

DESCRIPTION

BRANCHED CHAIN ALKYL HETEROAROMATIC RING DERIVATIVE

Technical Field

[0001]

- 5 The present invention relates to a compound having an orexin (OX) receptor antagonistic activity and a pharmaceutically acceptable salt thereof, and a therapeutic or preventive drug for disease such as sleep disorder, depression, anxiety disorder, panic disorder, schizophrenia, drug dependence, Alzheimer's disease, Parkinson's disease, Huntington's disease, eating disorder, headache, migraine, pain, gastrointestinal disease, epilepsy, inflammation,
- 10 immunological diseases, endocrine diseases or hypertension, containing such a compound or salt as an active ingredient.

Background Art

[0002]

- 15 Orexin is a neuropeptide spliced from prepro-orexin, which is expressed specifically in the lateral hypothalamic area. Up to date, OX-A composed of 33 amino acids and OX-B composed of 28 amino acids have been identified, both of which are involved in the regulation of sleep-wake pattern and the regulation of feeding.

[0003]

- 20 Both OX-A and OX-B act on OX receptors. Two subtypes, OX1 and OX2 receptors, of the OX receptors have been cloned so far, and both of which are known to be seven-transmembrane G protein-coupled receptors expressed mainly in the brain. OX1 receptor is coupled specifically with Gq among the G protein subclasses, whereas OX2 receptor is coupled with Gq and Gi/o (see Non Patent Literature 1 and Non Patent Literature 2).
- 25 Ox receptor subtypes are selectively expressed in the brain, and OX1 receptor is expressed in high density in the locus coeruleus, which is the nuclei originis of noradrenergic neurons, whereas OX2 receptor is expressed in high density in the tuberomammillary nucleus, which is the nuclei originis of histaminergic neuron (see Non Patent Literature 3, Non Patent Literature 4 and Non Patent Literature 5). The expression of both OX1 receptor and OX2
- 30 receptor are found in the raphe nucleus, which is the nuclei originis of serotonergic neuron, and in the ventral tegmental area, which is the nuclei originis of dopaminergic neuron (see Non Patent Literature 3). The orexin neurons project to the monoaminergic neuron at the brain stem

and the hypothalamus and have excitatory effects to these neurons, and further the expression of OX2 receptor is also found in the cholinergic neuron at the brain stem responsible for regulating REM sleep and have effects to the nucleus activities thereof (see Non Patent Literature 3 and Non Patent literature 4).

5 [0004]

In recent years, OX1 and OX2 receptors are focused on the role of the sleep-wake regulation, and the usefulness of OX receptor antagonists have been studied. When OX-A is intracerebroventricularly administered to a rat, increased spontaneous locomotor activity (see Non Patent Literature 6 and Non Patent Literature 7), increased stereotyped behavior (see Non
10 Patent Literature 7), increased time spent awake (see Non Patent Literature 6), and the like, were observed. Decreased REM sleep produced by OX-A administration is completely antagonized by the pretreatment of an OX receptor antagonist (see Non Patent Literature 8). Further, it is reported that locomotor activity is reduced, sleep latency is decreased, and amounts of non-REM sleep and REM sleep are increased by administering an orally available OX1 and OX2 receptors
15 antagonist (see Non Patent Literature 9 and Non Patent Literature 10).

Patent Literature 1 discloses a pyrazole derivative as the compound having OX receptor antagonistic activities but does not disclose the compound having the pyrazole-branched chain alkylamide skeleton as described in the present application. Also, compounds, for example, having various structures described in Non Patent Literature 11 are generally known as
20 OX receptor antagonists but the compounds having the heteroaromatic ring-branched chain alkylamide skeleton described in the present application are not disclosed. Meanwhile, Patent Literature 2 discloses compounds having a pyrazole-ethylamide skeleton and Patent Literature 3 discloses compounds having a heteroaromatic ring-branched chain alkylamide skeleton but Patent Literature 2 and Patent literature 3 do not disclose the OX receptor antagonistic activities
25 or the compounds having the heteroaromatic ring-branched chain alkylamide skeleton described in the present application.

Citation List

Patent Literature

30 [0005]

Patent Literature 1: WO2003/002559

Patent Literature 2: WO2008/062878

Patent Literature 3: WO2011/051540

[0006]

Non Patent Literature 1: Zhu Y et al., J. Pharmacol. Sci., 92, 259-266, 2003.

Non Patent Literature 2: Zeitzer JM et al., Trends Pharmacol. Sci., 27, 368-374, 2006.

Non Patent Literature 3: Marcus JN et al., J. Comp. Neurol., 435, 6-25, 2001.

Non Patent Literature 4: Trivedi JP et al., FEBS Lett., 438, 71-75, 1998.

- 5 Non Patent Literature 5: Yamanaka A et al., Biochem. Biophys. Res. Commun., 290, 1237-1245, 2002.

Non Patent Literature 6: Hagan JJ et al., Proc. Natl. Acad. Sci. USA, 96, 10911-10916, 1999.

Non Patent Literature 7: Nakamura T et al., Brain Res., 873, 181-187, 2000.

Non Patent Literature 8: Smith MI et al., Neurosci. Lett., 341, 256-258, 2003.

- 10 Non Patent Literature 9: Brisbare-Roch C et al., Nat. Med., 13, 150-155, 2007.

Non Patent Literature 10: Cox CD et al., J. Med. Chem., 53, 5320-5332, 2010.

Non Patent Literature 11: John G et al., ChemMedChem., 5, 1197-1214, 2010.

Summary of Invention

15 Technical Problem

[0007]

- An object of the present invention is to find a novel compound which has an OX receptor antagonistic activity and provide a therapeutic or preventive drug for disease such as sleep disorder, depression, anxiety disorder, panic disorder, schizophrenia, drug dependence,
- 20 Alzheimer's disease, Parkinson's disease, Huntington's disease, eating disorder, headache, migraine, pain, gastrointestinal disease, epilepsy, inflammation, immunological diseases, endocrine related disease or hypertension. More specifically, the object of the present invention is to provide a novel compound which exhibits good pharmacokinetics and safety together with a good OX receptor antagonistic activity.

25

Solution to Problems

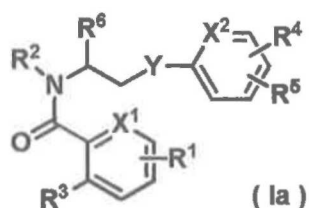
[0008]

- The present inventors extensively studied on novel skeleton compounds having an antagonistic activity against orexin receptors and found that certain branched chain alkyl
- 30 heteroaromatic ring derivatives represented by the following formulae have good OX receptor antagonistic activities, whereby the present invention was accomplished.

Hereinafter, the present invention is described in detail. The aspects of the present invention (hereinafter referred to as "compound of the present invention") are as follows.

- (1) A compound represented by formula (Ia):

[Formula 1]

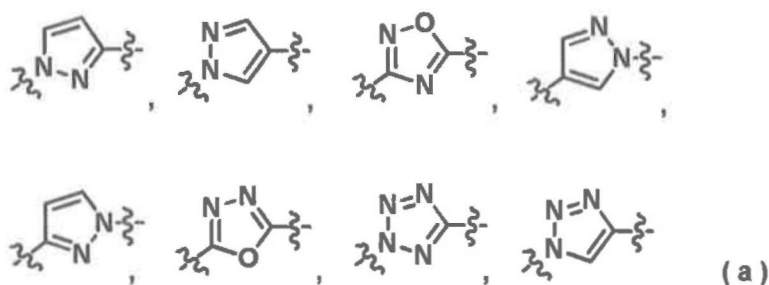


wherein,

X¹ and X² are the same or different and represent a nitrogen atom or a formula CH;

5 Y represents any of the structures in a following formula group (a):

[Formula 2]

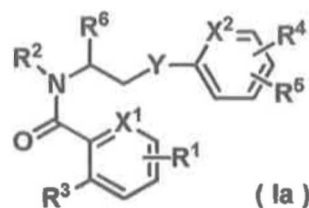
R¹ represents a hydrogen atom, a halogen atom or a C₁₋₆ alkyl group;R² represents a C₁₋₆ alkyl group (the C₁₋₆ alkyl group may optionally be substituted with one10 substituent selected from the group consisting of a hydroxy group, a C₁₋₆ alkoxy group, a C₁₋₆ alkylsulfonyl group, a diC₁₋₆ alkylamino group and a cyano group);R³ represents a triazolyl group or a pyrimidinyl group;R⁴ and R⁵ are the same or different and represent a hydrogen atom, a halogen atom, a C₁₋₆ alkyl group, a hydroxyl group or a C₁₋₆ alkoxy group; and15 R⁶ represents a C₁₋₆ alkyl group;

or a pharmaceutically acceptable salt thereof.

