 μL, 0.524 mmol) was added to a solution of the compound obtained in Example 13-A-(2) (31 mg, 75 μmol) in DCM (2 mL) at room temperature. The reaction mixture was stirred for 13 hours and then a saturated aqueous sodium bicarbonate solution and DCM were added to the reaction mixture. The organic layer was separated and dried over anhydrous magnesium sulfate. The organic layer was concentrated under reduced pressure. The resultant residue was purified serially by NH silica gel column chromatography (n-heptane/ethyl acetate) and silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (3.5 mg, 8.4 μmol).
^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.27(d,J=6.2Hz,3H),2.58(s,3H),3.16-3.25(m,1H),3.34-3.41(m,1H),3.63-3.71(m,1H),3.75-3.83(m,1H),3.95-4.02(m,1H),3.97(s,3H),4.20-4.29(m,2H),5.50(d,J=47.1Hz,2H),6.94(dd,J=1.8,7.9Hz,1H),7.19(d,J=1.8Hz,1H),7.42-7.48(m,3H).
ESI-MS m/z 416 [M+H]+

[0198] Example 14

Synthesis of (R)-3-(4-(difluoromethoxy)-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-

d][1,4]oxazepine



[0199] (1) Synthesis of (R)-methyl 3-(4-(difluoromethoxy)-3-methylphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

A mixture of the compound obtained in Production Example 8-(3) (300 mg, 1.23 mmol), 4-difluoromethoxy-3-methyl-benzeneboronic acid (CAS No. 958451-72-4; 297 mg, 1.47 mmol), tetrakis(triphenylphosphine)palladium(0) (142 mg, 0.123 mmol), an aqueous sodium carbonate solution (1 M, 2.45 mL, 2.45 mmol) and DME (6 mL) was stirred under microwave irradiation at 130°C for 30 minutes. The reaction mixture was cooled to room temperature and ethyl acetate and a saturated aqueous ammonium chloride solution were added. The organic layer was separated, washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The insolubles were separated through filtration and the filtrate was concentrated under reduced pressure. The resultant residue was purified by NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (290 mg, 0.792 mmol).

ESI-MS m/z 367 [M+H]+

[0200] (2) Synthesis of (R)-1-bromo-3-(4-(difluoromethoxy)-3-methylphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-

d][1,4]oxazepine

A 2 N aqueous sodium hydroxide solution (0.317 mL) was added to a solution of the compound obtained in Example 14-(1) (290 mg, 0.792 mmol) in ethanol (4 mL). The reaction mixture was heated under reflux for 2 hours. The reaction mixture was cooled to room temperature and acidified with a 5 N hydrochloric acid. The mixture was concentrated under reduced pressure and DMF (4 mL) was added to the residue. Potassium carbonate (273 mg, 1.98 mmol) and NBS (211 mg, 1.19 mmol) were added to the reaction mixture, and the mixture was stirred at room temperature for 14 hours. Water and ethyl acetate were added to the mixture to separate the organic layer. The resultant organic layer was washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The insolubles were separated through filtration and the filtrate was concentrated. The residue was purified by NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (135 mg, 0.349 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.22(d,J=6.5Hz,3H),2.32(s,3H),2.97-3.10(m,2H),3.57-3.74(m,2H),3.92(dd,J=8.4,14.7Hz,1H),4.14-4.23(m,2H),6.55(t,J=73.4Hz,1H),7.14(d,J=8.4Hz,1H),7.23(dd,J=2.3,8.4Hz,1H),7.40(d,J=2.0Hz,1H).

ESI-MS m/z 387 [M+H]+

[0201] (3) Synthesis of (R)-3-(4-(difluoromethoxy)-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

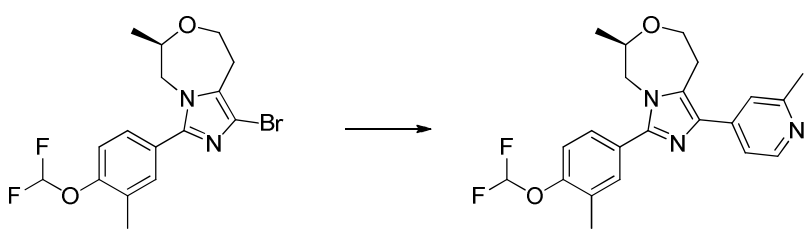
A mixture of the compound obtained in Example 14-(2) (135 mg, 0.349 mmol), 2,6-dimethyl-pyridine-4-boronic acid (73.7 mg, 0.488 mmol), tetrakis(triphenylphosphine)palladium(0) (20.1 mg, 0.017 mmol), an aqueous sodium carbonate solution (1 M, 0.697 mL), and DME (3.00 mL) was stirred under microwave irradiation at 150°C for 1 hour. The reaction mixture was cooled to room temperature and then purified serially by silica gel column chromatography (n-heptane/ethyl acetate → ethyl acetate/methanol) and NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (104 mg, 0.252 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.26(d,J=6.7Hz,3H),2.35(s,3H),2.55(s,6H),3.14-3.22(m,1H),3.32-3.39(m,1H),3.63-3.70(m,1H),3.74-3.82(m,1H),3.94-4.01(m,1H),4.19-4.26(m,2H),6.55(t,J=73.5Hz,1H),7.18(d,J=8.4Hz,1H),7.21(s,2H),7.28(dd,J=2.3,8.4Hz,1H),7.46(d,J=1.9Hz,1H).

ESI-MS m/z 414 [M+H]+

[0202] Example 15

Synthesis of (R)-3-(4-(difluoromethoxy)-3-methylphenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0203] According to the method of Example 8, a title compound

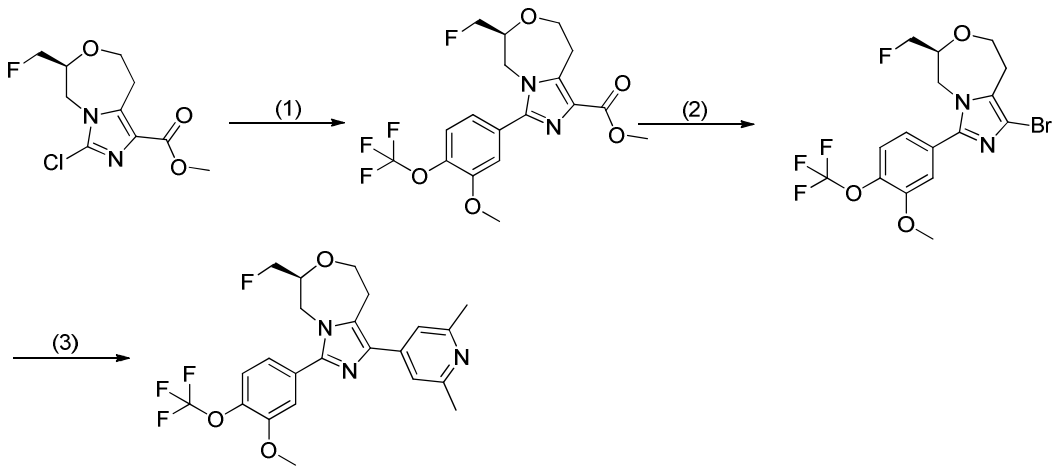
(8.1 mg, 0.020 mmol) was obtained from the compound obtained in Example 14-(2) (24 mg, 0.062 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.26(d,J=6.2Hz,3H),2.35(s,3H),2.58(s,3H),3.19(ddd,J=2.3,10.5,16.0Hz,1H),3.36(dd,J=3.9,16.0Hz,1H),3.62-3.71(m,1H),3.74-3.84(m,1H),3.98(dd,J=8.4,14,6Hz,1H),4.22(ddd,J=2.3,5.1,12.1Hz,1H),4.24(d,J=14.4Hz,1H)6.56(t,J=73.8Hz,1H),7.15-7.22(m,1H),7.26-7.32(m,2H),7.44-7.48(m,2H),8.47-8.50(m,1H).

ESI-MS m/z 400 [M+H]+

[0204] Example 16

Synthesis of (S)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0205] (1) Synthesis of (S)-methyl 6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

According to the method of Example 14-(1), a crude title

compound (319 mg) was obtained from the compound obtained in Production Example 9 (200 mg, 0.761 mmol) and the compound obtained in Production Example 21 (484 mg, 1.52 mmol).

ESI-MS m/z 419 [M+H]+.

[0206] (2) Synthesis of (S)-1-bromo-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 1-(4), a title compound (138 mg, 0.314 mmol) was obtained from the compound obtained in Example 16-(1) (319 mg).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.98-3.17(m,2H),3.62-3.70(m,1H),3.78-3.88(m,1H),3.92(s,3H),3.98-4.06(m,1H),4.24-4.63(m,4H),6.96(dd,J=2.0,8.2Hz,1H),7.20(d,J=2.0Hz,1H),7.28-7.33(m,1H).

[0207] (3) Synthesis of (S)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 1-(5), a title compound (42 mg, 0.09 mmol) was obtained from the compound obtained in Example 16-(2) (69.0 mg, 0.157 mmol) and 2,6-dimethyl-pyridine-4-boronic acid (35.6 mg, 0.236 mmol).

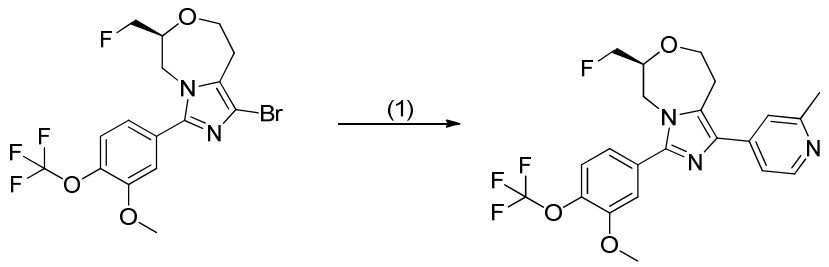
^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.56(s,6H),3.24(dd,J=2.3,10.9Hz,1H),3.42(dd,J=3.9,16.4Hz,1H),3.71(t,J=11.5Hz,1H),3.84-3.97(m,1H),3.93(s,3H),4.06(dd,J=8.6,14.8Hz,1H),4.28-4.66(m,4H),7.04(dd,J=2.0,8.2Hz,1H),7.22(s,2H),7.24(d,J=2.0Hz,1H),

7.34(m,1H).

ESI-MS m/z 466 [M+H]+

[0208] Example 17

Synthesis of (S)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

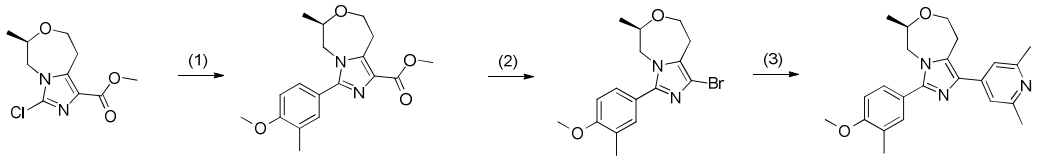


[0209] According to the method of Example 1-(5), a title compound (36 mg, 0.08 mmol) was obtained from the compound obtained in Example 16-(2) (69 mg, 0.157 mmol) and 2-picoline-4-boronic acid (32 mg, 0.24 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.59(s,3H),3.23(ddd,J=2.5,11.1,16.4Hz,1H),3.37-3.46(m,1H),3.72(t,J=11.3Hz,1H),3.85-3.95(m,1H),3.94(s,3H),4.07(dd,J=9.0,14.8Hz,1H),4.29-4.66(m,4H),7.04(dd,J=2.0,8.2Hz,1H),7.24(d,J=2.0Hz,1H),7.29(dd,J=1.2,5.1Hz,1H),7.34(dq,J=1.3,8.4Hz,1H),7.45-7.48(m,1H),8.51(d,J=4.7Hz,1H).

[0210] Example 18

Synthesis of (R)-1-(2,6-dimethylpyridin-4-yl)-3-(4-methoxy-3-methylphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0211] (1) Synthesis of (R)-methyl 3-(4-methoxy-3-methylphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

According to the method of Example 14-(1), a title compound (143 mg, 0.433 mmol) was obtained from the compound obtained in Production Example 8-(3) (150 mg, 0.613 mmol) and 4-methoxy-3-methylphenyl boronic acid (CAS No. 175883-62-2; 122 mg, 0.736 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.16-1.24(m,3H),2.24(s,3H),3.01-3.17(m,1H),3.56-3.76(m,2H),3.87(s,3H),3.89(s,3H),3.90-3.98(m,1H),4.00-4.09(m,1H),4.16-4.28(m,2H),6.87(d,J=8.4Hz,1H),7.24(dd,J=2.2,8.4Hz,1H),7.31(d,J=2.2 Hz, 1H).

[0212] (2) Synthesis of (R)-1-bromo-3-(4-methoxy-3-methylphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

A 5 N aqueous sodium hydroxide solution (433 μL, 2.16 mL) was added to a solution of the compound obtained in Example 18-(1) (143 mg, 0.433 mmol) in methanol (2.0 mL)/THF (2.0 mL), and the mixture was stirred at room temperature for 15 hours. A 5 N hydrochloric acid was added to the reaction mixture for neutralization and the solvent was evaporated under reduced pressure. DMF (2.0 mL) and ethanol (2.0 mL) were added to the residue, and potassium

carbonate (59.8 mg, 0.433 mL) and NBS (108 mg, 0.606 mmol) were added to the mixture. The reaction mixture was stirred for 1.5 hours at room temperature, then sodium sulfite (510 mg, 4.04 mL) and water were added to the reaction mixture. The water layer was extracted with ethyl acetate twice. The combined organic layer was washed with a saturated aqueous sodium chloride solution twice and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain and a title compound (81.0 mg, 0.231 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.15-1.24(m,3H),2.24(s,3H),2.91-3.11(m,2H),3.55-3.75(m,2H),3.87(s,3H),3.83-3.96(m,1H),4.12-4.30(m,2H),6.87(d,J=8.4Hz,1H),7.22(dd,J=22,8.4Hz,1H),7.28(d,J=2.2Hz,1H).

[0213] (3) Synthesis of (R)-1-(2,6-dimethylpyridin-4-yl)-3-(4-methoxy-3-methylphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 14-(3), a title compound (9.1 mg, 0.024 mmol) was obtained from the compound obtained in Example 18-(2) (30.0 mg, 0.085 mmol) and 2,6-dimethyl-pyridine-4-boronic acid (20.6 mg, 0.137 mmol).

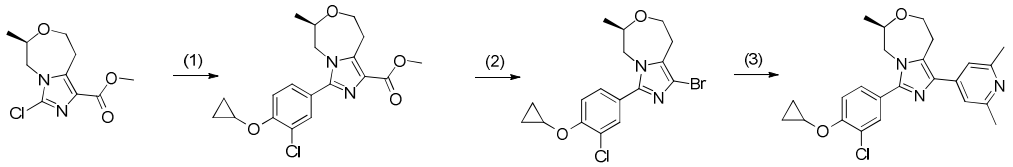
^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.18-1.32(m,3H),2.26(s,3H),2.55(s,6H),3.09-3.24(m,1H),3.30-3.41(m,1H),3.60-3.71(m,1H),3.73-3.83(m,1H),3.89(s,3H),3.90-4.00(m,1H),4.15-4.32(m,2H),6.90(d,J=8.4Hz,1H),7.22(s,2H),7.27(dd,J=2.1,8.4Hz,1H),

7.33(d,J=2.1Hz,1H).