(2) A compound represented by formula (Ia):

[0009]

[Formula 3]



20

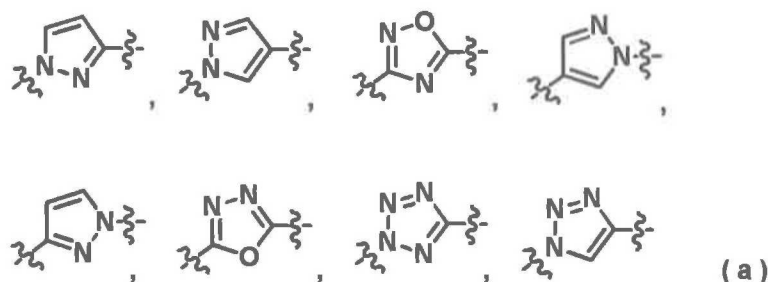
wherein,

X¹ and X² are the same or different and represent a nitrogen atom or a formula CH;

Y represents any of the structures in a following formula group (a):

[0010]

[Formula 4]



R^1 represents a hydrogen atom, a halogen atom or a C_{1-6} alkyl group;

- 5 R^2 represents a C_{1-6} alkyl group (the C_{1-6} alkyl group may optionally be substituted with one substituent selected from the group consisting of a hydroxy group and a C_{1-6} alkoxy group);

R^3 represents a triazolyl group or a pyrimidinyl group;

R^4 represents a halogen atom;

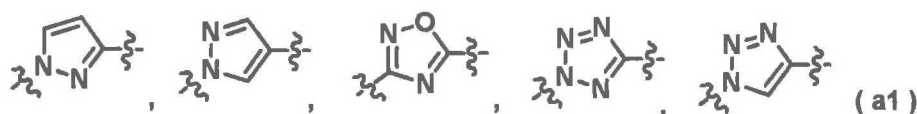
R^5 represents a hydrogen atom or a halogen atom; and

- 10 R^6 represents a C_{1-6} alkyl group;
or a pharmaceutically acceptable salt thereof.

(3) The compound or a pharmaceutically acceptable salt thereof according to (1) or (2), wherein Y in the above formula (Ia) is any of the structures in a following formula group (a1):

15 [0011]

[Formula 5]



- (4) The compound or a pharmaceutically acceptable salt thereof according to any one of (1) to (3), wherein R^1 in the above formula (Ia) is a hydrogen atom, a fluorine atom or a methyl group.

- (5) The compound or a pharmaceutically acceptable salt thereof according to any one of (1) to (4), wherein R^2 in the above formula (Ia) is a methyl group or an ethyl group (the ethyl group may optionally be substituted with one substituent selected from the group consisting of a hydroxyl group and a methoxy group).

- 25 (6) The compound or a pharmaceutically acceptable salt thereof according to any one of (1) to (5), wherein R^4 in the above formula (Ia) is a fluorine atom.

- (7) The compound or a pharmaceutically acceptable salt thereof according to any one of (1) to (6), wherein R^5 in the above formula (Ia) is a hydrogen atom or a fluorine atom.

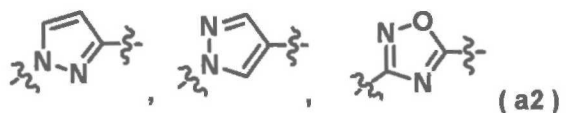
(8) The compound or a pharmaceutically acceptable salt thereof according to any one of (1) to (7), wherein R^6 in the above formula (Ia) is a C_{1-3} alkyl group.

(9) The compound or a pharmaceutically acceptable salt thereof according to any one of (1) to (8), wherein Y in the above formula (Ia) is any of the structures in a following formula

5 group (a2):

[0012]

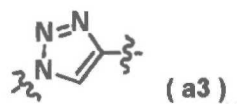
[Formula 6]



(10) The compound or a pharmaceutically acceptable salt thereof according to any one of (1) to (8), wherein Y in the above formula (Ia) is a following formula (a3):

[0013]

[Formula 7]



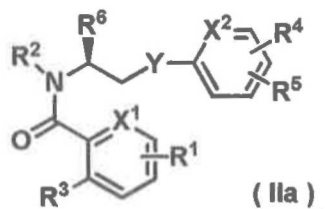
(11) The compound or a pharmaceutically acceptable salt thereof according to any one of (1) to (10), wherein R^2 in the above formula (Ia) is an ethyl group.

(12) The compound or a pharmaceutically acceptable salt thereof according to any one of (1) to (11), wherein R^6 in the above formula (Ia) is a methyl group.

(13) The compound or a pharmaceutically acceptable salt thereof according to any one of (1) to (12), wherein the above formula (Ia) is represented by formula (IIa):

20 [0014]

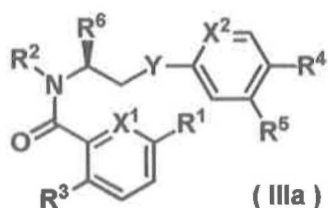
[Formula 8]



(14) The compound or a pharmaceutically acceptable salt thereof according to any one of (1) to (13), wherein the above formula (Ia) is represented by formula (IIIa):

25 [0015]

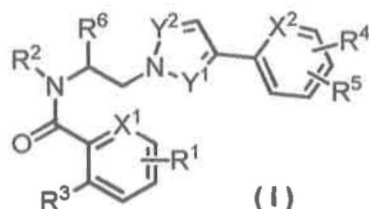
[Formula 9]



(15) A compound represented by formula (I):

[0016]

5 [Formula 10]



wherein,

X^1 and X^2 are the same or different and represent a nitrogen atom or a formula CH;
either one of Y^1 and Y^2 represents a nitrogen atom, and the other represents CH;

10 R^1 represents a hydrogen atom, a halogen atom or a C_{1-6} alkyl group;

R^2 represents a C_{1-6} alkyl group;

R^3 represents a triazolyl group or a pyrimidinyl group;

R^4 represents a halogen atom;

R^5 represents a hydrogen atom or a halogen atom; and

15 R^6 represents a C_{1-6} alkyl group;

or a pharmaceutically acceptable salt thereof.

(16) The compound or a pharmaceutically acceptable salt thereof according to (15),
wherein R^1 in the above formula (I) is a hydrogen atom, a fluorine atom or a methyl group.

(17) The compound or a pharmaceutically acceptable salt thereof according to any of

20 (15) or (16), wherein R^2 in the above formula (I) is a methyl group or an ethyl group.

(18) The compound or a pharmaceutically acceptable salt thereof according to any one
of (15) to (17), wherein R^4 in the above formula (I) is a fluorine atom.

(19) The compound or a pharmaceutically acceptable salt thereof according to any one
of (15) to (18), wherein R^5 in the above formula (I) is a hydrogen atom or a fluorine atom.

25 (20) The compound or a pharmaceutically acceptable salt thereof according to any one
of (15) to (19), wherein R^6 in the above formula (I) is a C_{1-3} alkyl group.

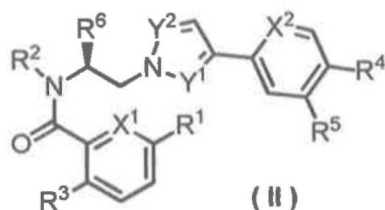
(21) The compound or a pharmaceutically acceptable salt thereof according to any one

of (15) to (20), wherein R^6 in the above formula (I) is a methyl group.

(22) The compound or a pharmaceutically acceptable salt thereof according to any one of (15) to (21), wherein the above formula (I) is represented by formula (II):

[0017]

5 [Formula 11]



(23) The compound or a pharmaceutically acceptable salt thereof according to (1) above, which is a species or a mixture of two or more species selected from:

- N-ethyl-N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- 10 N-ethyl-N-{(2R)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- N-ethyl-N-{(2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,
- 15 N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-N-methyl-2-(pyrimidin-2-yl)benzamide,
- 5-fluoro-N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-N-methyl-2-(pyrimidin-2-yl)benzamide,
- N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-N,5-dimethyl-2-(pyrimidin-2-yl)benzamide,
- 20 N-ethyl-N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide,
- N-ethyl-5-fluoro-N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide,
- 25 N-ethyl-N-{(2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide,
- N-ethyl-5-fluoro-N-{(2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide,
- N-ethyl-2-fluoro-N-{(2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-6-(pyrimidin-2-yl)benzamide,
- 30 N-ethyl-4-fluoro-N-{(2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-2-(pyrimidin-2-

yl)benzamide,

N-ethyl-N-((2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-6-methyl-3-(pyrimidin-2-yl)pyridine-2-carboxamide,

N-((2S)-1-[3-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-ethyl-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,

N-((2S)-1-[3-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-ethyl-5-fluoro-2-(pyrimidin-2-yl)benzamide,

N-ethyl-N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide,

10 N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

15 N-ethyl-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]butan-2-yl)-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

20 N-ethyl-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-((2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,

25 N-((2S)-1-[4-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-ethyl-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,

N-((2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N,6-dimethyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,

N-((2S)-1-[4-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N,6-dimethyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,

30 N-ethyl-5-fluoro-N-((2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide,

N-((2S)-1-[4-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-ethyl-5-fluoro-2-(pyrimidin-2-yl)benzamide,

5-fluoro-N-((2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-methyl-2-(pyrimidin-

- 2-yl)benzamide,
 N-((2S)-1-[4-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-5-fluoro-N-methyl-2-(pyrimidin-2-yl)benzamide,
 N-ethyl-5-fluoro-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide,
 5 N-ethyl-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-5-methyl-2-(pyrimidin-2-yl)benzamide,
 N-ethyl-5-fluoro-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide,
 10 5-chloro-N-ethyl-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide,
 N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N-(2-methoxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-((2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-(2-methoxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 15 N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N-(2-methoxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 20 N-((2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-((2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 25 N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-N,5-dimethyl-2-(pyrimidin-2-yl)benzamide,
 30 N-ethyl-N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-5-methyl-2-(pyrimidin-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-6-methyl-3-(2H-

- 1,2,3-triazol-2-yl)pyridine-2-carboxamide,
 N-ethyl-5-fluoro-N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide,
 5 N-ethyl-N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-6-methyl-3-(pyrimidin-2-yl)pyridine-2-carboxamide,
 N-ethyl-5-fluoro-N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide,
 10 N-ethyl-N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-5-methyl-2-(pyrimidin-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide,
 15 N-ethyl-5-fluoro-N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,
 20 N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-N,5-dimethyl-2-(pyrimidin-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 25 1,2,3-triazol-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-((2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl)-N-(2-methoxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 30 N-((2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl)-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl)-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,
 N-ethyl-5-fluoro-N-((2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl)-2-(2H-1,2,3-

triazol-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,

5 N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-5-methyl-2-(pyrimidin-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-6-methyl-3-(pyrimidin-2-yl)pyridine-2-carboxamide,

N-ethyl-5-fluoro-N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide,

10 N-ethyl-N-{(2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-{(2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

15 N-ethyl-N-{1-[1-(5-fluoropyridin-2-yl)-1H-pyrazol-4-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{1-[1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

20 N-ethyl-N-{(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,

25 N-ethyl-5-fluoro-N-{(2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[5-(5-fluoropyridin-2-yl)-2H-tetrazol-2-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-5-fluoro-N-{(2S)-1-[5-(5-fluoropyridin-2-yl)-2H-tetrazol-2-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,

30 N-ethyl-N-{(2S)-1-[5-(5-fluoropyridin-2-yl)-2H-tetrazol-2-yl]propan-2-yl}-5-methyl-2-(pyrimidin-2-yl)benzamide,

N-[2-(dimethylamino)ethyl]-N-{(2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-{(2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-N-[2-

(methylsulfonyl)ethyl]-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-((2S)-1-[4-(4-chlorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-N-ethyl-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-((2S)-1-[4-(3-hydroxyphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-5-methyl-N-((2S)-1-[4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-5-methyl-N-((2S)-1-[4-(phenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-5-methyl-N-((2S)-1-[4-(3-methylphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-((2S)-1-[4-(3-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-((2S)-1-[4-(4-fluoro-3-methoxyphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-((2S)-1-[4-(4-hydroxyphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-((2S)-1-[4-(3-methoxyphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide, and

N-((2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-(2-hydroxypropyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide.

(24) A pharmaceutical composition containing the compound or a pharmaceutically acceptable salt thereof according to any one of (1) to (23), as an active ingredient.

(25) A therapeutic or preventive drug for sleep disorder, depression, anxiety disorder, panic disorder, schizophrenia, drug dependence, Alzheimer's disease, Parkinson's disease, Huntington's disease, eating disorder, headache, migraine, pain, gastrointestinal disease, epilepsy, inflammation, immunological diseases, endocrine related disease or hypertension, containing the compound or a pharmaceutically acceptable salt thereof according to any one of (1) to (23), as an active ingredient.

Advantageous Effects of Invention

[0018]

It is revealed that the branched chain alkyl heteroaromatic ring derivative of the present invention shows an affinity to OX receptors and antagonistic activities against

stimulation to the receptors by a physiological ligand

Description of Embodiments

[0019]

5 The terms used in the present specification mean as follows.

 The "halogen atom" refers to a fluorine atom, a chlorine atom, a bromine atom and an iodine atom.

 The "C₁₋₆ alkyl group" means a linear or branched chain alkyl group having 1 to 6 carbon atoms and examples include groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, 10 isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, 1-ethylpropyl, n-hexyl, isohexyl and neoheyl.

 The "C₁₋₃ alkyl group" means a linear or branched chain alkyl group having 1 to 3 carbon atoms and examples include groups such as methyl, ethyl, n-propyl and isopropyl.

 The "C₁₋₆ alkoxy group" means a linear or branched chain alkoxyl group having 1 15 to 6 carbon atoms and examples include groups such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentyloxy, isopentyloxy, neopentyloxy, tert-pentyloxy, 1-ethylpropoxy and n-hexyloxy.

 The "C₁₋₆ alkylsulfonyl group" means a sulfonyl group substituted with the above "C₁₋₆ alkyl group" and examples include groups such as methylsulfonyl, ethylsulfonyl, n- 20 propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, isobutylsulfonyl, sec-butylsulfonyl, tert-butylsulfonyl, n-pentylsulfonyl, isopentylsulfonyl, neopentylsulfonyl, tert-pentylsulfonyl and n-hexylsulfonyl.

 The "di C₁₋₆ alkylamino group" means an amino group having 2 of the above "C₁₋₆ alkyl group" as substituents, which are the same or different, and examples include 25 dimethylamino, diethylamino, di(n-propyl)amino, di(isopropyl)amino, ethylmethylamino, methyl(n-propyl)amino and methyl (isopropyl)amino.

[0020]

 The "sleep disorder" used in the present specification refers to disorders at the disturbance of falling asleep, sleep, phase or awakening, where in including insomnia.

30 Further, the classification of insomnia includes disturbance of falling asleep, arousal during sleep, early-morning awakening and disturbance of deep sleep.

[0021]

 The "pharmaceutically acceptable salt" used in the present specification means a pharmaceutically acceptable acid addition salt and examples of the acid to be used include salts

with an inorganic acid such as sulfuric acid, hydrochloric acid, hydrobromic acid, phosphoric acid and nitric acid; and salts with an organic acid such as acetic acid, benzoic acid, oxalic acid, lactic acid, malic acid, tartaric acid, fumaric acid, maleic acid, citric acid, malonic acid, mandelic acid, gluconic acid, galactaric acid, glucoheptonic acid, glycolic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, camphor sulfonic acid and naphthalene-2-sulfonic acid. The conversion from a free compound

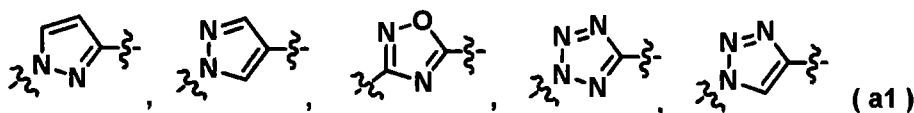
[0022]

Preferable embodiments of the compound of the present invention are described below.

Compounds, wherein Y is any of the structures in the following formula group (a1), are preferable,

[0023]

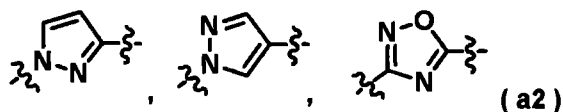
[Formula 12]



and compounds, wherein Y is any of the structures in the following formula group (a2), are further preferable.