ESI-MS m/z 378 [M+H]+

[0214] Example 19

Synthesis of (R)-3-(3-chloro-4-cyclopropoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0215] (1) Synthesis of (R)-methyl 3-(3-chloro-4-cyclopropoxyphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

According to the method of Example 14-(1), a title compound (89.0 mg, 0.236 mmol) was obtained from the compound obtained in Production Example 8-(3) (115 mg, 0.470 mmol) and the compound obtained in Production Example 12 (115 mg, 0.541 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.84-0.93(m,4H),1.21-1.26(m,3H),3.00-3.21(m,1H),3.56-3.76(m,2H),3.81-3.88(m,1H),3.90(s,3H),3.93-4.10(m,2H),4.16-4.24(m,2H),7.34(dd,J=1.8,8.6Hz,1H),7.36(dd,J=0.6,8.6Hz,1H),7.51(dd,J=0.6,1.8Hz,1H).

[0216] (2) Synthesis of (R)-1-bromo-3-(3-chloro-4-cyclopropoxyphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 18-(2), a title compound (48.0 mg, 0.121 mmol) was obtained from the compound obtained in

Example 19-(1) (89.0 mg, 0.236 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.84-0.91(m,4H),1.21-1.26(m,3H),2.88-3.15(m,2H),3.55-3.76(m,2H),3.80-3.88(m,1H),3.89-3.98(m,1H),4.13-4.25(m,2H),7.32(dd,J=2.0,8.5Hz,1H),7.36(d,J=8.5Hz,1H),7.48(d,J=2.0Hz,1H).

[0217] (3) Synthesis of (R)-3-(3-chloro-4-cyclopropoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

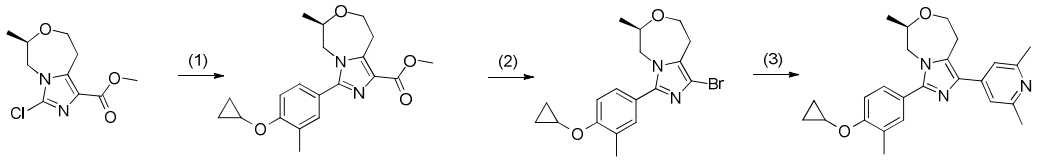
According to the method of Example 1-(5), a title compound (15 mg, 0.035 mmol) was obtained from the compound obtained in Example 19-(2) (25.0 mg, 0.063 mmol) and 2,6-dimethyl-pyridine-4-boronic acid (15.2 mg, 0.101 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.85-0.93(m,4H),1.24-1.32(m,3H),2.55(s,6H),3.11-3.24(m,1H),3.28-3.42(m,1H),3.59-3.71(m,1H),3.72-3.90(m,2H),3.92-4.05(m,1H),4.16-4.30(m,2H),7.21(s,2H),7.37-7.40(m,2H),7.52-7.55(m,1H).

ESI-MS m/z 424 [M+H]+

[0218] Example 20

Synthesis of (R)-3-(4-cyclopropoxy-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0219] (1) Synthesis of (R)-methyl 3-(4-cyclopropoxy-3-

methylphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

According to the method of Example 14-(1), a title compound (248 mg, 0.696 mmol) was obtained from the compound obtained in Production Example 8-(3) (200 mg, 0.817 mmol) and the compound obtained in Production Example 16 (269 mg, 0.981 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.69-0.92(m,4H),1.12-1.33(m,3H),2.19(s,3H),3.00-3.18(m,1H),3.58-3.80(m,3H),3.89(s,3H),3.90-3.98(m,1H),4.00-4.09(m,1H),4.15-4.31(m,2H),7.22-7.25(m,2H),7.28-7.30(m,1H).

[0220] (2) Synthesis of (R)-1-bromo-3-(4-cyclopropoxy-3-methylphenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 18-(2), a title compound (115 mg, 0.305 mmol) was obtained from the compound obtained in Example 20-(1) (248 mg, 0.696 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.73-0.90(m,4H),1.17-1.27(m,3H),2.19(s,3H),2.90-3.01(m,1H),3.02-3.11(m,1H),3.57-3.65(m,1H),3.66-3.81(m,2H),3.84-3.96(m,1H),4.12-4.21(m,1H),4.22-4.32(m,1H),7.17-7.31(m,3H).

[0221] (3) Synthesis of (R)-3-(4-cyclopropoxy-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 1-(5), a title compound (2.7 mg, 6.7 μmol) was obtained from the compound obtained in Example 20-(2) (30.0 mg, 0.080 mmol) and 2,6-dimethyl-pyridine-4-

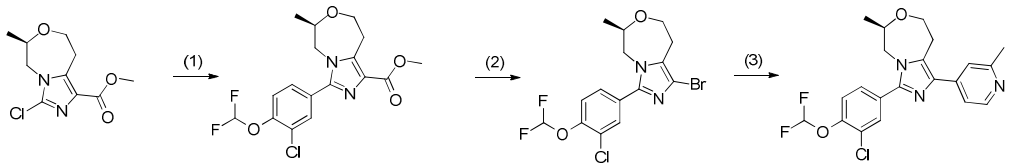
boronic acid (19.2 mg, 0.127 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.73-0.90(m,4H),1.21-1.32(m,3H),2.21(s,3H),2.55(s,6H),3.11-3.24(m,1H),3.28-3.43(m,1H),3.60-3.72(m,1H),3.73-3.86(m,2H),3.88-4.03(m,1H),4.16-4.35(m,2H),7.22(s,2H),7.25-7.28(m,2H),7.29-7.32(m,1H).

ESI-MS m/z 404 [M+H]+

[0222] Example 21

Synthesis of (R)-3-(3-chloro-4-(difluoromethoxy)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0223] (1) Synthesis of (R)-methyl 3-(3-chloro-4-(difluoromethoxy)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

According to the method of Example 14-(1), a title compound (177 mg, 0.458 mmol) was obtained from the compound obtained in Production Example 8-(3) (150 mg, 0.613 mmol) and 2-(3-chloro-4-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (CAS No. 1310949-92-8; 224 mg, 0.736 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.16-1.30(m,3H),3.01-3.22(m,1H),3.59-3.77(m,2H),3.90(s,3H),3.95-4.11(m,2H),4.14-4.28(m,2H),6.60(t,J=72.8Hz,1H),7.33(d,J=8.4Hz,1H),7.37(dd,J=2.0,8.4Hz,1H),7.66(d,J=2.0Hz,1H).

[0224] (2) Synthesis of (R)-1-bromo-3-(3-chloro-4-

(difluoromethoxy)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 18-(2), a title compound (98.0 mg, 0.240 mmol) was obtained from the compound obtained in Example 21-(1) (177 mg, 0.458 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.13-1.34(m,3H),2.91-3.03(m,1H),3.04-3.16(m,1H),3.56-3.79(m,2H),3.89-4.03(m,1H),4.14-4.25(m,2H),6.59(t,J=72.8Hz,1H),7.32(d,J=8.4Hz,1H),7.35(dd,J=1.9,8.4Hz,1H),7.62(d,J=1.9Hz,1H).

[0225] (3) Synthesis of (R)-3-(3-chloro-4-(difluoromethoxy)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 17, a title compound (13.8 mg, 0.033 mmol) was obtained from the compound obtained in Example 21-(2) (30.0 mg, 0.074 mmol) and 2-picoline-4-boronic acid (15.1 mg, 0.110 mmol).

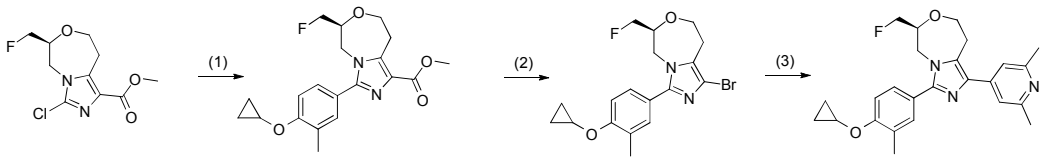
^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.22-1.38(m,3H),2.59(s,3H),3.12-3.29(m,1H),3.31-3.43(m,1H),3.61-3.72(m,1H),3.74-3.87(m,1H),3.96-4.08(m,1H),4.16-4.28(m,2H),6.60(t,J=72.9Hz,1H),7.28(brd,J=5.2Hz,1H),7.36(brd,J=8.4
Hz,1H),7.41(dd,J=2.0,8.4Hz,1H),7.44(brs,1H),7.68(d,J=2.0Hz,1H),8.50(d,J=5.2Hz,1H).

ESI-MS m/z 420 [M+H]+

[0226] Example 22

Synthesis of (S)-3-(4-cyclopropoxy-3-methylphenyl)-1-(2,6-

dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0227] (1) Synthesis of (S)-methyl 3-(4-cyclopropoxy-3-methylphenyl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

According to the method of Example 14-(1), a title compound (107 mg, 0.286 mmol) was obtained from the compound obtained in Production Example 9 (200 mg, 0.761 mmol) and the compound obtained in Production Example 16 (251 mg, 0.914 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.73-0.87(m,4H),2.18(s,3H),2.97-3.19(m,1H),3.63-3.72(m,1H),3.73-3.85(m,2H),3.90(s,3H),3.96-4.06(m,1H),4.12-4.20(m,1H),4.24-4.64(m,4H),7.22-7.27(m,2H),7.29-7.32(m,1H).

[0228] (2) Synthesis of (S)-1-bromo-3-(4-cyclopropoxy-3-methylphenyl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 18-(2), a title compound (75.0 mg, 0.190 mmol) was obtained from the compound obtained in Example 22-(1) (107 mg, 0.286 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.72-0.87(m,4H),2.18(d,J=0.8Hz,3H),2.94-3.18(m,2H),3.57-3.70(m,1H),3.71-3.88(m,2H),3.91-4.05(m,1H),4.20-4.63(m,4H),7.24(d,J=1.4Hz,2H),7.28(qd,J=0.8,1.4Hz,1H).

[0229] (3) Synthesis of (S)-3-(4-cyclopropoxy-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

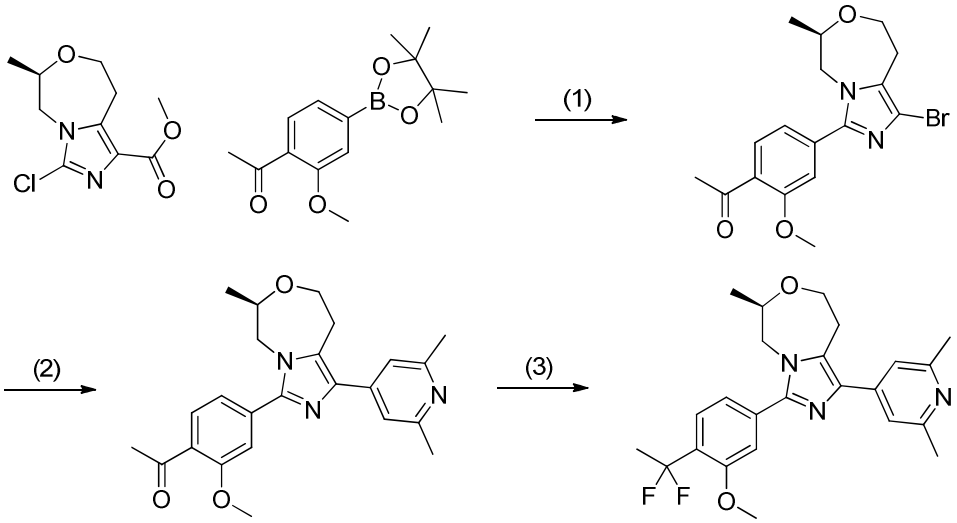
According to the method of Example 14-(3), a title compound (12.0 mg, 0.028 mmol) was obtained from the compound obtained in Example 22-(2) (26 mg, 0.066 mmol) and 2,6-dimethylpyridine-4-boronic acid (15.9 mg, 0.105 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):0.70-0.93(m,4H),2.20(s,3H),2.55(s,6H),3.12-3.29(m,1H),3.33-3.45(m,1H),3.64-3.74(m,1H),3.75-3.94(m,2H),3.97-4.09(m,1H),4.23-4.66(m,4H),7.22(s,2H),7.25-7.35(m,3H).

ESI-MS m/z 422 [M+H]+

[0230] Example 23

Synthesis of (R)-3-(4-(1,1-difluoroethyl)-3-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0231] (1) Synthesis of (R)-1-(4-(1-bromo-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepin-3-yl)-2-

methoxyphenyl)ethanone

According to the methods of Examples 14-(1) and 18-(2), a title compound (79.4 mg, 0.209 mmol) was obtained from 1-(2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (CAS No. 638214-65-0; 293 mg, 1.06 mmol) and the compound obtained in Production Example 8-(3) (173 mg, 0.707 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.23(d,J=6.2Hz,3H),2.64(s,3H),2.99(ddd,J=2.7,10.9,16.4Hz,1H),3.09(ddd,J=1.6,4.3,16.4Hz,1H),3.62(ddd,J=1.4,10.6,12.2Hz,1H),3.67-3.76(m,1H),3.95(dd,J=8.2,14.8Hz,1H),3.97(s,3H),4.19(ddd,J=2.7,3.9,12.5Hz,1H),4.28(d,J=14.4Hz,1H),6.93(dd,J=1.6,7.8Hz,1H),7.24(d,J=1.2Hz,1H),7.79(d,J=7.8Hz,1H).

ESI-MS m/z 379, 381 [M+H]+ 401, 403 [M+Na]+

[0232] (2) Synthesis of (R)-1-(4-(1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepin-3-yl)-2-methoxyphenyl)ethanone

According to Example 1-(5), a title compound (35 mg, 0.086 mmol) was obtained from the compound obtained in Example 23-(1) (39 mg, 0.10 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.27(d,J=6.6Hz,3H),2.56(s,6H),2.65(d,J=0.8Hz,3H),3.19(ddd,J=2.3,10.9,16.0Hz,1H),3.37(dd,J=4.5,16.2Hz,1H),3.67(t,J=11.5Hz,1H),3.75-3.85(m,1H),3.96-4.05(m,1H),3.99(s,3H),4.23(ddd,J=2.3,4.3,12.5Hz,1H),4.30(d,J=14.8Hz,1H),6.96-

7.04(m,1H),7.22(s,2H),7.28(d,J=0.8Hz,1H),7.82(d,J=7.8Hz,1H).

ESI-MS m/z 406 [M+H]+, 428 [M+Na]+

[0233] (3) Synthesis of (R)-3-(4-(1,1-difluoroethyl)-3-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

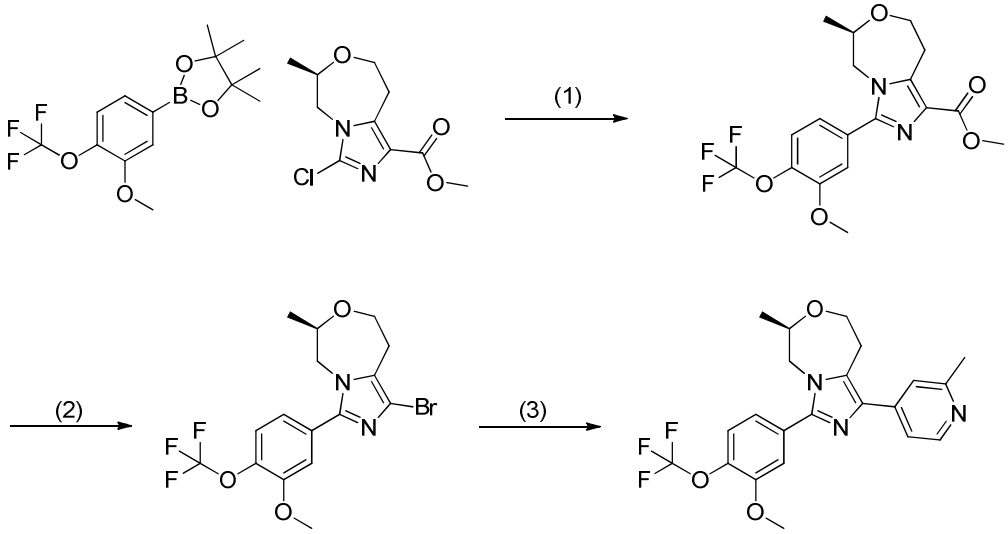
DAST (23 μL, 0.17 mmol) was added to a solution of the compound obtained in Example 23-(2) (35 mg, 0.073 mmol) in DCM (1.0 mL), at -78°C. The reaction mixture was warmed to room temperature and stirred for 16 hours, and then DCE (1 mL) and BAST (0.080 mL, 0.43 mmol) were added. The reaction mixture was heated to 80°C and stirred for 2 hours, and then BAST (0.20 mL, 1.1 mmol) was added. The reaction mixture was stirred at 80°C for 5 hours, and then BAST (0.50 mL, 2.7 mmol) was added. The reaction mixture was stirred at 80°C for 5 hours, then cooled to room temperature, and then purified by NH silica gel column chromatography (n-heptane/ethyl acetate). The resultant compound was purified serially by silica gel thin layer chromatography (ethyl acetate) and NH silica gel thin layer chromatography (n-heptane/ethyl acetate) to obtain a title compound (3.4 mg, 0.0080 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.28(d,J=6.2Hz,3H),2.03(t,J=18.7Hz,3H),2.63(s,6H),3.21(ddd,J=2.3,10.7,16.2Hz,1H),3.38(dd,J=3.9,16.0Hz,1H),3.68(t,J=11.1Hz,1H),3.76-3.84(m,1H),3.95(s,3H),4.00(dd,J=8.2,14.8Hz,1H),4.24(ddd,J=2.3,4.7,12.1Hz,1H),4.30(d,J=14.8Hz,1H),7.00(dd,J=1.6,7.8Hz,1H),7.21(s,1H),7.30(s,2H),7.62(d,J=7.8Hz,1H).