[0024]

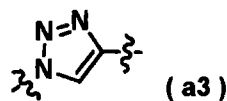
[Formula 13]



In another embodiment, compounds, wherein Y is the structure of the following formula (a3), are preferable.

[0025]

[Formula 14]



Compounds, wherein R¹ is a hydrogen atom, a fluorine atom or a methyl group, are preferable.

Compounds, wherein R² is a methyl group or an ethyl group (the ethyl group may optionally be substituted with one substituent selected from the group consisting of a hydroxyl group and a methoxy group), are preferable, with compounds, wherein R² is an ethyl group,

being more preferable.

Compounds, wherein R^3 is a 1,2,3-triazol-2-yl group or a pyrimidin-2-yl group, are preferable.

Compounds, wherein R^4 is a fluorine atom, are preferable.

5 Compounds, wherein R^5 is a hydrogen atom or a fluorine atom, are preferable.

Compounds, wherein R^6 is a C_{1-3} alkyl group, are preferable, with compounds, wherein R^6 is a methyl group, being more preferable. Also, compounds, wherein the configuration of R^6 substitution position is (S)-enantiomer, are preferable.

10 Examples of the preferable compound among the compounds of the present invention include:

N-ethyl-N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-((2R)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

15 N-ethyl-N-((2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,

N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N-methyl-2-(pyrimidin-2-yl)benzamide,

5-fluoro-N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N-methyl-2-(pyrimidin-2-yl)benzamide,

20 N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N,5-dimethyl-2-(pyrimidin-2-yl)benzamide,

N-ethyl-N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide,

25 N-ethyl-5-fluoro-N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide,

N-ethyl-N-((2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide,

30 N-ethyl-5-fluoro-N-((2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide,

N-ethyl-2-fluoro-N-((2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-6-(pyrimidin-2-yl)benzamide,

N-ethyl-4-fluoro-N-((2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide,

- N-ethyl-N-((2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-6-methyl-3-(pyrimidin-2-yl)pyridine-2-carboxamide,
- N-((2S)-1-[3-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-ethyl-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,
- 5 N-((2S)-1-[3-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-ethyl-5-fluoro-2-(pyrimidin-2-yl)benzamide,
- N-ethyl-N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide,
- N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- 10 N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- N-ethyl-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide,
- 15 N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]butan-2-yl)-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- N-ethyl-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- 20 N-ethyl-N-((2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,
- N-((2S)-1-[4-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-ethyl-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,
- 25 N-((2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N,6-dimethyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,
- N-((2S)-1-[4-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N,6-dimethyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,
- N-ethyl-5-fluoro-N-((2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide,
- 30 N-((2S)-1-[4-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-ethyl-5-fluoro-2-(pyrimidin-2-yl)benzamide,
- 5-fluoro-N-((2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-methyl-2-(pyrimidin-2-yl)benzamide,

- N-((2S)-1-[4-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-5-fluoro-N-methyl-2-(pyrimidin-2-yl)benzamide,
- N-ethyl-5-fluoro-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide,
- 5 N-ethyl-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-5-methyl-2-(pyrimidin-2-yl)benzamide,
- N-ethyl-5-fluoro-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,
- 5-chloro-N-ethyl-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-2-
- 10 (pyrimidin-2-yl)benzamide,
- N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-N-(2-methoxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- N-((2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-N-(2-methoxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- 15 N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-N-(2-methoxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- N-((2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-N-(2-hydroxyethyl)-5-methyl-2-
- 20 (2H-1,2,3-triazol-2-yl)benzamide,
- N-((2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- 25 N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-N,5-dimethyl-2-(pyrimidin-2-yl)benzamide,
- N-ethyl-N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-5-methyl-2-(2H-
- 30 1,2,3-triazol-2-yl)benzamide,
- N-ethyl-N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-5-methyl-2-(pyrimidin-2-yl)benzamide,
- N-ethyl-N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,

- N-ethyl-5-fluoro-N-{(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,
- N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,
- 5 N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-6-methyl-3-(pyrimidin-2-yl)pyridine-2-carboxamide,
- N-ethyl-5-fluoro-N-{(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide,
- N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide,
- 10 N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-5-methyl-2-(pyrimidin-2-yl)benzamide,
- N-ethyl-N-{(2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,
- 15 N-ethyl-5-fluoro-N-{(2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,
- N-ethyl-N-{(2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,
- N-{(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- 20 N-{(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-N,5-dimethyl-2-(pyrimidin-2-yl)benzamide,
- N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- 25 N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-N-(2-methoxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- 30 N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,
- N-ethyl-5-fluoro-N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-5-methyl-2-(pyrimidin-2-yl)benzamide,

5 N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-6-methyl-3-(pyrimidin-2-yl)pyridine-2-carboxamide,

N-ethyl-5-fluoro-N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide,

10 N-ethyl-N-{(2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-{(2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{1-[1-(5-fluoropyridin-2-yl)-1H-pyrazol-4-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

15 N-ethyl-N-{1-[1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

20 N-ethyl-N-{(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,

N-ethyl-5-fluoro-N-{(2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,

25 N-ethyl-N-{(2S)-1-[5-(5-fluoropyridin-2-yl)-2H-tetrazol-2-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-5-fluoro-N-{(2S)-1-[5-(5-fluoropyridin-2-yl)-2H-tetrazol-2-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,

30 N-ethyl-N-{(2S)-1-[5-(5-fluoropyridin-2-yl)-2H-tetrazol-2-yl]propan-2-yl}-5-methyl-2-(pyrimidin-2-yl)benzamide,

N-[2-(dimethylamino)ethyl]-N-{(2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-{(2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-N-[2-(methylsulfonyl)ethyl]-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-{(2S)-1-[4-(4-chlorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-N-ethyl-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[4-(3-hydroxyphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

- 5 N-ethyl-5-methyl-N-{(2S)-1-[4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,
- N-ethyl-5-methyl-N-[(2S)-1-(4-phenyl-1H-1,2,3-triazol-1-yl)propan-2-yl]-2-(2H-1,2,3-triazol-2-yl)benzamide,
- N-ethyl-5-methyl-N-{(2S)-1-[4-(3-methylphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,
- 10 1,2,3-triazol-2-yl)benzamide,
- N-ethyl-N-{(2S)-1-[4-(3-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- N-ethyl-N-{(2S)-1-[4-(4-fluoro-3-methoxyphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- 15 N-ethyl-N-{(2S)-1-[4-(4-hydroxyphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- N-ethyl-N-{(2S)-1-[4-(3-methoxyphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide, and
- N-{(2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-N-(2-hydroxypropyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
- 20 (2H-1,2,3-triazol-2-yl)benzamide,
- or pharmaceutically acceptable salts thereof.

Additionally, when the compound of the present invention forms a hydrate or a solvate, they are also encompassed in the scope of the present invention. Similarly, pharmaceutically acceptable salts of the hydrates or solvates of the compound of the present invention are also encompassed in the scope of the present invention.

[0026]

The compound of the present invention encompasses all of the enantiomers, diastereomers, equilibrium compounds, mixtures thereof in any ratio, racemic compounds, and the like.

30 The compound according to the present invention also includes those wherein at least one hydrogen atom, carbon atom, nitrogen atom, oxygen atom and halogen atom is substituted with a radioactive isotope or a stable isotope. These labelled compounds are useful for the studies on metabolism and pharmacokinetics and for biological analysis, or the like, as a receptor ligand, or the like.

The compound according to the present invention can be administered orally or parenterally. Dosage form thereof may be tablets, capsules, granules, powders, dusts, troches, ointments, creams, plasters, emulsions, suspensions, suppositories, injections, or the like, and any of which can be produced by a routine pharmaceutical preparation technique (for example, methods stipulated in The Japanese Pharmacopoeia Fifteenth Edition, or the like). These dosage forms can suitably be selected in accordance with patient's symptoms, age, body weight and purpose of treatment.

These pharmaceutical preparations can be produced by adding pharmacologically acceptable carriers, more specifically, excipients (for example, crystalline cellulose, starch, lactose, mannitol), binders (for example, hydroxypropylcellulose, polyvinylpyrrolidone), lubricants (for example, magnesium stearate, talc), disintegrators (for example, carboxymethyl cellulose calcium) and other pharmacologically acceptable various additives, to a composition containing the compound of the present invention.

The compound of the present invention can be orally or parenterally administered to an adult patient in a single dose of 0.001 to 500 mg once or in several divided times a day. Additionally, the dose can suitably be increased or reduced depending on the disease type to be treated, patient's age, body weight, symptoms, and the like.

[0027]

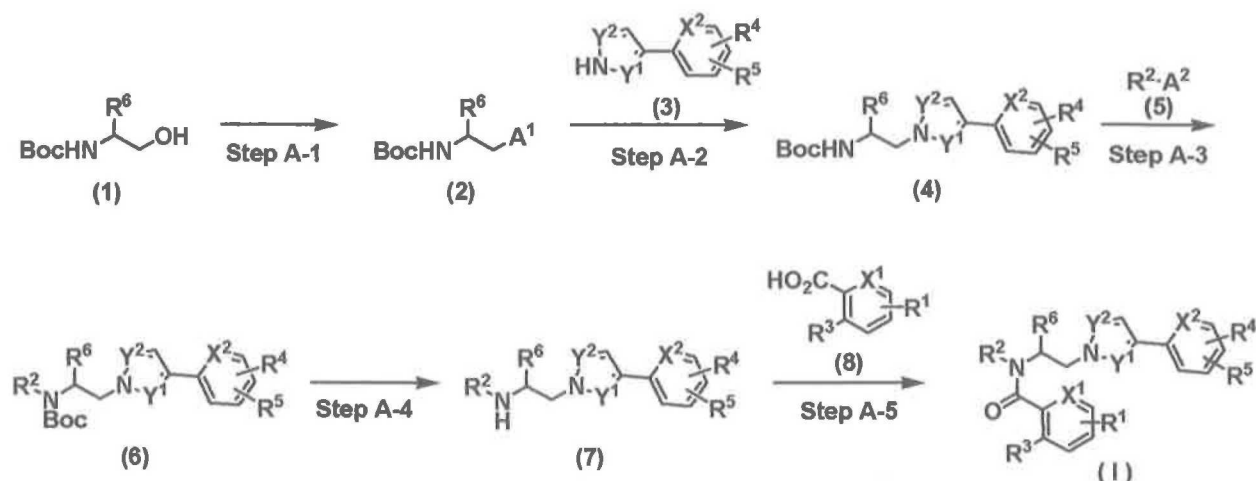
Typical production methods of the compounds (I) and (Ia) of the present invention are shown below in Schemes A to J.

The following methods are examples of the production method of the compounds of the present invention, and the present invention is not limited thereto. Additionally, in the following examples of the production method, the compounds may form a salt unless the reactions are affected.

Scheme A

[0028]

[Formula 15]



[0029]

wherein A^1 and A^2 represent a halogen atom, a methanesulfonyloxy group, a p-

- 5 toluenesulfonyloxy group or a trifluoromethanesulfonyloxy group, and other symbols are as defined above.)

[0030]

- Step A-1: The compound (2) can be obtained by converting the hydroxy group of the compound (1) to a general leaving group. Examples of the reaction in Step A-1 include chlorination, bromination, iodization, methanesulfonylation and p-toluenesulfonylation. An example of the chlorination reaction includes a method wherein a leaving group is obtained using, for example, methanesulfonyl chloride, or the like, followed by substitution with a chlorine atom. A method which uses carbon tetrachloride and triphenyl phosphine and a method which uses thionyl chloride or phosphorus oxychloride are further included. During these procedures, a chloride such as sodium chloride or potassium chloride may be added. An example of the bromination reaction includes a method wherein, for example, carbon tetrabromide and triphenyl phosphine are used. An example of the iodization reaction includes a method wherein, for example, iodine, triphenyl phosphine and imidazole are used. The methanesulfonylation and p-toluenesulfonylation of the compound (1) can be achieved using, for example, methanesulfonyl chloride, p-toluenesulfonyl chloride, or the like, respectively. During these reactions, a suitable base may be added. Examples of the base to be added include organic bases such as triethylamine and diisopropylethylamine or inorganic bases such as potassium carbonate. Examples of the reaction solvent include ether solvents such as tetrahydrofuran, aprotic polar solvents such as N,N-dimethylformamide, halogen solvents such as chloroform, acetonitrile or mixed solvents thereof, and therein the reactions can be carried out under the temperature condition of about -80°C to about the boiling point of such a solvent.

[0031]

Step A-2: The compound (4) can be obtained by reacting the compound (2) and the compound (3). The reaction in Step A-2 proceeds in an alcohol solvent such as ethanol, an ether solvent such as tetrahydrofuran, an aprotic polar solvent such as N,N-dimethylformamide, a halogen solvent such as chloroform, dimethyl sulfoxide, acetonitrile or a mixed solvent thereof, in the presence of an inorganic base such as sodium hydride, sodium hydroxide, sodium carbonate, potassium carbonate or cesium carbonate, an alkali metal such as sodium ethoxide or potassium tert-butoxide, or an organic base such as a lower alkoxide of the alkaline earth metal, under the temperature condition of about -80°C to about the boiling point of such a solvent.

[0032]

Step A-3: The compound (6) can be obtained by the alkylation reaction of the compound (4). The reaction in Step A-3 can be carried out by a general method of amide alkylation. Examples of the base to be used in the present reaction include inorganic bases such as sodium hydride and sodium hydroxide, and metal lower alkoxides such as sodium ethoxide and tert-butoxy potassium. Examples of the solvent to be used in the present reaction include ether solvents such as tetrahydrofuran and 1,4-dioxane, aprotic polar solvents such as N,N-dimethylformamide, dimethyl sulfoxide and acetonitrile, aromatic hydrocarbon solvents such as toluene, or mixed solvents thereof. The present reaction can be carried out usually at 0°C to 150°C, preferably 20°C to 100°C.

[0033]

Step A-4: The compound (7) can be obtained by deprotecting the tert-butoxycarbonyl group of the compound (6) in the presence of an acid such as hydrochloric acid, sulfuric acid, trifluoroacetic acid, p-toluenesulfonic acid or methanesulfonic acid. The comprehensive overview of the reaction in Step A-3 can be found in Protective Groups in Organic Chemistry, written by J. F.W. McOmie and Protective Groups in Organic Synthesis written by T. W. Greene and P. G. M. Wuts.

[0034]

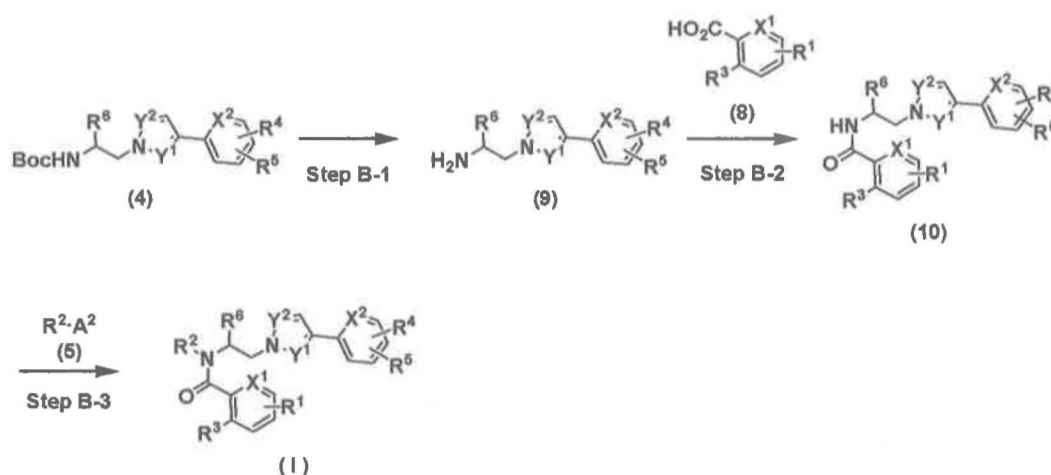
Step A-5: The compound (I) of the present invention can be obtained by the condensation reaction of the amine compound (7) and the carboxylic acid compound (8). The reaction in Step A-5 can be carried out by a general amidation method of carboxylic acid and amine. Examples include a method wherein carboxylic acid is converted to a carboxylic acid halide such as carboxylic acid chloride or carboxylic acid bromide and subsequently reacted with amine and a method wherein carboxylic acid is reacted with amine in the presence of a dehydration condensation agent. These reactions can be carried out in the presence or absence of a base in a

solvent. Examples of the halogenating agent to be used in the present reaction can include thionyl chloride, oxalyl chloride, phosphorus oxychloride or phosphorus oxybromide. Also, examples of the dehydration condensation agent to be used in the present reaction include 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide-hydrochloride (EDC-HCl), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate (HATU), propane phosphonic acid anhydride, dicyclohexyl carbodiimide (DDC), diphenylphosphoryl azide (DPPA) and carbonyldiimidazole (CDI), and an activator such as 1-hydroxybenzotriazole or hydroxysuccinimide may be used as necessary. Examples of the solvent to be used in the present reaction include ether solvents such as tetrahydrofuran and 1,4-dioxane, aprotic polar solvents such as N,N-dimethylformamide and acetonitrile, halogen solvents such as dichloromethane and chloroform, aromatic hydrocarbon solvents such as toluene, ethyl acetate or mixed solvents thereof. Examples of the base to be used in the present reaction include organic amines such as pyridine, triethylamine and diisopropylethylamine and inorganic bases such as potassium carbonate, sodium carbonate and sodium hydrogen carbonate. The present reaction can be carried out usually at 0°C to 150°C, preferably 25°C to 80°C.