ESI-MS m/z 428[M+H]+

[0234] Example 24

Synthesis of (R)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0235] (1) Synthesis of (R)-methyl 3-(3-methoxy-4-(trifluoromethoxy)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

A mixture of the compound obtained in Production Example 8-(3) (600 mg, 2.45 mmol), the compound obtained in Production Example 21 (1.56 g, 4.90 mmol), tetrakis(triphenylphosphine)palladium(0) (283 mg, 0.245 mmol), an aqueous sodium carbonate solution (2 M, 4.9 mL) and DME (15 mL) was stirred under microwave irradiation at 130°C for 30 minutes. The reaction mixture was cooled to room temperature, and then ethyl acetate and a saturated aqueous ammonium chloride solution were added. The insolubles were filtered off through Celite (trademark)

and the organic layer of the resultant filtrate was separated. The resultant organic layers were washed with a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, the drying agent was filtered off, and the solvent was evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (982 mg, 2.45 mmol).

ESI-MS m/z 401 [M+H]+

[0236] (2) Synthesis of (R)-1-bromo-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

A 5 N aqueous sodium hydroxide solution (0.981 mL) was added to a solution of the compound obtained in Example 24-(1) (982 mg, 2.45 mmol) in ethanol (10.0 mL). The reaction mixture was heated and stirred at 45°C for 4 hours. The reaction mixture was cooled to room temperature, then a 5 N hydrochloric acid (0.98 mL) was added for neutralization. The insolubles were filtered off, then the filtrate was concentrated under reduced pressure, and then DMF (5 mL) was added to the resultant residue. Potassium carbonate (678 mg, 4.91 mmol) and NBS (480 mg, 2.70 mmol) were added to the reaction mixture, and the mixture was stirred at room temperature for 14 hours. Water and ethyl acetate were added to the mixture to separate the organic layer. The resultant organic layers were washed with a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, the drying agent was filtered off, and then the solvent was evaporated under reduced pressure. The

resultant residue was purified by NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (640 mg, 1.52 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.24(d,J=6.3Hz,3H),2.94-3.12(m,2H),3.58-3.66(m,1H),3.67-3.76(m,1H),3.93(s,3H),3.94-3.99(m,1H),4.15-4.22(m,1H),4.23-4.30(m,1H),6.83-6.93(m,1H),7.20-7.24(m,1H),7.27-7.33(m,1H).

[0237] (3) Synthesis of (R)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

A mixture of the compound obtained in Example 24-(2) (640 mg, 1.52 mmol), 2-picoline-4-boronic acid (312 mg, 2.28 mmol), tetrakis(triphenylphosphine)palladium(0) (176 mg, 0.152 mmol), an aqueous sodium carbonate solution (2 M, 3.04 mL, 6.08 mmol), and DME (10 mL) was stirred under microwave irradiation at 150°C for 30 minutes. The reaction mixture was cooled to room temperature and ethyl acetate and a saturated aqueous ammonium chloride solution were added for separation. The resultant organic layer was washed with a saturated aqueous sodium chloride solution, then dried over anhydrous magnesium sulfate, the drying agent was filtered off, and then the solvent was evaporated under reduced pressure. The resultant residue was purified serially by NH silica gel column chromatography (heptane-ethyl acetate) and silica gel column chromatography (methanol-ethyl acetate) to obtain a title compound (152 mg, 0.351 mmol).

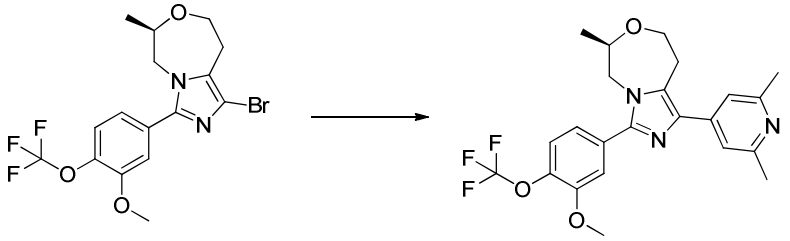
^{1}H-

NMR(400MHz,CDCl3) δ(ppm):1.28(d,J=6.3Hz,3H),2.59(s,3H),3.16-3.26(m,1H),3.33-3.42(m,1H),3.64-3.73(m,1H),3.76-3.85(m,1H),3.95(s,3H),3.96-4.05(m,1H),4.19-4.32(m,2H),6.95-7.00(m,1H),7.25-7.36(m,3H),7.45-7.48(m,1H),8.47-8.52(m,1H).

ESI-MS m/z 434 [M+H]+.

[0238] Example 25

Synthesis of (R)-1-(2,6-dimethylpyridin-4-yl)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



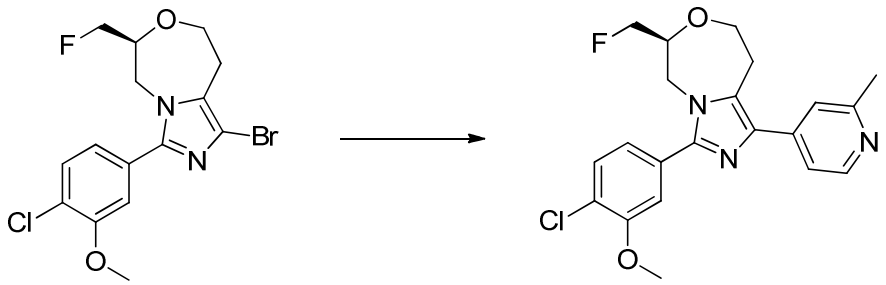
[0239] According to the method of Example 7-(5), a title compound (6.7 mg, 0.015 mmol) was obtained from the compound obtained in Example 24-(2) (19 mg, 0.045 mmol) and 2,6-dimethyl-pyridine-4-boronic acid (14 mg, 0.093 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.28(d,J=6.2Hz,3H),2.56(s,6H),3.19(ddd,J=2.3,10.5,16.0Hz,1H),3.37(dd,J=3.9,16.0Hz,1H),3.67(t,J=11.3Hz,1H),3.75-3.84(m,1H),3.94(s,3H),4.00(dd,J=8.6,14.8Hz,1H),4.23(ddd,J=2.3,4.7,12.5Hz,1H),4.27(d,J=14.8Hz,1H),6.97(dd,J=2.0,8.6Hz,1H),7.22(s,2H),7.26(d,J=2.0Hz,1H),7.33(d,J=1.2,8.2Hz,1H).

ESI-MS m/z 448 [M+H]+.

[0240] Example 26

Synthesis of (S)-3-(4-chloro-3-methoxyphenyl)-6-fluoromethyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



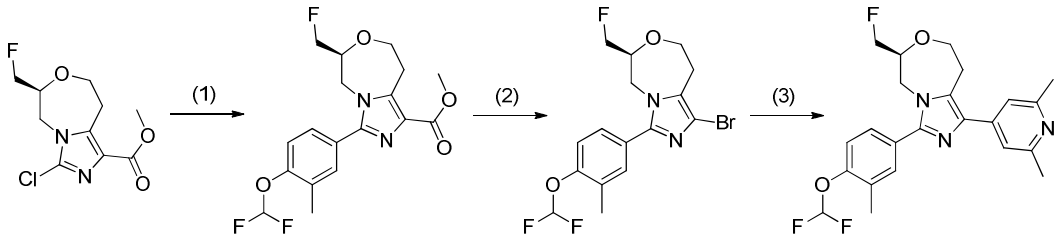
[0241] According to the method of Example 1-(5), a title compound (13.3 mg, 0.033 mmol) was obtained from the compound obtained in Example 11-(2) (30.0 mg, 0.077 mmol) and 2-picoline-4-boronic acid (21.1 mg, 0.154 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.59(s,3H),3.15-3.28(m,1H),3.41(dd,J=4.1,16.2Hz,1H),3.70(t,J=11.5Hz,1H),3.84-3.93(m,1H),3.95(s,3H),4.04(dd,J=9.0,14.8Hz,1H),4.26-4.44(m,2H),4.47-4.64(m,2H),6.96-7.03(m,1H),7.16(d,J=2.0Hz,1H),7.30(d,J=5.1Hz,1H),7.44-7.51(m,2H),8.50(d,J=5.5Hz,1H).

ESI-MS m/z 402 [M+H]+

[0242] Example 27

Synthesis of (S)-3-(4-(difluoromethoxy)-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0243] (1) Synthesis of (S)-methyl 3-(4-(difluoromethoxy)-3-methylphenyl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

A mixture of the compound obtained in Production Example 9 (203 mg, 0.773 mmol), 4-difluoromethoxy-3-methyl-benzeneboronic acid (234 mg, 1.16 mmol), tetrakis(triphenylphosphine)palladium(0) (89 mg, 0.077 mmol), and an aqueous sodium carbonate solution (1 M, 1.47 mL) in DME (3.09 mL) was stirred under microwave irradiation at 130°C for 30 minutes. Ethyl acetate and an aqueous sodium chloride solution were added to the mixture. The organic layer was separated. The water layer was extracted with ethyl acetate three times, then the resultant organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (281 mg, 0.731 mmol).

ESI-MS m/z 385 [M+H]+

[0244] (2) Synthesis of (S)-1-bromo-3-(4-(difluoromethoxy)-3-methylphenyl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

A solution of the compound obtained in Example 27-(1) (281 mg, 0.731 mmol) and a 5 N aqueous sodium hydroxide solution

(0.731 mL, 3.66 mmol) in THF (1.8 mL)-methanol (1.8 mL) was stirred at room temperature for 2 hours. The reaction mixture was neutralized with hydrochloric acid. The mixture was concentrated under reduced pressure and the resultant residue was azeotroped with toluene. DMF (3.6 mL), ethanol (3.6 mL), potassium carbonate (101 mg, 0.731 mmol), and NBS (260 mg, 1.46 mmol) were added to the residue, and the mixture was stirred at room temperature for 16 hours. Sodium sulfite was added to the reaction mixture and ethanol was evaporated under reduced pressure. Ethyl acetate was added to the resultant solution, and then the mixture was washed with water five times and then with a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (140 mg, 0.346 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.33(s,3H),3.02(ddd,J=2.7,10.9,16.4Hz,1H),3.12(ddd,J=1.2,3.5,16.4Hz,1H),3.65(dt,J=1.2,11.7Hz,1H),3.74-3.86(m,1H),4.00(dd,J=8.8,14.6Hz,1H),4.23-4.30(m,1H),4.40(ddd,J=6.6,9.4,46.9Hz,1H)4.51(ddd,J=4.7,9.8,46.1Hz,1H),4.53(d,J=14.8Hz,1H),6.55(t,J=73.4Hz,1H),7.15(d,J=8.6Hz,1H),7.27(dd,J=2.0,8.2Hz,1H),7.41(d,J=2.0Hz,1H).

ESI-MS m/z 405, 407 [M+H]+ 427, 429 [M+Na]+

[0245] (3) Synthesis of (S)-3-(4-(difluoromethoxy)-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

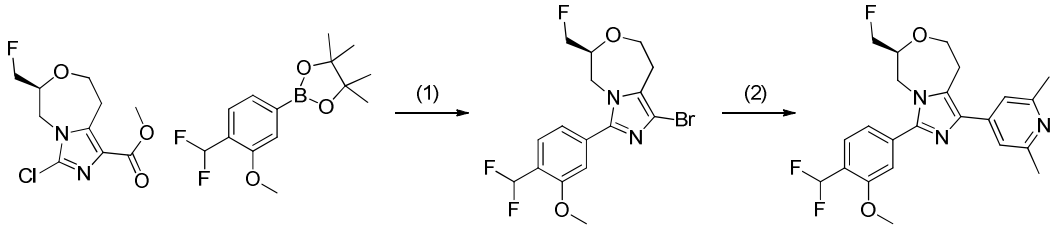
A mixture of the compound obtained in Example 27-(2) (28 mg, 0.069 mmol), 2,6-dimethyl-pyridine-4-boronic acid (20.9 mg, 0.138 mmol), tetrakis(triphenylphosphine)palladium(0) (8.0 mg, 0.0069 mmol), an aqueous sodium carbonate solution (1 M, 0.35 mL), and DME (0.70 mL) was stirred under microwave irradiation at 150°C for 30 minutes. Ethyl acetate was added to the mixture, then the mixture was filtered through a silica gel pad (NH silica gel), and then the filtrate was concentrated under reduced pressure. The resultant residue was purified by silica gel thin layer chromatography (ethyl acetate) to obtain a title compound (21.0 mg, 0.049 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.35(s,3H),2.56(s,6H),3.21(ddd,J=2.7, 11.3,16.4Hz,1H),3.41(dd,J=3.9,16.0Hz,1H),3.70(t,J=11.3Hz,1H),3.83-3.94(m,1H),4.05(d,J=9.0,14.8Hz,1H),4.28-4.46(m,2H),4.55(ddd,J=5.1,9.8,46.5Hz,1H),4.55(d,J=14.8Hz,1H),6.56 (t,J=73.4Hz,1H),7.17-7.21(m,1H),7.21(s,2H),7.33(d,J=2.1,8.4Hz,1H),7.47(d,J=2.0Hz,1H).

ESI-MS m/z 432 [M+H]+

[0246] Example 28

Synthesis of (S)-3-(4-(difluoromethyl)-3-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0247] (1) Synthesis of (S)-1-bromo-3-(4-(difluoromethyl)-3-methoxyphenyl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the methods of Examples 27-(1) and 27-(2), a title compound (107 mg, 0.264 mmol) was obtained from the compound obtained in Production Example 9 (140 mg, 0.533 mmol) and 2-(4-(difluoromethyl)-3-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (CAS No. 1310949-77-9; 267 mg, 0.940 mmol).