Scheme B

[0035]

[Formula 16]



[0036]

wherein the symbols are as defined above.

The compound (I) of the present invention can alternatively be produced by the method shown in Scheme B.

[0037]

Step B-1: The compound (9) can be obtained by deprotecting the tert-butoxycarbonyl group of

the compound (4) in the presence of an acid. The reaction in Step B-1 can be carried out in accordance with the same reaction conditions as in Step A-4.

[0038]

Step B-2: The compound (10) can be obtained by the condensation reaction of the carboxylic

5 acid compound (8) and the amine compound (9). The reaction in Step B-2 can be carried out in accordance with the same reaction conditions as in Step A-5.

[0039]

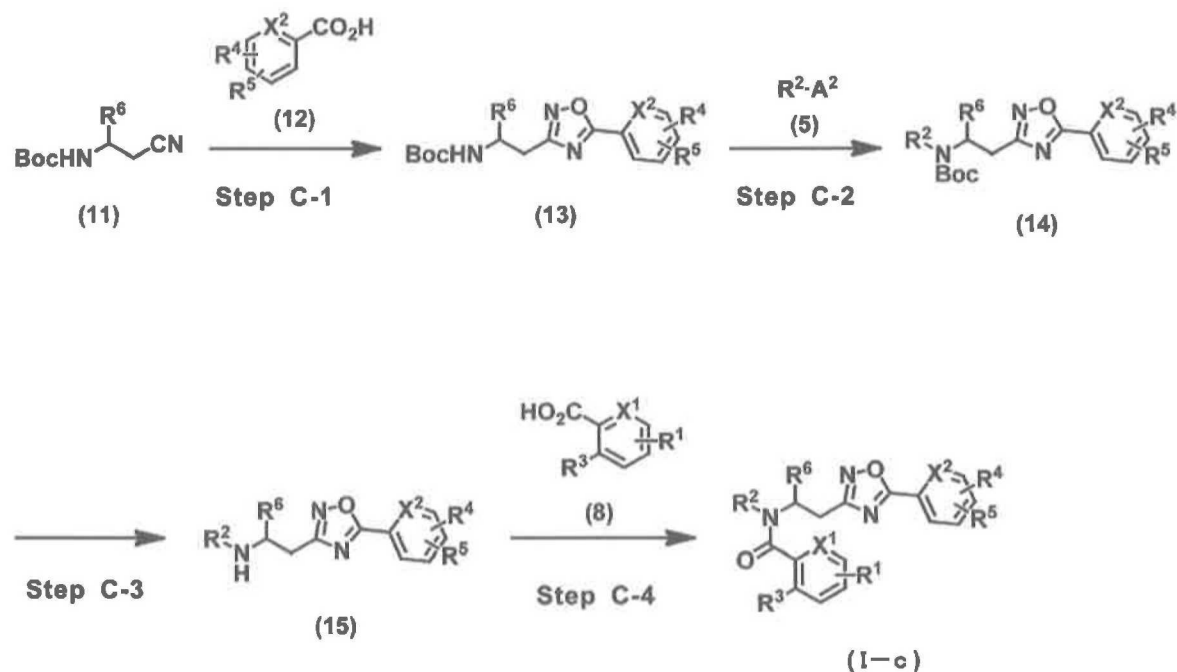
Step B-3: The compound (I) of the present invention can be obtained by the alkylation reaction of the compound (10). The reaction in Step B-3 can be carried out in accordance with the same

10 reaction conditions as in Step A-3.

Scheme C

[0040]

[Formula 17]



15

[0041]

wherein the symbols are as defined above.

The compound of the present invention represented by the formula (I-c) can be produced by the method shown in Scheme C.

20 [0042]

Step C-1: The compound (13) can be obtained by the amidoximation reaction of the compound (11), followed by the oxadiazole cyclization reaction. The reaction in Step C-1 can be carried

out under the conditions in which the cyano compound (11) is first amidoximated by being treated with hydroxyl amine or hydrochloride thereof in an alcohol solvent such as methanol or ethanol, and subsequently reacted with the carboxylic acid compound (12) and a dehydration condensation agent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide-hydrochloride, dicyclohexylcarbodiimide or carbonyldiimidazole in an ether solvent such as tetrahydrofuran or 1,4-dioxane, an aprotic polar solvent such as N,N-dimethylformamide, a halogen solvent such as dichloromethane or chloroform, an aromatic hydrocarbon solvent such as toluene, ethyl acetate, acetonitrile or a mixed solvent thereof.

[0043]

- 10 Step C-2: The compound (14) can be obtained by the alkylation reaction of the compound (13). The reaction in Step C-2 can be carried out in accordance with the same reaction conditions as in Step A-3.

[0044]

Step C-3: The compound (15) can be obtained by reacting the compound (14) with an acid.

- 15 The reaction in Step C-3 can be carried out in accordance with the same reaction conditions as in Step A-4.

[0045]

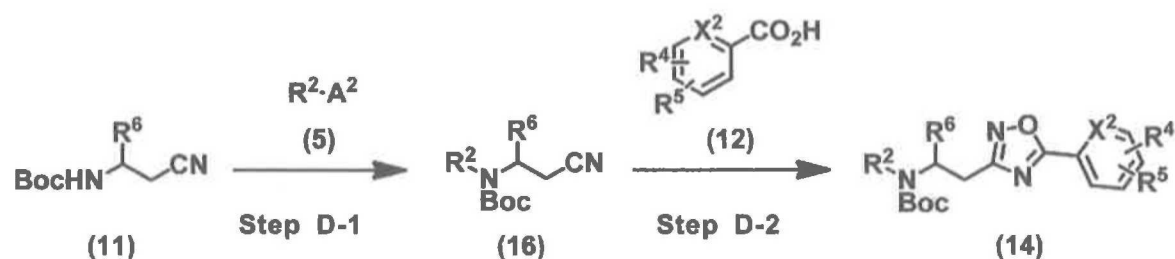
Step C-4: The compound (I-c) of the present invention can be obtained by the condensation reaction of the compound (15) and the compound (8). The reaction in Step C-4 can be carried out in accordance with the same reaction conditions as in Step A-5.

20

Scheme D

[0046]

[Formula 18]



[0047]

wherein the symbols are as defined above.

The intermediate (14) can alternatively be produced by the method shown in Scheme D.

- 30 Step D-1: The compound (16) can be obtained by the alkylation reaction of the compound (11).

The reaction in Step D-1 can be carried out in accordance with the same reaction conditions as in Step A-3.

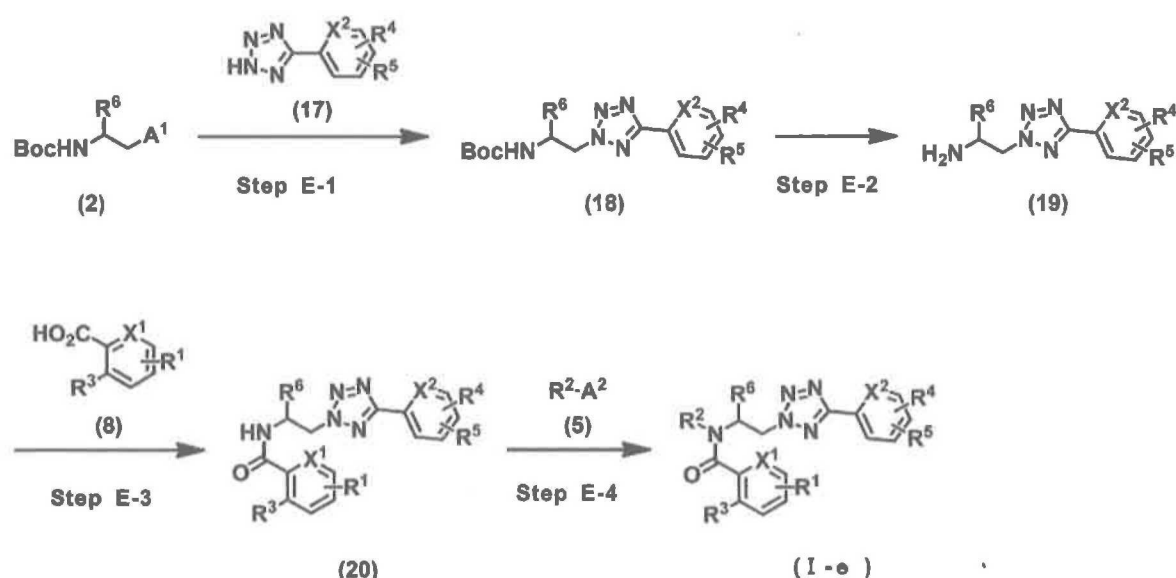
[0048]

Step D-2: The compound (14) can be obtained by the amidoximation reaction of the compound (16), followed by the oxadiazole cyclization reaction. The reaction in Step D-2 can be carried out in accordance with the same reaction conditions as in Step C-1.

Scheme E

[0049]

10 [Formula 19]



[0050]

wherein the symbols are as defined above.

The compound of the present invention represented by the formula (I-e) can be produced by the method shown in Scheme E.

Step E-1: The compound (18) can be obtained by reacting the compound (2) and the compound (17). The reactions in Step E-1 can be carried out in accordance with the same reaction conditions as in Step A-2.

[0051]

Step E-2: The compound (19) can be obtained by reacting the compound (18) with an acid. The reaction in Step E-2 can be carried out in accordance with the same reaction conditions as in Step A-4.

[0052]

Step E-3: The compound (20) can be obtained by the condensation reaction of the compound

(19) and the compound (8). The reaction in Step E-3 can be carried out in accordance with the same reaction conditions as in Step A-5.

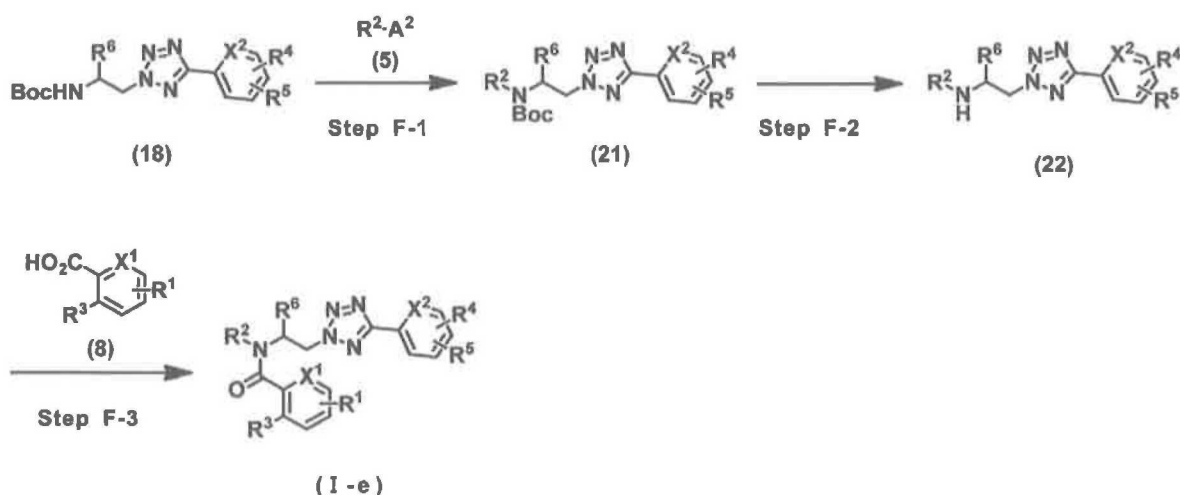
[0053]

Step E-4: The compound (I-e) of the present invention can be obtained by the alkylation reaction of the compound (20). The reaction in Step E-1 can be carried out in accordance with the same reaction conditions as in Step A-3.

Scheme F

[0054]

10 [Formula 20]



wherein the symbols are as defined above.

The compound of the present invention represented by the formula (I-e) can be produced by the method shown in Scheme F.

15 [0055]

Step F-1: The compound (21) can be obtained by the alkylation reaction of the compound (18). The reaction in Step F-1 can be carried out in accordance with the same reaction conditions as in Step A-3.

[0056]

20 Step F-2: The compound (22) can be obtained by reacting the compound (21) with an acid. The reaction in Step F-2 can be carried out in accordance with the same reaction conditions as in Step A-4.

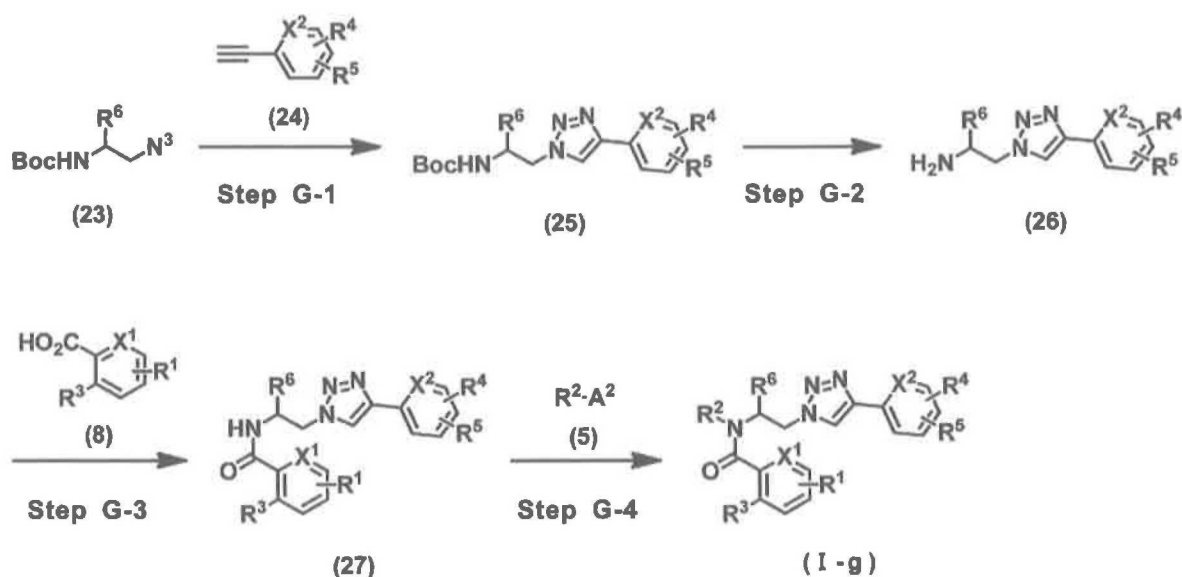
[0057]

Step F-3: The compound (I-e) of the present invention can be obtained by the condensation reaction of the compound (22) and the compound (8). The reaction in Step F-3 can be carried out in accordance with the same reaction conditions as in Step A-5.

Scheme G

[0058]

[Formula 21]



5

wherein the symbols are as defined above.

The compound of the present invention represented by the formula (I-g) can be produced by the method shown in Scheme G.

[0059]

- 10 Step G-1: The compound (25) can be obtained by the 1,3-dipolar cycloaddition reaction of the compound (23) and the compound (24). The reaction in Step G-1 can be carried out by a method in which treatment is performed with a copper catalyst in the presence of a reducing agent. Examples of the reducing agent to be used in the present reaction include (L)-ascorbic acid and sodium ascorbate. Examples of the copper catalyst to be used in the present reaction
- 15 include copper sulfate, iodination copper, copper bromide and copper chloride. When a copper halide is used as the copper catalyst, a base is required and triethylamine, diisopropylethylamine, or the like, can be used. Examples of the solvent to be used in the present reactions include alcohol solvents such as methanol and ethanol, ether solvents such as tetrahydrofuran and 1,4-dioxane, aprotic polar solvents such as N,N-dimethylformamide, dimethyl sulfoxide and
- 20 acetonitrile, aromatic hydrocarbon solvents such as toluene, water or mixed solvents thereof. The present reaction can be carried out usually at 0°C to 150°C, preferably 25°C to 100°C.