ESI-MS m/z 405, 407 [M+H]+ 427, 429 [M+Na]+

[0248] (2) Synthesis of (S)-3-(4-(difluoromethyl)-3-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

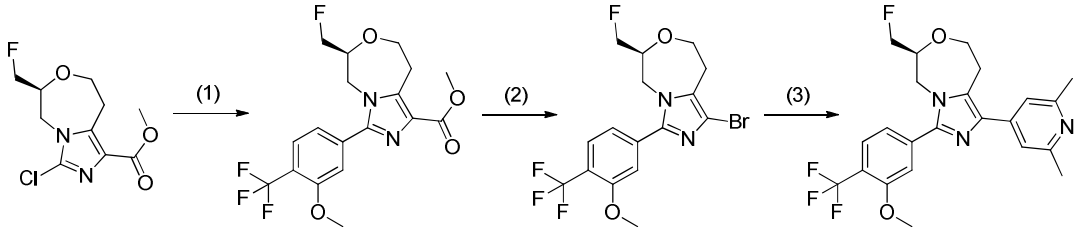
According to the method of Example 27-(3), a title compound (16 mg, 0.037 mmol) was obtained from the compound obtained in Example 28-(1) (21 mg, 0.052 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.57(s,6H),3.22(ddd,J=2.3,10.9,16.4Hz,1H),3.42(dd,J=3.7,16.2Hz,1H),3.71(t,J=11.3Hz,1H),3.84-3.96(m,1H),3.93(s,3H),4.06(dd,J=8.6,14.8,1H),4.28-4.66(m,4H),6.98(t,J=55.5Hz,1H),7.10-7.25(m,4H),7.67(d,J=7.8Hz,1H).

ESI-MS m/z 432 [M+H]+

[0249] Example 29

Synthesis of (S)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0250] (1) Synthesis of (S)-methyl 6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

A mixture of the compound obtained in Production Example 9 (202 mg, 0.769 mmol), 2-(3-methoxy-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (CAS No. 1004775-33-0; 465 mg, 1.54 mmol), tetrakis(triphenylphosphine)palladium(0) (89 mg, 0.077 mmol), and an aqueous sodium carbonate solution (1 M, 1.46 mL) in DME (3.08 mL) was stirred under microwave irradiation at 130°C for 30 minutes. Ethyl acetate and sodium chloride were added to the mixture. The organic layer was separated. The aqueous layer was extracted with ethyl acetate four times, and then the resultant organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a crude title compound (391 mg).

ESI-MS m/z 403 [M+H]+

[0251] (2) Synthesis of (S)-1-bromo-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

A solution of the compound obtained in Example 29-(1) (391 mg) and a 5 N aqueous sodium hydroxide solution (0.972 mL) in THF

(2.4 mL)/methanol (2.4 mL) was stirred at room temperature for 3 hours. The reaction mixture was neutralized with hydrochloric acid. The mixture was concentrated under reduced pressure and the resultant residue was azeotroped with toluene. DMF (2.4 mL), ethanol (2.4 mL), potassium carbonate (134 mg, 0.972 mmol), and NBS (346 mg, 1.94 mmol) were added to the residue at room temperature. The reaction mixture was stirred at room temperature for 20 hours. NBS (346 mg, 1.94 mmol) was added to the reaction mixture and then the mixture was stirred for 5 hours. Sodium sulfite was added to the reaction mixture and ethanol was evaporated under reduced pressure. Ethyl acetate was added to the resultant solution and the mixture was washed with water five times and then with a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography to obtain a title compound (179 mg, 0.423 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):3.06(ddd,J=2.7,10.9,16.0Hz,1H),3.14(ddd,J=1.6,3.9,16.4Hz,1H),3.66(ddd,J=1.4,10.9,12.3Hz,1H),3.79-3.89(m,1H),3.95(s,3H),4.02(dd,J=8.6,14.8Hz,1H),4.25-4.42(m,2H),4.53(ddd,J=4.7,9.4,46.1Hz,1H),4.59(d,J=15.6Hz,1H),7.03(d,J=7.8Hz,1H),7.22(s,1H),7.64(d,J=7.8Hz,1H).

ESI-MS m/z 423, 425 [M+H]+ 445, 447 [M+Na]+

[0252] (3) Synthesis of (S)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

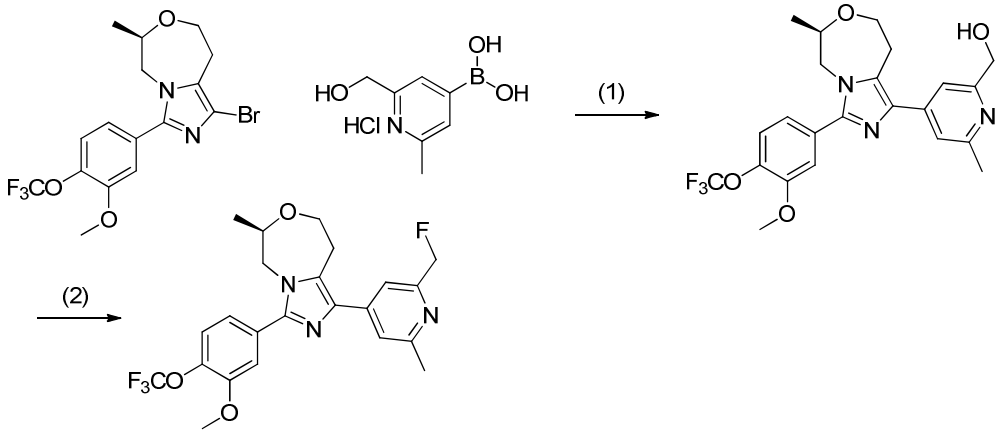
A mixture of the compound obtained in Example 29-(2) (26 mg, 0.061 mmol), 2,6-dimethyl-pyridine-4-boronic acid (18.6 mg, 0.123 mmol), tetrakis(triphenylphosphine)palladium(0) (7.1 mg, 0.0061 mmol), an aqueous sodium carbonate solution (1 M, 0.40 mL), and DME (0.80 mL) was stirred under microwave irradiation at 150°C for 30 minutes. Ethyl acetate was added to the mixture, and then the mixture was filtered through a silica gel pad (NH silica gel) and concentrated under reduced pressure. The resultant residue was purified by silica gel thin layer chromatography (ethyl acetate) to obtain a title compound (17.3 mg, 0.038 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.57(s,6H),3.21(ddd,J=2.7,11.3,16.4Hz,1H)3.42(dd,J=4.1,16.2Hz,1H),3.71(t,J=11.7Hz,1H),3.87-3.99(m,1H),3.97(s,3H),4.07(dd,J=9.0,14.8Hz,1H),4.28-4.47(m,2H),4.57(ddd,J=4.5,9.6,46.1Hz,1H),4.62(d,J=14.4Hz,1H),7.10(d,J=7.8Hz,1H),7.21(s,2H),7.26(s,1H),7.67(d,J=7.8Hz,1H).

ESI-MS m/z 450 [M+H]+

[0253] Example 30

Synthesis of (R)-1-(2-(fluoromethyl)-6-methylpyridin-4-yl)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0254] (1) Synthesis of (R)-(4-(3-(3-methoxy-4-(trifluoromethoxy)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepin-1-yl)-6-methylpyridin-2-yl)methanol

According to the method of Example 1-(5), a title compound (7.1 mg, 0.015 mmol) was obtained from the compound obtained in Example 24-(2) (39 mg, 0.093 mmol) and the compound obtained in Production Example 23 (37.7 mg, 0.185 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.28(d,J=6.6Hz,3H),2.59(s,3H),3.20(ddd,J=2.3,10.5,16.0Hz,1H),3.37(dd,J=4.1,16.2Hz,1H),3.67(t,J=11.3Hz,1H),3.76-3.84(m,1H),3.95(s,3H),4.00(dd,J=8.6,14.8Hz,1H),4.23(ddd,J=2.3,5.1,12.5Hz,1H),4.28(d,J=14.8Hz,1H),4.75(s,2H),6.97(dd,2.0,8.2Hz,1H),7.25(d,J=1.6Hz,1H),7.26-7.29(m,1H),7.31-7.40(m,2H).

ESI-MS m/z 464 [M+H]+

[0255] (2) Synthesis of (R)-1-(2-(fluoromethyl)-6-methylpyridin-4-yl)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

DAST (12 μL, 0.091 mmol) was added to a solution of the

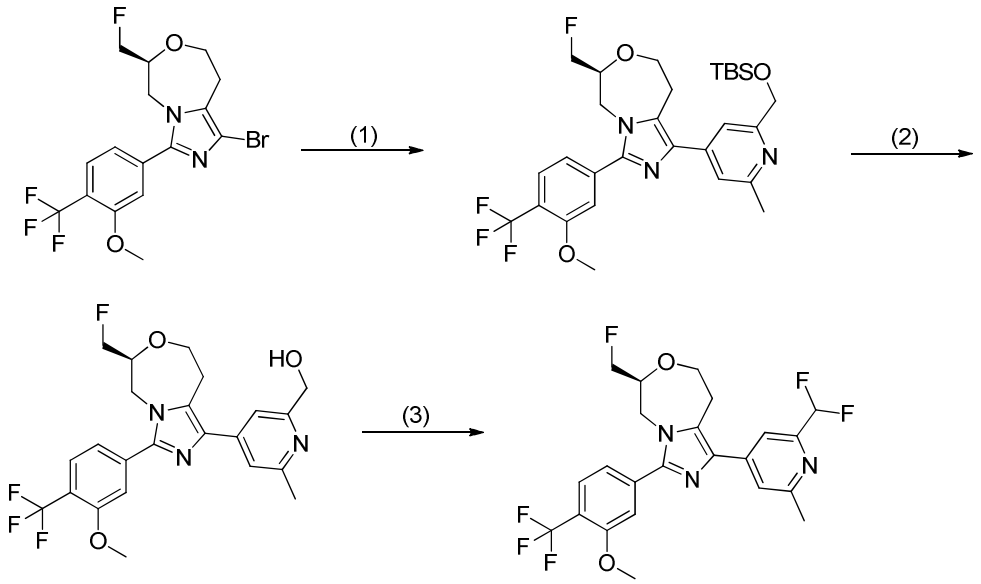
compound obtained in Example 30-(1) (7.1 mg, 0.015 mmol) in DCM (1.0 mL) at -78°C. The reaction solution was warmed to room temperature, stirred for 16 hours, and then filtered through a silica gel pad (NH silica gel). The filtrate was concentrated under reduced pressure, and then the resultant residue was purified by silica gel thin layer chromatography (ethyl acetate) to obtain a title compound (3.5 mg, 0.0075 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.28(d,J=6.6Hz,3H),2.58(s,3H),3.22(ddd,J=2.3,10.7,16.2Hz,1H),3.38(dd,J=4.7,16.4Hz,1H),3.68(dd,J=10.5,11.7Hz,1H),3.75-3.84(m,1H),3.95(s,3H),4.01(dd,J=8.2,14.8Hz,1H),4.24(ddd,J=2.3,4.7,12.1Hz,1H),4.28(d,J=14.4Hz,1H),5.49(d,J=46.9Hz,2H),6.98(dd,2.0,8.6Hz,1H),7.24-7.27(m,1H),7.31-7.36(m,1H),7.43(s,1H), 7.46(s,1H).

ESI-MS m/z 466 [M+H]+ 488 [M+Na]+

[0256] Example 31

Synthesis of (S)-1-(2-(difluoromethyl)-6-methylpyridin-4-yl)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0257] (1) Synthesis of (S)-1-(2-(((tert-butyldimethylsilyl)oxy)methyl)-6-methylpyridin-4-yl)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 1-(5), a crude title compound (148 mg, 0.255 mmol) was obtained from the compound obtained in Example 29-(2) (140 mg, 0.331 mmol) and the compound obtained in Production Example 24-(2) (162 mg, 0.446 mmol).

ESI-MS m/z 580 [M+H]+

[0258] (2) Synthesis of (S)-(4-(6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepin-1-yl)-6-methylpyridin-2-yl)methanol

TBAF (a 1 M THF solution, 0.373 mL, 0.373 mmol) was added to a solution of the compound obtained in Example 31-(1) (144 mg, 0.248 mmol) in THF (3 mL) at room temperature. The mixture was stirred at room temperature for 30 minutes, then ethyl acetate and water were added to separate the organic layer. The resultant

organic layer was washed with a saturated aqueous sodium chloride solution and then dried over anhydrous magnesium sulfate. The drying agent was filtered off and then the solvent was evaporated under reduced pressure. The resultant residue was purified by NH silica gel column chromatography (ethyl acetate) to obtain a title compound (88.0 mg, 0.189 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.60(s,3H),3.17-3.29(m,1H),3.42(dd,J=4.0,16.0Hz,1H),3.71(t,J=12.0Hz,1H),3.84-3.95(m,2H),3.97(s,3H),4.08(dd,J=8.0,16.0Hz,1H),4.28-4.66(m,4H),4.76(s,2H),7.10(d,J=7.8Hz,1H),7.24(s,1H),7.27(s,1H),7.33(s,1H),7.68(d,J=7.8Hz,1H).

[0259] (3) Synthesis of (S)-1-(2-(difluoromethyl)-6-methylpyridin-4-yl)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

DMPI (82.0 mg, 0.193 mmol) was added to a solution of the compound obtained in Example 31-(2) (60.0 mg, 0.129 mmol) in DCM (2.5 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 hour and then a saturated aqueous sodium thiosulfate solution, a saturated aqueous sodium bicarbonate solution and ethyl acetate were added to separate the organic layer. The resultant organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, the drying agent was filtered off, and then the solvent was evaporated under reduced pressure. The resultant residue was dissolved in DCM (2.5 mL), and DAST (0.043 mL, 0.32 mmol) was added

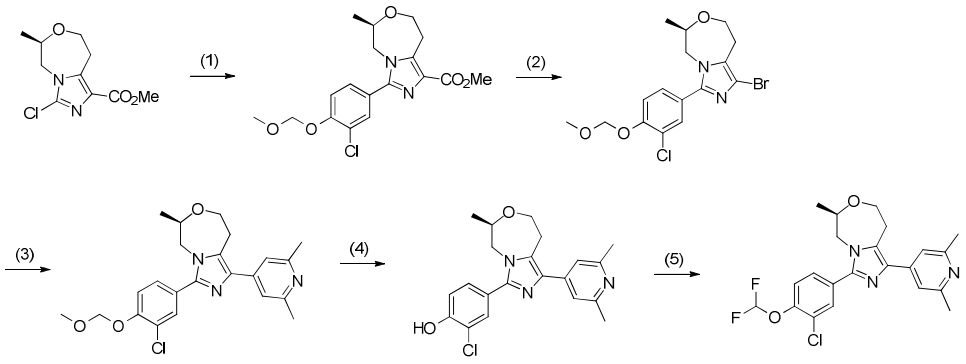
dropwise thereto at -20°C. The mixture was slowly warmed to room temperature, stirred for 3 hours, and then ice water, a saturated aqueous sodium bicarbonate solution, and ethyl acetate were added to the reaction mixture to separate the organic layer. The resultant organic layer was washed with a saturated aqueous sodium chloride solution and then dried over anhydrous magnesium sulfate, the drying agent was filtered off, and then the solvent was evaporated under reduced pressure. The resultant residue was purified by NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (55.3 mg, 0.114 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.63(s,3H),3.22-3.32(m,1H),3.42(dd,J=4.0,16.0Hz,1H),3.72(t,J=11.1Hz,1H),3.87-3.96(m,1H),3.97(s,3H),4.09(dd,J=8.6,14.8Hz,1H),4.29-4.66(m,4H),6.64(t,J=56.0Hz,1H),7.09-7.13(m,1H),7.25(s,1H),7.58(s,1H),7.63(s,1H),7.68(d,J=8.2Hz,1H).

ESI-MS m/z 486 [M+H]+.

[0260] Example 32

Synthesis of (R)-3-(3-chloro-4-(difluoromethoxy)phenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0261] (1) Synthesis of (R)-methyl 3-(3-chloro-4-(methoxymethoxy)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

A mixture of the compound obtained in Production Example 8-(3) (470 mg, 1.92 mmol), the compound obtained in Production Example 13 (688 mg, 2.31 mmol), tetrakis(triphenylphosphine)palladium(0) (166 mg, 0.144 mmol), an aqueous sodium carbonate solution (2 M, 1.92 mL) and DME (7.5 mL) was stirred under microwave irradiation at 130°C for 2 hours. The reaction mixture was cooled to room temperature and ethyl acetate and water were added to separate the organic layer. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (460 mg, 1.21 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.20-1.26(m,3H),3.02-3.17(m,1H),3.54(s,3H),3.59-3.77(m,2H),3.90(s,3H),3.92-4.09(m,2H),4.16-4.24(m,2H),5.31(s,2H),7.25(d,J=8.6Hz,1H),7.30(dd,J=2.1,8.6Hz,1H),7.57(d,J=2.1Hz,1H).

[0262] (2) Synthesis of (R)-1-bromo-3-(3-chloro-4-(methoxymethoxy)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

The compound obtained in Example 32-(1) (460 mg, 1.21 mmol) was dissolved in THF (5 mL) and methanol (5 mL), and a 5 N

aqueous sodium hydroxide solution (1.21 mL, 6.04 mmol) was added. The mixture was stirred at room temperature for 15 hours, neutralized with a 5 N hydrochloric acid, and concentrated under reduced pressure. The resultant residue was dissolved in ethanol (5 mL) and DMF (5 mL), potassium carbonate (167 mg, 1.21 mmol) and NBS (301 mg, 1.69 mmol) were added, and the mixture was stirred at room temperature for 2 hours. Sodium sulfite (1.22 g, 9.66 mmol), water, and ethyl acetate were added to the reaction mixture to separate the organic layer. The resultant organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (240 mg, 0.597 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.20-1.26(m,3H),2.91-3.01(m,1H),3.02-3.14(m,1H),3.54(s,3H),3.56-3.77(m,2H),3.84-4.01(m,1H),4.10-4.28(m,2H),5.30(s,2H),7.24(d,J=8.6Hz,1H),7.28(dd,J=2.0,8.6Hz,1H),7.53(d,J=2.0Hz,1H).

[0263] (3) Synthesis of (R)-3-(3-chloro-4-(methoxymethoxy)phenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

A mixture of the compound obtained in Example 32-(2) (200 mg, 0.498 mmol), 2,6-dimethylpyridine-4-boronic acid (120 mg, 0.797 mmol), tetrakis(triphenylphosphine)palladium(0) (43.2 mg, 0.0370 mmol), an aqueous sodium carbonate solution (2 M, 0.80 mL) and

DME (1.7 mL) was stirred under microwave irradiation at 120°C for 1 hour. The reaction mixture was cooled to room temperature and water and ethyl acetate were added to separate the organic layer. The resultant organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resultant residue was purified by NH silica gel column chromatography (n-heptane/ethyl acetate). The resultant was further purified by silica gel chromatography (ethyl acetate/methanol) to obtain a title compound (175 mg, 0.409 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.23-1.32(m,3H),2.55(s,6H),3.10-3.25(m,1H),3.29-3.40(m,1H),3.55(s,3H),3.60-3.71(m,1H),3.73-3.85(m,1H),3.91-4.04(m,1H),4.17-4.28(m,2H),5.31(s,2H),7.20(s,2H),7.27(d,J=8.6Hz,1H),7.33(dd,J=2.0, 8.6Hz,1H),7.59(d,J=2.0Hz,1H).

[0264] (4) Synthesis of (R)-2-chloro-4-[1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepin-3-yl]phenol

The compound obtained in Example 32-(3) (175 mg, 0.409 mmol) was dissolved in methanol (8 mL), a 5 N hydrochloric acid (0.818 mL, 4.09 mmol) was added at room temperature, and the mixture was stirred at 70°C for 3 hours. The reaction mixture was cooled to room temperature, and then a saturated aqueous sodium bicarbonate solution was added, and then the methanol was evaporated under reduced pressure. Ethyl acetate and water were added to the residue and the resultant solid was collected by filtration.

The resultant solid was dried under reduced pressure to obtain a crude title compound (360 mg).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.23-1.29(m,3H),2.55(s,6H),3.10-3.24(m,1H),3.29-3.40(m,1H),3.59-3.85(m,2H),3.90-4.04(m,1H),4.16-4.27(m,2H),7.10(d,J=8.2Hz,1H),7.20(s,2H),7.27(dd,J=2.0,8.2Hz,1H),7.56(d,J=2.0Hz,1H).

[0265] (5) Synthesis of (R)-3-(3-chloro-4-(difluoromethoxy)phenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

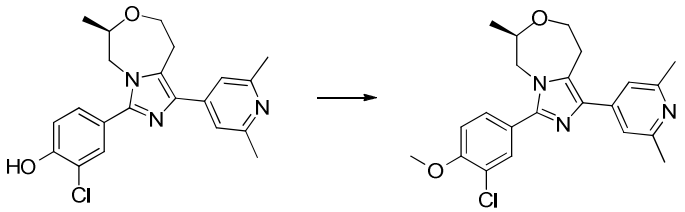
A mixture of a crude product of the compound obtained in Example 32-(4) (69 mg), sodium chlorodifluoroacetate (29.8 mg, 0.195 mmol), cesium carbonate (33.1 mg, 0.102 mmol), and water (35.2 μL, 1.95 mmol) in DMF (0.30 mL) was stirred at 80°C for 4 hours. The reaction mixture was cooled to room temperature and then water and ethyl acetate were added to separate the organic layer. The organic layer was dried over anhydrous magnesium sulfate and the solvent was concentrated under reduced pressure. The resultant residue was purified serially by NH silica gel column chromatography (n-heptane/ethyl acetate) and silica gel thin layer chromatography (ethyl acetate/methanol) to obtain a title compound (6.7 mg, 0.015 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.22-1.35(m,3H),2.56(s,6H),3.11-3.28(m,1H),3.29-3.43(m,1H),3.60-3.72(m,1H),3.73-3.88(m,1H),3.93-4.08(m,1H),4.14-4.29(m,2H),6.60(t,J=73.0Hz,1H),7.19(s,2H),7.35(d,J=8.4Hz,1H),7.40(dd,J=2.0,8.4Hz,1H),7.68(d,J=2.0Hz,1H).

ESI-MS m/z 434 [M+H]+

[0266] Example 33

Synthesis of (R)-3-(3-chloro-4-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0267] Cesium carbonate (34.0 mg, 0.104 mmol) was added to a mixture of the compound obtained in Example 32-(4) (46 mg), dimethyl sulfate (9.86 μL, 0.104 mmol) and DMF (0.3 mL), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with DCM and the resultant solid was separated through filtration. The filtrate was concentrated under reduced pressure and the resultant residue was purified by NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (8.1 mg, 0.020 mmol).

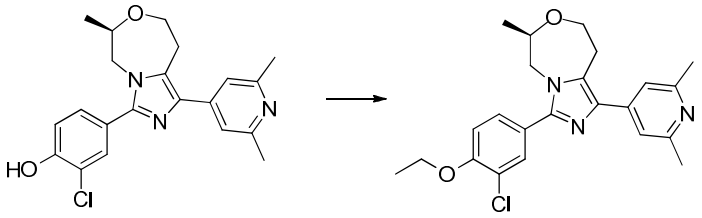
^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.23-1.35(m,3H),2.55(s,6H),3.10-3.24(m,1H),3.28-3.42(m,1H),3.59-3.71(m,1H),3.72-3.85(m,1H),3.89-4.05(m,1H),3.97(s,3H),4.16-4.29(m,2H),7.02(d,J=8.4Hz,1H),7.20(s,2H),7.38(dd,J=2.1,8.4Hz,1H),7.56(d,J=2.1Hz,1H).

ESI-MS m/z 398 [M+H]+

[0268] Example 34

Synthesis of (R)-3-(3-chloro-4-ethoxyphenyl)-1-(2,6-

dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



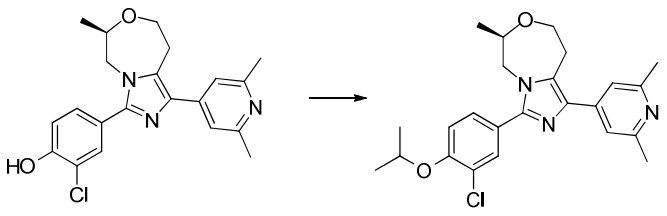
[0269] According to the method of Example 33, a title compound (10.6 mg, 0.026 mmol) was obtained from the compound obtained in Example 32-(4) (46 mg) and iodoethane (8.33 μL, 0.104 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.22-1.33(m,3H),1.51(t,J=7.0Hz,3H),2.55(s,6H),3.10-3.25(m,1H),3.29-3.42(m,1H),3.59-3.72(m,1H),3.72-3.84(m,1H),3.91-4.04(m,1H),4.17(q,J=7.0Hz,2H),4.17-4.28(m,2H),7.00(d,J=8.5Hz,1H),7.20(s,2H),7.35(dd,J=2.1,8.5Hz,1H),7.55(d,J=2.1Hz,1H).

ESI-MS m/z 412 [M+H]+

[0270] Example 35

Synthesis of (R)-3-(3-chloro-4-isopropoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0271] Cesium carbonate (50.9 mg, 0.156 mmol) was added to a

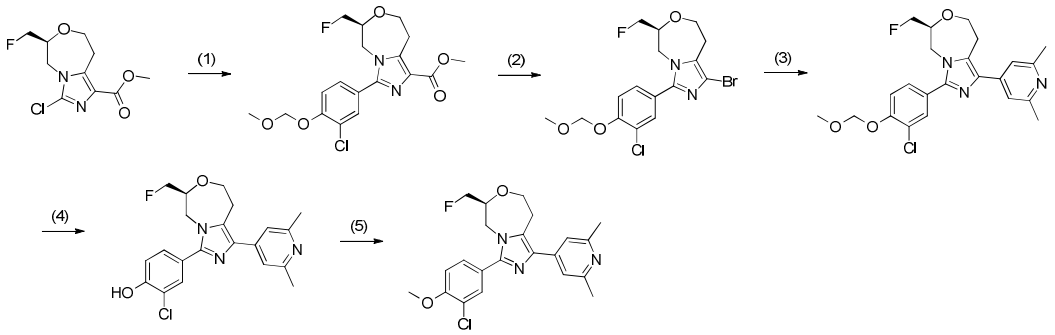
mixture of the compound obtained in Example 32-(4) (46 mg), 2-bromopropane (9.78 μL, 0.104 mmol) and DMF (0.3 mL). The reaction mixture was stirred at 100°C for 2 hours. The reaction mixture was cooled to room temperature and then diluted with DCM. The generated insolubles were separated through filtration and the filtrate was concentrated under reduced pressure. The resultant residue was purified by NH silica gel column chromatography (n-heptane/ethyl acetate) to obtain a title compound (12.0 mg, 0.028 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.24-1.30(m,3H),1.42(d,J=6.1Hz,6H),2.55(s,6H),3.09-3.25(m,1H),3.29-3.42(m,1H),3.59-3.71(m,1H),3.72-3.86(m,1H),3.88-4.04(m,1H),4.15-4.29(m,2H),4.63(sep,J=6.1Hz,1H),7.03(d,J=8.5Hz,1H),7.21(s,2H),7.35(dd,J=2.1,8.5Hz,1H),7.53(d,J=2.1Hz,1H).

ESI-MS m/z 426 [M+H]+

[0272] Example 36

Synthesis of (S)-3-(3-chloro-4-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0273] (1) Synthesis of (S)-methyl 3-(3-chloro-4-(methoxymethoxy)phenyl)-6-(fluoromethyl)-5,6,8,9-

tetrahydroimidazo[1,5-d][1,4]oxazepine-1-carboxylate

According to the method of Example 32-(1), a title compound (760 mg, 1.91 mmol) was obtained from the compound obtained in Production Example 9 (600 mg, 2.28 mmol) and the compound obtained in Production Example 13 (818 mg, 2.74 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):3.00-3.17(m,1H),3.54(s,3H),3.62-3.72(m,1H),3.73-3.86(m,1H),3.91(s,3H),3.99-4.10(m,1H),4.12-4.21(m,1H),4.23-4.66(m,4H),5.30(s,2H),7.25(d,J=8.6Hz,1H),7.31(dd,J=2.1,8.6Hz,1H),7.60(d,J=2.1Hz,1H).

[0274] (2) Synthesis of (S)-1-bromo-3-(3-chloro-4-(methoxymethoxy)phenyl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 32-(2), a title compound (530 mg, 1.26 mmol) was obtained from the compound obtained in Example 36-(1) (760 mg, 1.91 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.85-3.18(m,2H),3.54(s,3H),3.59-3.70(m,1H),3.73-3.87(m,1H),3.95-4.09(m,1H),4.19-4.63(m,4H),5.30(s,2H),7.25(d,J=8.6Hz,1H),7.29(dd,J=2.1,8.6Hz,1H),7.56(d,J=2.1Hz,1H).

[0275] (3) Synthesis of (S)-3-(3-chloro-4-(methoxymethoxy)phenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 32-(3), a title compound (154 mg, 0.345 mmol) was obtained from the compound obtained in Example 36-(2) (200 mg, 0.477 mmol) and 2,6-dimethylpyridine-4-

boronic acid (115 mg, 0.762 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.56(s,6H),3.11-3.30(m,1H),3.33-3.48(m,1H),3.55(s,3H),3.62-3.77(m,1H),3.79-3.95(m,1H),3.99-4.11(m,1H),4.24-4.69(m,4H),5.31(s,2H),7.20(s,2H),7.28(d,J=8.6Hz,1H),7.35(dd,J=2.2, 8.6Hz,1H),7.61(d,J=2.2Hz,1H).

[0276] (4) Synthesis of (S)-2-chloro-4-(1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepin-3-yl)phenol

According to the method of Example 32-(4), a crude title compound (330 mg) was obtained from the compound obtained in Example 36-(3) (154 mg, 0.345 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.56(s,6H),3.14-3.28(m,1H),3.34-3.47(m,1H),3.62-3.76(m,1H),3.78-3.94(m,1H),3.98-4.09(m,1H),4.24-4.67(m,4H),7.10(d,J=8.4Hz,1H),7.20(s,2H),7.30(dd,J=2.1,8.4Hz,1H), 7.58(d,J=2.1Hz,1H).

[0277] (5) Synthesis of (S)-3-(3-chloro-4-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 33, a title compound (5.1 mg, 0.012 mmol) was obtained from the compound obtained in Example 36-(4) (48 mg) and dimethyl sulfate (9.42 μL, 0.100 mmol).

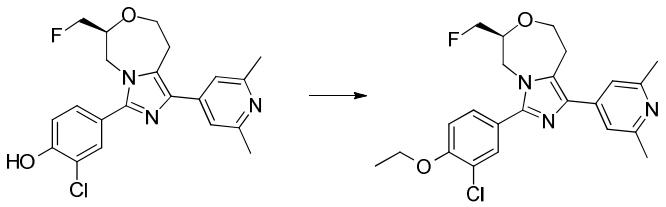
^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.56(s,6H),3.14-3.29(m,1H),3.33-3.44(m,1H),3.62-3.76(m,1H),3.79-3.92(m,1H),3.97(s,3H),4.00-4.10(m,1H),4.25-4.67(m,4H),7.03(d,J=8.6Hz,1H),7.20(s,2H),7.39(dd,J=2.1,8.6Hz,1H),

7.60(d,J=2.1Hz,1H).

ESI-MS m/z 416 [M+H]+

[0278] Example 37

Synthesis of (S)-3-(3-chloro-4-ethoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



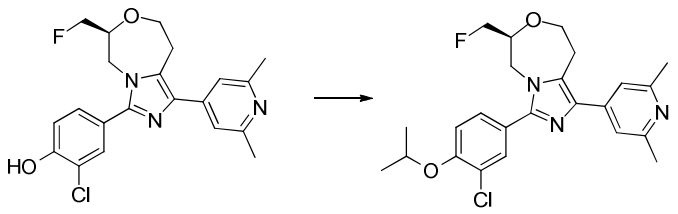
[0279] According to the method of Example 33, a title compound (8.8 mg, 0.020 mmol) was obtained from the compound obtained in Example 36-(4) (48 mg) and iodoethane (7.96 μL, 0.100 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.51(t,J=7.0Hz,3H),2.56(s,6H),3.11-3.29(m,1H),3.33-3.46(m,1H),3.60-3.77(m,1H),3.79-3.94(m,1H),3.98-4.10(m,1H),4.17(q,J=7.0Hz,2H),4.24-4.66(m,4H),7.01(d,J=8.6Hz,1H),7.20(s,2H),7.36(dd,J=2.1,8.6Hz,1H),7.59(d,J=2.1Hz,1H).

ESI-MS m/z 430 [M+H]+

[0280] Example 38

Synthesis of (S)-3-(3-chloro-4-isopropoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



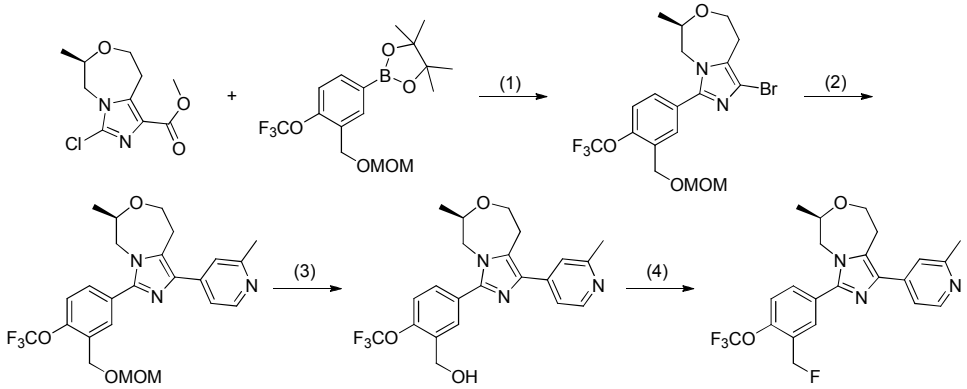
[0281] According to the method of Example 35, a title compound (14.0 mg, 0.032 mmol) was obtained from the compound obtained in Example 36-(4) (48 mg) and 2-bromopropane (9.35 μL, 0.100 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.42(d,J=6.1Hz,6H),2.56(s,6H),3.11-3.29(m,1H),3.33-3.48(m,1H),3.63-3.75(m,1H),3.78-3.95(m,1H),3.98-4.11(m,1H),4.24-4.63(m,4H),4.64(sep,J=6.1Hz,1H),7.03(d,J=8.6Hz,1H),7.20(s,2H),7.36(dd,J=2.2,8.6Hz,1H),7.57(d,J=2.2Hz,1H).

ESI-MS m/z 444 [M+H]+

[0282] Example 39

Synthesis of (R)-3-(3-(fluoromethyl)-4-(trifluoromethoxy)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0283] (1) Synthesis of (R)-1-bromo-3-(3-

((methoxymethoxy)methyl)-4-(trifluoromethoxy)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the methods of Examples 27-(1) and 18-(2), a title compound (101 mg, 0.217 mmol) was obtained from the compound obtained in Production Example 19 (370 mg, 1.02 mmol) and the compound obtained in Production Example 8-(3) (125 mg, 0.511 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.23(d,J=6.6Hz,3H),2.97(ddd,J=2.7,10.5,16.0Hz,1H),3.07(ddd,J=1.2,3.9,16.0Hz,1H),3.40(s,3H),3.61(ddd,J=1.6,10.5,12.5Hz,1H),3.67-3.79(m,1H),3.94(dd,J=8.4,14.6Hz,1H),4.14-4.27(m,2H),4.63-4.73(m,2H),4.74(s,2H),7.28-7.37(m,1H),7.43(dd,J=2.3,8.6Hz,1H),7.67(d,J=2.0Hz,1H).

ESI-MS m/z 465, 467 [M+H]+ 487, 489 [M+Na]+

[0284] (2) Synthesis of (R)-3-(3-((methoxymethoxy)methyl)-4-(trifluoromethoxy)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

According to the method of Example 1-(5), a title compound (46.8 mg, 0.098 mmol) was obtained from the compound obtained in Example 39-(1) (50.0 mg, 0.107 mmol) and 2-picoline-4-boronic acid (29.4 mg, 0.215 mmol).

ESI-MS m/z 478 [M+H]+

[0285] (3) Synthesis of (R)-(5-(6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepin-3-yl)-2-(trifluoromethoxy)phenyl)methanol

A solution of the compound obtained in Example 39-(2) (46.8

mg, 0.098 mmol) and CSA (68.3 mg, 0.294 mmol) in methanol (1.0 mL) was stirred and heated under reflux for 4 hours. The reaction mixture was cooled to room temperature, TEA (0.1 mL) was added, and then the mixture was concentrated under reduced pressure. The resultant residue was filtered through a silica gel pad (NH silica gel) and then the eluate was concentrated under reduced pressure. The resultant residue was purified by NH silica gel thin layer chromatography (ethyl acetate) to obtain a title compound (25.2 mg, 0.058 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.26(d,J=6.6Hz,3H),2.59(s,3H),3.20(ddd,J=2.3,10.5,16.4Hz,1H),3.36(dd,J=3.9,15.6,1H),3.59-3.73(m,1H),3.74-3.87(m,1H),4.00(dd,J=8.6,14.8Hz,1H),4.18-4.32(m,2H),4.80(s,2H),7.29-7.38(m,2H),7.43-7.52(m,2H),7.77(d,J=2.3Hz,1H),8.49(d,J=4.7Hz,1H).

ESI-MS m/z 434 [M+H]+

[0286] (4) Synthesis of (R)-3-(3-(fluoromethyl)-4-(trifluoromethoxy)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine

DAST (0.033 mL, 0.25 mmol) was added to a solution of the compound obtained in Example 39-(3) (21.3 mg, 0.049 mmol) and TEA (69 μL, 0.50 mmol) in DCM (1.0 mL) under ice-cooling. The reaction solution was warmed to room temperature, stirred for 20 hours, and then filtered through a silica gel pad (NH silica gel). The resultant solution was concentrated under reduced pressure and the residue was purified serially by silica gel thin layer chromatography

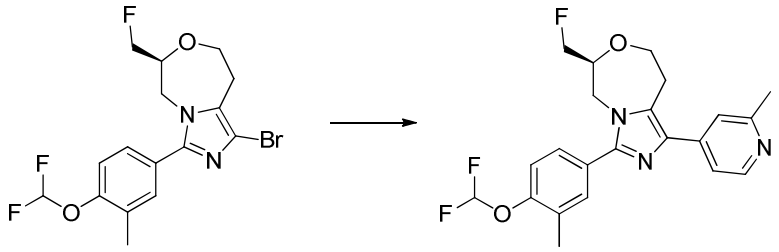
(ethyl acetate) and NH silica gel thin layer chromatography (n-heptane/ethyl acetate) to obtain a title compound (3.0 mg, 0.0069 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):1.28(d,J=6.6Hz,3H),2.59(s,3H),3.21(ddd,J=2.3,10.5,16.0Hz,1H),3.37(dd,J=4.3,16.0Hz,1H),3.68(t,J=11.1Hz,1H),3.76-3.87(m,1H),4.03(dd,J=8.6,14.8Hz,1H),4.19-4.28(m,2H),5.55(d,J=46.9Hz,2H),7.29(dd,J=1.4,5.3Hz,1H),7.37-7.43(m,1H),7.45(s,1H),7.58(dd,J=1.8,8.4Hz,1H),7.71(d,J=2.0Hz,1H),8.50(d,J=5.1Hz,1H).

ESI-MS m/z 436 [M+H]+

[0287] Example 40

Synthesis of (S)-3-(4-(difluoromethoxy)-3-methylphenyl)-6-(fluoromethyl)-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



[0288] According to the method of Example 39-(2), a title compound (18 mg, 0.043 mmol) was obtained from the compound obtained in Example 27-(2) (28 mg, 0.069 mmol).

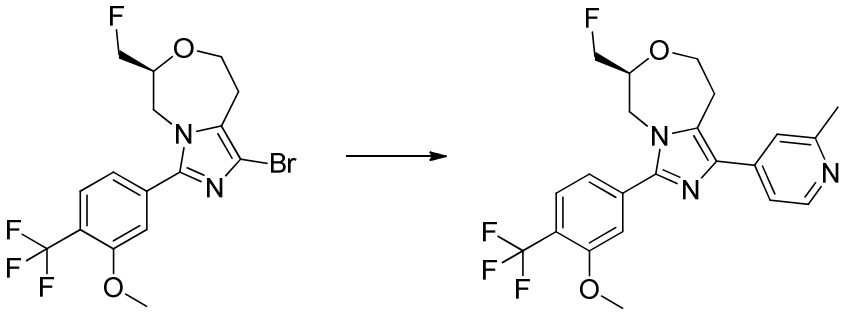
^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.35(s,3H),2.59(s,3H),3.22(ddd,J=2.3,10.9,16.0Hz,1H),3.41(dd,J=3.7,16.2Hz,1H),3.66-3.75(m,1H),3.83-3.95(m,1H),4.06(dd,J=8.6,14.8Hz,1H),4.28-

4.46(m,2H),4.55(ddd,J=4.7,9.8,46.1Hz,1H),4.56(d,J=14.8Hz,1H),6.57(t,J=73.4Hz,1H),7.19(d,J=8.2Hz,1H),7.29(dd,J=1.4,4.9Hz,1H),7.33(dd,J=2.3,8.6Hz,1H),7.45-7.48(m,2H),8.50(d,J=5.1Hz,1H).

ESI-MS m/z 418 [M+H]+

[0289] Example 41

Synthesis of (S)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine



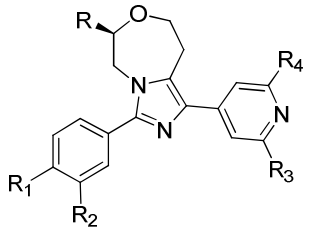
[0290] According to the method of Example 39-(2), a title compound (13 mg, 0.030 mmol) was obtained from the compound obtained in Example 29-(2) (26 mg, 0.061 mmol).

^{1}H-NMR(400MHz,CDCl3) δ(ppm):2.60(s,3H)3.19-3.29(m,1H)3.42(dd,J=4.3,16.4Hz,1H),3.72(t,J=11.9Hz,1H),3.86-4.00(m,4H)4.08(dd,J=9.0,14.8Hz,1H),4.28-4.47(m,2H),4.48-4.66(m,2H),7.11(d,J=8.2Hz,1H),7.26(d,J=4.7Hz,1H),7.30(d,J=5.1Hz,1H),7.46(s,1H),7.68(d,J=8.2Hz,1H),8.52(d,J=5.1Hz,1H).

ESI-MS m/z 436 [M+H]+

[0291] Each compound illustrated in Tables 1 to 7 was synthesized according to the method(s) of any of Examples described above.

[0292] [Table 1]



Example No.	R	R_1	R_2	R_3	R_4	ESI-MS $[M+H]^+$
42	H	OCF_3	H	CH_3	CH_3	404
43	H	OCF_3	H	H	CH_3	390
44	H	Cl	OCH_3	CH_3	CH_3	384
45	H	F	OCF_3	CH_3	CH_3	422
46	H	CH_3	OCH_3	CH_3	CH_3	364
47	CH_3	Cl	OCH_3	H	CH_2OH	400
48	H	Cl	OCF_3	CH_3	CH_3	438
49	H	OBn	F	CH_3	CH_3	444
50	CH_3	OCF_3	H	H	CH_3	404
51	CH_3	OCF_3	H	CH_3	CH_3	418
52	CH_3	Cl	CH_3	CH_3	CH_3	382
53	CH_3	CH_3	OCH_3	CH_3	CH_3	378
54	CH_3	Cl	CH_3	H	CH_3	368
55	CH_3	CH_3	OCH_3	H	CH_3	364
56	CH_3	Cl	F	CH_3	CH_3	386
57	CH_3	Cl	OCH_3	CH_3	OCH_3	414
58	CH_3	Cl	F	H	CH_3	372
59	CH_3	OCH_3	F	CH_3	CH_3	382
60	CH_3	OCH_3	F	H	CH_3	368
61	CH_3	Cl	H	CH_3	CH_3	368
62	CH_3	H	Cl	CH_3	CH_3	368
63	CH_3	H	Cl	H	CH_3	354
64	CH_3	H	OCF_3	CH_3	CH_3	418
65	CH_3	Cl	Cl	CH_3	CH_3	402
66	CH_3	Cl	Cl	H	CH_3	388
67	CH_3	OCF_3	CH_3	CH_3	CH_3	432
68	CH_3	Cl	OCF_3	CH_3	CH_3	452
69	CH_2F	OCF_3	H	CH_3	CH_3	436
70	CH_2F	OCF_3	H	H	CH_3	422

[0293] [Table 2]

Example No.	R	R_1	R_2	R_3	R_4	ESI-MS $[M+H]^+$
71	CH_2F	CH_3	OCH_3	CH_3	CH_3	396
72	CH_2F	CH_3	OCH_3	H	CH_3	382
73	CH_2F	Cl	CH_3	CH_3	CH_3	400
74	CH_2F	Cl	CH_3	H	CH_3	386
75	CH_2F	Cl	Cl	H	CH_3	406
76	CH_2F	Cl	Cl	CH_3	CH_3	420
77	CH_2CH_3	Cl	OCH_3	CH_3	CH_3	412
78	CH_2CH_3	Cl	OCH_3	H	CH_3	398
79	CHF_2	Cl	OCH_3	CH_3	CH_3	434
80	CH_3	CH_3	OCH_3	CH_3	CHF_2	414
81	CH_2F	CH_3	OCH_3	CH_3	CHF_2	432
82	CH_3	CF_3	OCH_2CH_3	CH_3	CH_3	446
83	CH_3	CF_3	OCH_2CH_3	H	CH_3	432
84	H	Cl	OCH_3	CH_3	CH_2F	402
85	CH_3	OCF_3	H	H	CH_2F	422
86	CH_3	OCF_3	H	CH_3	CH_2F	436
87	CH_3	Cl	F	CH_3	CH_2F	404
88	CH_3	Cl	CH_3	CH_3	CH_2F	400
89	CH_3	Cl	Cl	CH_3	CH_2F	420
90	CH_3	CH_3	OCH_3	CH_3	CH_2F	396
91	CH_2F	Cl	OCH_3	CH_3	CH_2F	434
92	H	F	OCH_2CHF_2	CH_3	CH_3	418
93	H	F	OCH_2CF_3	CH_3	CH_3	436
94	H	F		CH_3	CH_3	408
95	H	F	$OCH_2CH(CH_3)_2$	CH_3	CH_3	410
96	H	F	$OCH_2CH_2CH_3$	CH_3	CH_3	396
97	H	F		CH_3	CH_3	422
98	CH_3	F		CH_3	CH_3	436
99	CH_3	F		CH_3	CH_3	452
100	CH_3	F		H	CH_3	422
101	CH_3	CH_2CH_3	OCH_3	H	CH_3	378
102	H	Cl	OCH_2CH_3	CH_3	CH_3	398

[0294] [Table 3]

Example No.	R	R_1	R_2	R_3	R_4	ESI-MS $[M+H]^+$
103	H	Cl	Cl	CH_3	CH_3	388
104	H	OCF_3	CH_3	CH_3	CH_3	418
105	H	Cl	F	CH_3	CH_3	372
106	H	OCF_3	F	CH_3	CH_3	422
107	H	CF_3	F	CH_3	CH_3	406
108	H	Cl	CF_3	CH_3	CH_3	422
109	H	CF_3	Cl	CH_3	CH_3	422
110	H	Cl	CH_3	CH_3	CH_3	368
111	H	Cl	CN	CH_3	CH_3	379
112	H	OCF_3	Cl	CH_3	CH_3	438
113	H	CF_3	CH_3	CH_3	CH_3	402
114	CH_3	Cl	OCH_3	H	CH_3	384
115	H	OCF_3	CH_3	H	F	408
116	H	OCF_3	CN	CH_3	CH_3	429
117	H	OCF_3	OCH_3	CH_3	CH_3	434
118	H	OCF_3	CH_3	H	CH_3	404
119	H	$OCHF_2$	F	CH_3	CH_3	404
120	H	$OCHF_2$	F	H	CH_3	390
121	H	CHF_2	OCH_3	CH_3	CH_3	400
122	H	CF_3	OCH_3	CH_3	CH_3	418
123	H	CF_3	OCH_3	H	CH_3	404
124	CH_3	CF_3	CH_3	CH_3	CH_3	416
125	H	Cl	CHF_2	CH_3	CH_3	404
126	H	Cl	CHF_2	H	CH_3	390
127	H	$OCHF_2$	OCH_3	CH_3	CH_3	416
128	CH_3	CHF_2	OCH_3	CH_3	CH_3	414
129	CH_3	CF_3	Cl	CH_3	CH_3	436
130	CH_3	Cl	CN	CH_3	CH_3	393
131	CH_3	Cl	CHF_2	CH_3	CH_3	418
132	CH_3	CF_3	Cl	H	CH_3	422
133	CH_3	OCF_3	Cl	CH_3	CH_3	452
134	CH_3	CF_3	F	CH_3	CH_3	420
135	H		Cl	CH_3	CH_3	410
136	CH_3	F	OCH_3	CH_3	CH_3	382
137	H	CHF_2	Cl	CH_3	CH_3	404
138	CH_3	F	Cl	CH_3	CH_3	386
139	CH_3	CF_3	F	H	CH_3	406

[0295] [Table 4]

Example No.	R	R_1	R_2	R_3	R_4	ESI-MS $[M+H]^+$
140	CH_3	Cl	CF_3	CH_3	CH_3	436
141	CH_3	F	OCH_3	H	CH_3	368
142	CH_3	CF_3	H	CH_3	CH_3	402
143	CH_3	F	CF_3	CH_3	CH_3	420
144	H		OCF_3	CH_3	CH_3	460
145	CH_3	F	Cl	H	CH_3	372
146	CH_3	CHF_2	Cl	CH_3	CH_3	418
147	CH_3	OCF_3	F	CH_3	CH_3	436
148	CH_3	$OCHF_2$	OCH_3	CH_3	CH_3	430
149	CH_3	$OCHF_2$	OCH_3	H	CH_3	416
150	CH_3	OCF_3	F	H	CH_3	422
151	CH_3	F	CF_3	H	CH_3	406
152	CH_3	Cl	CF_3	H	CH_3	422
153	CH_3	OCF_3	Cl	H	CH_3	438
154	CH_3	OCH_3	OCF_3	CH_3	CH_3	448
155	CH_3	OCH_3	OCF_3	H	CH_3	434
156	CH_2F	CF_3	OCH_3	CH_3	CH_2OH	466
157	CH_3	F	OCF_3	CH_3	CH_3	436
158	CH_3	F	OCF_3	H	CH_3	422
159	CH_3		Cl	H	CH_3	410
160	CH_2F	CHF_2	OCH_3	H	CH_3	418
161	CH_2F	OCF_3	CH_3	CH_3	CH_3	450
162	CH_2F	OCF_3	CH_3	H	CH_3	436
163	CH_2F	$OCHF_2$	OCH_3	CH_3	CH_3	448
164	CH_2F	$OCHF_2$	OCH_3	H	CH_3	434
165	CH_2F	OCF_3	F	CH_3	CH_3	454
166	CH_2F	OCF_3	F	H	CH_3	440
167	CH_2F		Cl	CH_3	CH_3	442
168	CH_3	OCF_3	CN	CH_3	CH_3	443
169	CH_3	OCF_3	CN	H	CH_3	429
170	CH_2F	OCF_3	F	CH_3	CH_2OH	470
171	CH_2F	F	Cl	CH_3	CH_3	404
172	CH_2F	F	Cl	H	CH_3	390
173	CH_2F	F	CF_3	CH_3	CH_3	438

[0296] [Table 5]

Example No.	R	R_1	R_2	R_3	R_4	ESI-MS $[M+H]^+$
174	CH_2F	F	CF_3	H	CH_3	424
175	CH_2F	OCH_3	OCF_3	CH_3	CH_3	466
176	CH_2F	Cl	OCH_3	CH_3	CHF_2	452
177	CH_3	$OCHF_2$	CH_3	CH_3	CH_2OH	430
178	CH_3	OCH_3	CH_3	CH_3	CHF_2	414
179	CH_3	OCF_3	CH_3	CH_3	CH_2OH	448
180	CH_3	OCF_3	F	CH_3	CH_2OH	452
181	CH_3	$OCHF_2$	F	CH_3	CH_3	418
182	CH_3	$OCHF_2$	F	H	CH_3	404
183	CH_3	CH_3	CF_3	CH_3	CH_3	416
184	CH_3	F	$OCHF_2$	CH_3	CH_3	418
185	CH_3	F	$OCHF_2$	H	CH_3	404
186	CH_2F	CF_3	CH_3	CH_3	CH_3	434
187	CH_2F	CF_3	CH_3	H	CH_3	420
188	CH_2F	$OCHF_2$	CH_3	CH_3	CHF_2	468
189	CH_3	CHF_2	OCH_3	CH_3	CHF_2	450
190	CH_3	OCH_3	Cl	CH_3	CHF_2	434
191	CH_2F	$OCHF_2$	CH_3	CH_3	CH_2OH	448
192	CH_3	$OCHF_2$	OCH_3	CH_3	CHF_2	466
193	CH_2F	$OCHF_2$	OCH_3	CH_3	CHF_2	484
194	CH_2F	$OCHF_2$	OCH_3	CH_3	CH_2OH	464
195	CH_2F	OCF_3	CN	CH_3	CH_3	461
196	CH_2F	OCF_3	CN	H	CH_3	447
197	CH_2F	CHF_2	Cl	CH_3	CH_3	436
198	H	OCF_3	CH_3	CH_3	CH_2F	436
199	CH_3	$OCHF_2$	CH_3	CH_3	CH_2F	432
200	CH_3	CF_3	OCH_3	CH_3	CH_2F	450
201	CH_2F	CF_3	OCH_3	CH_3	CH_2F	468
202	CH_2F	OCF_3	F	CH_3	CH_2F	472
203	CH_3	OCF_3	CN	CH_3	CH_2F	461
204	CH_3	OCF_3	CH_3	CH_3	CH_2F	450
205	CH_3		Cl	CH_3	CH_2F	442
206	CH_3	OCF_3	F	CH_3	CH_2F	454
207	CH_2F	$OCHF_2$	CH_3	CH_3	CH_2F	450

[0297] [Table 6]

Example No.	R	R_1	R_2	R_3	R_4	ESI-MS $[M+H]^+$
208	CH_3		CH_3	CH_3	CH_2F	422
209	CH_2F	$OCHF_2$	OCH_3	CH_3	CH_2F	466
210	CH_3	OCH_3	OCF_3	CH_3	CH_2F	466
211	H	OCF_3	CH_2F	CH_3	CH_3	436
212	H	Cl	$OCHF_2$	CH_3	CH_3	420
213	H	CH_2CH_3	OCH_2CH_3	CH_3	CH_3	392
214	H	CH_2CH_3	OCH_2CH_3	H	CH_3	378
215	H	$OCHF_2$	Cl	CH_3	CH_3	420
216	H	OCH_2CH_3	Cl	CH_3	CH_3	398
217	H		Cl	CH_3	CH_3	424
218	H	OCH_2CHF_2	Cl	CH_3	CH_3	434
219	CH_3	CH_2CH_3	OCH_2CH_3	H	CH_3	392
220	CH_3	CH_2CH_3	OCH_2CH_3	CH_3	CH_3	406
221	CH_3	CH_2CH_3		H	CH_3	418
222	CH_3	CH_2CH_3		CH_3	CH_3	432
223	CH_3	CH_3	OCH_2CH_3	H	CH_3	378
224	CH_3	CH_3		H	CH_3	404
225	CH_3	CH_3	OCH_2CH_3	CH_3	CH_3	392
226	CH_3	CH_3		CH_3	CH_3	418
227	CH_3	CH_3	$OCH_2CH(CH_3)_2$	CH_3	CH_3	420
228	CH_3	CH_3		CH_3	CH_3	462
229	CH_3	OCF_3	CH_2OH	CH_3	CH_3	448
230	CH_3	OCF_3	CH_2OH	H	CH_3	434
231	CH_3	OCF_3	CH_2F	CH_3	CH_3	450
232	CH_3		Cl	CH_3	CH_3	440
233	CH_2F	$OCHF_2$	Cl	CH_3	CH_3	452
234	CH_3	$OCHF_2$	CH_2F	CH_3	CH_3	432
235	CH_3	$OCHF_2$	CH_2OH	CH_3	CH_3	430

[0298] [Table 7]

Example No.	R	R_1	R_2	R_3	R_4	ESI-MS $[M+H]^+$
236	CH_3	$OCHF_2$	CH_2F	H	CH_3	418
237	CH_3	$OCHF_2$	CH_2OH	H	CH_3	416
238	CH_3	Cl	CH_2F	CH_3	CH_3	400
239	CH_3	OCH_2CH_2F	Cl	CH_3	CH_3	430
240	CH_3	CF_2CH_3	OCH_3	H	CH_3	414
241	CH_3	OCH_2CH_3	CH_3	CH_3	CH_3	392
242	CH_3	$OCH(CH_3)_2$	CH_3	CH_3	CH_3	406
243	CH_2F	OCH_2CH_3	CH_3	CH_3	CH_3	410
244	CH_2F	$OCH(CH_3)_2$	CH_3	CH_3	CH_3	424
245	CH_2F	OCH_3	CH_3	CH_3	CH_3	396

[0299] Test Example 1: Affinity to mGluR2

(Preparation of cell membrane fraction of HEK293 cells stably expressing human metabotropic glutamate receptor 2 (mGluR2))

HEK293 cells stably expressing human mGluR2 and human glutamate transporter SLC1A3 were cultured in a Dulbecco's modified Eagle's medium with 10% fetal bovine serum (50 units/mL of penicillin, 50 μg/mL of streptomycin, 60 μg/mL of geneticin, 400 μg/mL of hygromycin B and 2 mM of glutamine) at 37°C under 5% CO_2. Confluent cell cultures were washed twice with PBS(−), and then scraped off with a cell scraper, and subjected to centrifugal separation at 4°C and 1500 rpm for 5 minutes for collecting cells. The centrifuged sediment (cell pellet) was homogenized in a 20 mM HEPES buffer containing 10 mM EDTA (pH 7.4) by using sonicator and centrifuged at 4°C and 1500 x g for 30 minutes. The supernatant (soluble fraction) was subjected to the centrifugal separation at 4°C and 40,000 x g for 30 minutes, and thus, insoluble fraction was

obtained. After additional centrifugally washing the obtained fraction with 20 mM HEPES buffer containing 10 mM EDTA (pH 7.4), the pellet was centrifugally suspended with a 20 mM HEPES buffer containing 0.1 mM EDTA, and the cell membrane fraction was obtained by the centrifugal separation at 4°C and 40,000 x g for 30 minutes. The thus obtained cell membrane fraction was suspended in a 20 mM HEPES buffer containing 0.1 mM EDTA in a protein concentration of 3 mg/mL, which was stored at −80°C.

([^{35}S]GTPγS binding assay)

The frozen cell membrane fraction prepared as described above was thawed before use, and the resultant was diluted with a buffer for a binding assay (final concentrations: 20 mM HEPES, 100 mM NaCl, 1 mM $MgCl_2$, 3 μM GDP, 300 μg/mL saponin, 0.1% BSA). The compound of each example was added to a cell membrane fraction containing 1.8 to 3 μg/assay of membrane protein on a plate, followed by incubation at room temperature for 30 minutes. Thereafter, with glutamic acid (in a final concentration of 10 μM) added thereto, incubation was performed at room temperature for 15 minutes, and thereafter, [^{35}S]GTPγS (in a final concentration of 0.8 kBq) and 588 μg WGA-SPA beads were added thereto, followed by incubation at room temperature for 1 hour. After the incubation, the plate was subjected to the centrifugal separation at 2,500 rpm and room temperature, and then, membrane cell binding radioactivity was measured with a top count.

A [^{35}S]GTPγS binding amount obtained by performing the above-described reaction in the absence of glutamic acid was defined

as nonspecific binding, and a difference from a [^{35}S]GTPγS binding amount obtained in the presence of glutamic acid was defined as specific binding. On the basis of ratios of inhibiting the specific binding at various concentrations of the compounds of the respective examples, inhibition curves were obtained. Concentrations of the compounds of the respective examples at which the specific [^{35}S]GTPγS binding amount was suppressed by 50% (IC50 values) were calculated on the basis of the inhibition curves and shown in Tables 8 and 9.

[0300] [Table 8]

Example No.	GTPγS binding assay IC_{50} (nM)	Example No.	GTPγS binding assay IC_{50} (nM)	Example No.	GTPγS binding assay IC_{50} (nM)	Example No.	GTPγS binding assay IC_{50} (nM)
1	10.0	36	10.0	71	18.9	106	20.9
2	97.4	37	6.0	72	29.4	107	54.0
3	13.9	38	5.4	73	24.8	108	19.2
4	31.9	39	2.5	74	35.3	109	9.1
5	26.5	40	4.7	75	31.0	110	64.2
6	13.0	41	4.1	76	20.9	111	25.2
7	4.2	42	45.3	77	11.5	112	17.9
8	13.2	43	90.0	78	3.8	113	27.0
9	1.9	44	22.3	79	30.4	114	19.2
10	4.2	45	73.9	80	6.3	115	61.7
11	11.4	46	65.6	81	7.1	116	33.8
12	28.3	47	242.5	82	1.1	117	22.0
13	5.7	48	40.0	83	1.7	118	10.9
14	5.6	49	11.4	84	25.3	119	31.8
15	7.4	50	14.2	85	29.7	120	47.2
16	2.7	51	7.8	86	4.4	121	40.9
17	3.8	52	20.5	87	22.0	122	22.1
18	12.3	53	21.3	88	16.7	123	36.0
19	3.0	54	19.4	89	13.2	124	4.5
20	3.4	55	21.9	90	12.7	125	16.5
21	7.5	56	21.9	91	16.1	126	8.4
22	4.1	57	28.5	92	95.8	127	12.1
23	19.4	58	41.8	93	28.7	128	9.1
24	4.8	59	96.3	94	34.9	129	15.7
25	3.2	60	119.3	95	49.5	130	26.0
26	13.5	61	21.7	96	59.8	131	25.5
27	3.5	62	37.7	97	25.4	132	33.3
28	16.2	63	78.6	98	3.1	133	4.4
29	3.8	64	31.2	99	103.4	134	27.8
30	5.2	65	14.0	100	25.3	135	36.9
31	7.9	66	12.6	101	7.6	136	33.9
32	2.8	67	4.7	102	22.7	137	18.7
33	5.0	68	13.2	103	26.0	138	21.2
34	2.8	69	20.9	104	19.4	139	47.5
35	2.7	70	25.5	105	92.1	140	5.7

[0301] [Table 9]

Example No.	GTPγS binding assay IC_{50} (nM)	Example No.	GTPγS binding assay IC_{50} (nM)	Example No.	GTPγS binding assay IC_{50} (nM)	Example No.	GTPγS binding assay IC_{50} (nM)
141	51.9	168	4.2	195	3.7	222	17.2
142	20.2	169	4.6	196	3.8	223	16.7
143	13.6	170	43.1	197	15.1	224	50.4
144	27.7	171	26.7	198	13.2	225	3.9
145	45.5	172	38.3	199	5.2	226	10.5
146	22.2	173	19.2	200	4.4	227	22.0
147	10.5	174	24.3	201	2.4	228	82.0
148	9.6	175	18.5	202	14.0	229	18.0
149	18.9	176	38.8	203	4.9	230	19.8
150	18.1	177	29.4	204	4.0	231	2.4
151	26.4	178	17.8	205	5.3	232	9.7
152	14.5	179	17.9	206	18.7	233	2.0
153	3.0	180	100.5	207	6.0	234	1.9
154	6.7	181	16.1	208	4.7	235	21.7
155	19.2	182	19.3	209	5.1	236	2.9
156	7.3	183	7.4	210	4.7	237	30.3
157	12.7	184	13.7	211	27.1	238	36.8
158	44.6	185	19.5	212	72.5	239	11.9
159	5.0	186	19.3	213	10.7	240	46.9
160	24.1	187	19.3	214	21.0	241	2.9
161	4.0	188	20.8	215	58.1	242	2.4
162	5.0	189	15.1	216	48.0	243	1.7
163	15.8	190	42.2	217	60.6	244	1.8
164	36.8	191	30.3	218	78.8	245	5.2
165	9.4	192	5.0	219	7.9		
166	15.2	193	9.0	220	5.9		
167	1.8	194	108.5	221	26.7		

[0302] Test Example 2: Novel object recognition (NOR) test in rats

Six-week old male Long-Evans rats were used for this test. For 2 days before starting the test, the rats were acclimated to experimental operations such as administration and a test device (that is, a black or gray plastic cage with a width of 40 cm, a depth of 30

cm and a height of 45 cm). Each test compound was dissolved in a 0.1 N hydrochloric acid to be orally administered. Thirty minutes after the administration, scopolamine hydrobromide was intraperitoneally administered at a 0.3 mg/kg dose, so as to induce cognitive impairment. After another 30 minutes, each rat was acclimated in the test device for 3 minutes, and thereafter, two blocks in the same shape were put in the test device as acquisition trial, and exploring time for each block was measured for 5 minutes. Two hours after the acquisition trial, the rat was acclimated in the test device for 3 minutes, and thereafter, the same block as those used in the acquisition trial and a new block in a different shape were put in the cage for retention trial. The exploring time for each block was measured for 3 minutes, and a ratio of the exploring time for the newly used block to the sum of the exploring times for the respective blocks was calculated as a discrimination index. The thus obtained discrimination indexes were compared among a group of rats to which a medium alone was administered (medium group), a group of rats to which scopolamine alone was administered (scopolamine alone group) and a group of rats to which both the test compound and scopolamine were administered, so as to evaluate the action of the test compound on the novel object recognition function (cognitive function) of the rats.

Each discrimination index was shown as an average and a standard error. The statistical significance between the medium group and the scopolamine alone group was analyzed by the independent t-test. The statistical significance between the

scopolamine alone group and each sample group was analyzed by one-way analysis of variance and then by Dunnett's multiple comparison test. The significance level was set to 5% on both sides. If the discrimination index was significantly lower in the scopolamine alone group than in the medium group, it was determined that the cognitive impairment was sufficiently induced, and hence, the test compound was evaluated in the corresponding group. The analysis was carried out by using Prism 5 for Windows for Japanese, ver. 5.03.

A minimum effective dose at which a statistically significant difference was found between a group suffering from the cognitive impairment induced by scopolamine and a group treated with each compound is shown in Table 10.

[0303] [Table 10]

Example No.	Test dose (mg/kg, p.o.)	Minimum effective dose (mg/kg, p.o.)
1	0.3, 1, 3	3
7	0.3, 1	0.3
11	0.3, 1	>1*
14	1, 3	1
24	0.3, 1	1
44	0.3, 1, 3, 10	1
87	1, 3	3

* No statistically significant difference was found at the test dose.

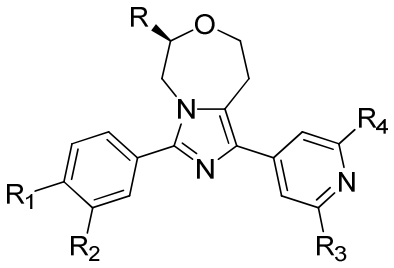
INDUSTRIAL APPLICABILITY

[0304] As described above, the tetrahydroimidazo[1,5-d][1,4]oxazepine derivative of the present invention or a pharmaceutically acceptable acid addition salt thereof is an antagonist against group II metabotropic glutamate receptor and showed an action to suppress downstream signaling of the mGluR2. Furthermore, the compound of the present invention showed an action

to improve the novel object recognition function in rats suffering from cognitive impairment induced by scopolamine. Accordingly, the compound of the present invention is applicable as a therapeutic agent for neurological disorders related to glutamate dysfunction and diseases involving the mGluR2, that is, a subtype of the metabotropic receptors, such as Alzheimer's disease.

WHAT IS CLAIMED IS:

1. A compound represented by the following formula (I) or a pharmaceutically acceptable acid addition salt thereof:



(I)

wherein R is a hydrogen atom or a C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms, wherein

when R is a hydrogen atom,

R_1 is a chlorine atom, a bromine atom, a trifluoromethyl group, an ethyl group, a trifluoromethoxy group, a methoxy group substituted with a phenyl group, a methoxy group substituted with a C_{3-8} cycloalkyl group, an ethoxy group optionally substituted with 1 to 3 fluorine atoms, or C_{3-8} cycloalkyloxy group,

R_2 is a fluorine atom, a chlorine atom, a methyl group optionally substituted with 2 to 3 fluorine atoms, a methoxy group optionally substituted with 1 to 3 fluorine atoms, or an ethoxy group optionally substituted with 1 to 3 fluorine atoms,

R_3 is a hydrogen atom or a methyl group, and

R_4 is a fluorine atom or a methyl group optionally substituted with 1 to 3 fluorine atoms, or

when R is a C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms,

R_1 is a hydrogen atom, a halogen atom, a C_{1-6} alkyl group

optionally substituted with 1 to 3 fluorine atoms, a C_{1-6} alkoxy group optionally substituted with 1 to 3 substituents selected from a fluorine atom and a C_{3-8} cycloalkyl group, a C_{3-8} cycloalkyloxy group, or a 4- to 6-membered heterocycloalkyloxy group,

R_2 is a hydrogen atom, a cyano group, a halogen atom, a C_{1-6} alkyl group optionally substituted with 1 to 3 substituents selected from a fluorine atom and a hydroxyl group, or a C_{1-6} alkoxy group optionally substituted with 1 to 3 substituents selected from a fluorine atom, a C_{3-8} cycloalkyl group and a 4- to 6-membered heterocycloalkyl group,

R_3 is a hydrogen atom or a C_{1-6} alkyl group, and

R_4 is a C_{1-6} alkyl group optionally substituted with 1 to 3 substituents selected from a fluorine atom and a hydroxyl group, or a C_{1-6} alkoxy group.

2. The compound or a pharmaceutically acceptable acid addition salt thereof according to claim 1, wherein

R is a C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms,

R_1 is a hydrogen atom, a halogen atom, a C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms, a C_{1-6} alkoxy group optionally substituted with 1 to 3 substituents selected from a fluorine atom and a C_{3-8} cycloalkyl group, a C_{3-8} cycloalkyloxy group, or a 4- to 6-membered heterocycloalkyloxy group,

R_2 is a hydrogen atom, a cyano group, a halogen atom, a C_{1-6} alkyl group optionally substituted with 1 to 3 substituents selected from a fluorine atom and a hydroxyl group, or a C_{1-6} alkoxy group

optionally substituted with 1 to 3 substituents selected from a fluorine atom, a C_{3-8} cycloalkyl group and a 4- to 6-membered heterocycloalkyl group,

R_3 is a hydrogen atom or a C_{1-6} alkyl group, and

R_4 is a C_{1-6} alkyl group optionally substituted with 1 to 3 substituents selected from a fluorine atom and a hydroxyl group, or a C_{1-6} alkoxy group.

3. The compound or a pharmaceutically acceptable acid addition salt thereof according to claim 2, wherein R is a methyl group, an ethyl group, a fluoromethyl group or a difluoromethyl group.

4. The compound or a pharmaceutically acceptable acid addition salt thereof according to claim 3,

wherein R_1 is a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, an ethyl group, a 1,1-difluoroethyl group, a methoxy group, a fluoromethoxy group, a difluoromethoxy group, a trifluoromethoxy group, an ethoxy group, a 2-fluoroethoxy group, a 2-propyloxy group, a cyclopropylmethoxy group, a cyclopropyloxy group or an (oxetan-3-yl)oxy group.

5. The compound or a pharmaceutically acceptable acid addition salt thereof according to claim 4,

wherein R_2 is a hydrogen atom, a cyano group, a fluorine atom, a chlorine atom, a methyl group, a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a hydroxymethyl group, an ethyl group, a methoxy group, a fluoromethoxy group, a difluoromethoxy group, a trifluoromethoxy group, an ethoxy group, a

2-fluoroethoxy group, a 2-propyloxy group, a cyclopropylmethoxy group, a cyclobutylmethoxy group or a (tetrahydro-2H-pyran-4-yl)methoxy group.

6. The compound or a pharmaceutically acceptable acid addition salt thereof according to claim 5, wherein R_3 is a hydrogen atom or a methyl group.

7. The compound or a pharmaceutically acceptable acid addition salt thereof according to claim 6, wherein R_4 is a methyl group, a fluoromethyl group, a difluoromethyl group, a hydroxymethyl group or a methoxy group.

8. The compound or a pharmaceutically acceptable acid addition salt thereof according to claim 2, wherein

R is a methyl group optionally substituted with 1 to 2 fluorine atoms,

R_1 is a hydrogen atom, a chlorine atom, a methyl group optionally substituted with 1 to 3 fluorine atoms, an ethyl group, a C_{1-6} alkoxy group optionally substituted with 1 to 3 fluorine atoms, or a C_{3-6} cycloalkyloxy group,

R_2 is a cyano group, a chlorine atom, a C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms, or a C_{1-6} alkoxy group optionally substituted with 1 to 3 fluorine atoms,

R_3 is a hydrogen atom or a methyl group, and

R_4 is a methyl group optionally substituted with 1 to 3 fluorine atoms.

9. The compound or a pharmaceutically acceptable acid addition salt thereof according to claim 2, wherein

R is a methyl group optionally substituted with 1 to 2 fluorine atoms,

R_1 is a hydrogen atom, a halogen atom, a C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms, a C_{1-6} alkoxy group optionally substituted with 1 to 3 fluorine atoms, or a C_{3-6} cycloalkyloxy group,

R_2 is a cyano group, a halogen atom, a C_{1-6} alkyl group optionally substituted with 1 to 3 fluorine atoms, or a C_{1-6} alkoxy group optionally substituted with 1 to 3 fluorine atoms,

R_3 is a methyl group, and

R_4 is a methyl group optionally substituted with 1 to 3 fluorine atoms, with a proviso that

when R_1 is an unsubstituted methoxy group, R_2 is not a fluorine atom.

10. A compound selected from the following compounds or a pharmaceutically acceptable acid addition salt thereof:

(R)-3-(4-chloro-3-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-1-(2,6-dimethylpyridin-4-yl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-6-methyl-3-(3-methyl-4-(trifluoromethoxy)phenyl)-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(4-(difluoromethoxy)-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(4-(difluoromethoxy)-3-methylphenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(3-chloro-4-cyclopropoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(4-cyclopropoxy-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(3-chloro-4-(difluoromethoxy)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-3-(4-cyclopropoxy-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-1-(2,6-dimethylpyridin-4-yl)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-3-(4-(difluoromethoxy)-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(3-chloro-4-(difluoromethoxy)phenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(3-chloro-4-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-me

thyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(3-chloro-4-ethoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-meth yl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(3-chloro-4-isopropoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-3-(3-chloro-4-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fl uoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-3-(3-chloro-4-ethoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluo romethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

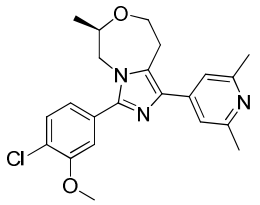
(S)-3-(3-chloro-4-isopropoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(R)-3-(3-(fluoromethyl)-4-(trifluoromethoxy)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine,

(S)-3-(4-(difluoromethoxy)-3-methylphenyl)-6-(fluoromethyl)-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine, and

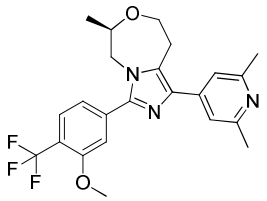
(S)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine.

11. (R)-3-(4-chloro-3-methoxyphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



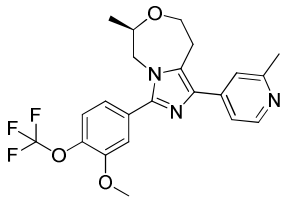
or a pharmaceutically acceptable acid addition salt thereof.

12. (R)-1-(2,6-dimethylpyridin-4-yl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



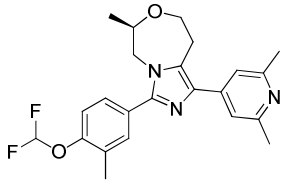
or a pharmaceutically acceptable acid addition salt thereof.

13. (R)-3-(3-methoxy-4-(trifluoromethoxy)phenyl)-6-methyl-1-(2-methylpyridin-4-yl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



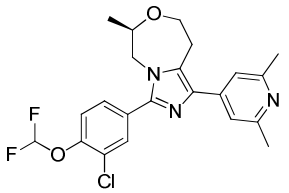
or a pharmaceutically acceptable acid addition salt thereof.

14. (R)-3-(4-(difluoromethoxy)-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



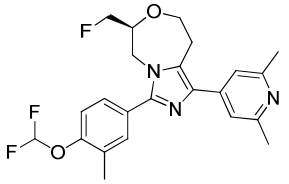
or a pharmaceutically acceptable acid addition salt thereof.

15. (R)-3-(3-chloro-4-(difluoromethoxy)phenyl)-1-(2,6-dimethylpyridin-4-yl)-6-methyl-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



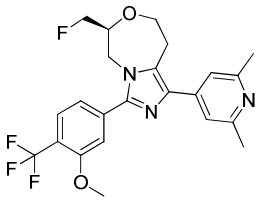
or a pharmaceutically acceptable acid addition salt thereof.

16. (S)-3-(4-(difluoromethoxy)-3-methylphenyl)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



or a pharmaceutically acceptable acid addition salt thereof.

17. (S)-1-(2,6-dimethylpyridin-4-yl)-6-(fluoromethyl)-3-(3-methoxy-4-(trifluoromethyl)phenyl)-5,6,8,9-tetrahydroimidazo[1,5-d][1,4]oxazepine represented by the following formula:



or a pharmaceutically acceptable acid addition salt thereof.

18. A pharmaceutical composition comprising the compound or a pharmaceutically acceptable acid addition salt according to any one of claims 1 to 17, and one or more pharmaceutically acceptable excipients.

19. The pharmaceutical composition according to claim 18, for treatment of a disease or symptom in which an antagonistic action against a group II metabotropic glutamate receptor is effective.

20. The pharmaceutical composition according to claim 19, wherein the disease or symptom is Alzheimer's disease.