[0060]

Step G-2: The compound (26) can be obtained by reacting the compound (25) with an acid.

The reaction in Step G-2 can be carried out in accordance with the same reaction conditions as in

Step A-4.

[0061]

Step G-3: The compound (27) can be obtained by the condensation reaction of the compound (26) and the compound (8). The reactions in Step G-3 can be carried out in accordance with the same reaction conditions as in Step A-5.

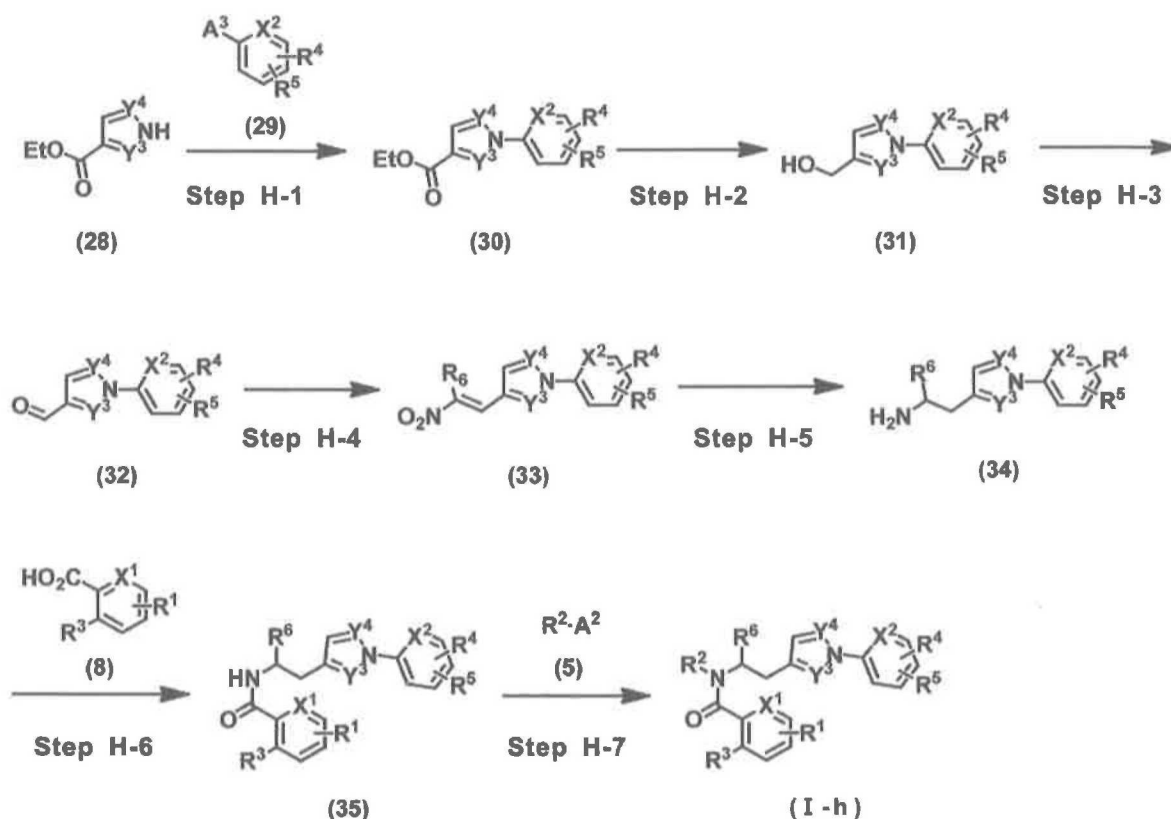
[0062]

Step G-4: The compound (I-g) of the present invention can be obtained by the alkylation reaction of the compound (27). The reactions in Step G-4 can be carried out in accordance with the same reaction conditions as in Step A-3.

Scheme H

[0063]

[Formula 22]



[0064]

wherein either one of Y^3 and Y^4 represents a nitrogen atom, and the other represents CH, A^3 represents a halogen atom, a methanesulfonyloxy group, a p-toluenesulfonyloxy group or a trifluoromethanesulfonyloxy group. Other symbols are as defined above.)

The compound of the present invention represented by the formula (I-h) can be produced by the method shown in Scheme H.

Step H-1: The compound (30) can be obtained by the coupling reaction of the compound (28) and the compound (29). The reaction in Step H-1 can be carried out by a general method in which the nitrogen atom of the azole compound is substituted with an aromatic ring using a catalyst and a ligand in the presence of a base. Examples include the method described in

- 5 Synlett, 2003, 15, 2428-2439 or a method in accordance therewith. Examples of the catalyst to be used in the present reaction include copper catalyst such as copper (0), copper (I) iodine, copper (I) chloride and copper (I) oxide. Examples of the ligand to be used in the present reaction include N,N'-dimethylethylenediamine, N,N'-dimethylcyclohexane-1,2-diamine, 2-aminopyridine, 1,10-phenanthroline and 2-hydroxybenzaldehyde oxime. Examples of the base
- 10 to be used in the present reaction include potassium carbonate, potassium phosphate, potassium hydroxide, potassium tert-butoxide, cesium carbonate, sodium carbonate, sodium bicarbonate, sodium acetate, sodium methoxide and tetrabutyl ammonium hydroxide. Examples of the solvent to be used in the present reaction include alcohol solvents such as methanol and ethanol, ether solvents such as tetrahydrofuran and 1,4-dioxane, aprotic polar solvents such as N,N-
- 15 dimethylformamide, dimethyl sulfoxide and acetonitrile, halogen solvents such as dichloromethane and chloroform, aromatic hydrocarbon solvents such as toluene, water or mixed solvents thereof. The present reaction can be carried out usually at 0°C to 150°C, preferably 25°C to 100°C.

[0065]

- 20 Step H-2: The compound (31) can be obtained by the reduction reaction of the ester of the compound (30). The reaction in Step H-2 can be carried out under the conditions in which the compound (30) is reacted with a reducing agent such as lithium aluminium hydride, diisobutyl aluminium hydride, sodium borohydride or lithium borohydride in an alcohol solvent such as methanol or ethanol, an ether solvent such as tetrahydrofuran or 1,4-dioxane, an aromatic
- 25 hydrocarbon solvent such as toluene or a mixed solvent thereof. The present reaction can be carried out at -80°C to 150°C, preferably 0°C to 25°C.

[0066]

- Step H-3: The compound (32) can be obtained by the oxidation reaction of the hydroxyl group of the compound (31). The reaction in Step H-3 can be carried out under the conditions in which
- 30 the compound (31) is reacted with a hypervalent iodine compound such as Dess-Martin reagent or 2-iodoxybenzoic acid, chromate such as pyridinium chlorochromate or pyridinium dichromate, an oxidizing agent such as tetrapropylammonium perruthenate or manganese dioxide in a halogen solvent such as dichloromethane or chloroform, dimethyl sulfoxide or acetonitrile. The present reaction can be carried out at 0°C to 150°C, preferably 25°C to 80°C.

[0067]

Step H-4: The compound (33) can be obtained by the condensation reaction of the compound (32) and nitroalkane ($R^6-CH_2-NO_2$). The reaction in Step H-4 can be carried out under the conditions in which the compound (32) is reacted with nitroalkane ($R^6-CH_2-NO_2$) in a halogen solvent such as chloroform, an ether solvent such as tetrahydrofuran or 1,4-dioxane, an alcohol solvent such as methanol or ethanol, or an aprotic solvent such as dimethylformamide, or without a solvent, in the presence of an organic base such as triethylamine, diisopropylethylamine or ethanolamine, or an inorganic base such as sodium hydroxide. The present reactions can be carried out at 0°C to 50°C.

10 [0068]

Step H-5: The compound (34) can be obtained by the double bond of the compound (33) and the reduction reaction of the nitro group. The reaction in Step H-5 can be carried out under the conditions in which the compound (33) is reduced in an alcohol solvent such as methanol or ethanol, an ether solvent such as tetrahydrofuran or 1,4-dioxane, ethyl acetate or a mixed solvent thereof, in the presence of a metal catalyst such as palladium or platinum in a hydrogen atmosphere. The present reaction can be carried out at 25°C to 80°C. Alternatively, the reaction can also be carried out in the same reaction conditions as in Step H-2.

[0069]

Step H-6: The compound (35) can be obtained by the condensation reaction of the compound (34) and the compound (8). The reaction in Step H-6 can be carried out in accordance with the same reaction conditions as in Step A-5.

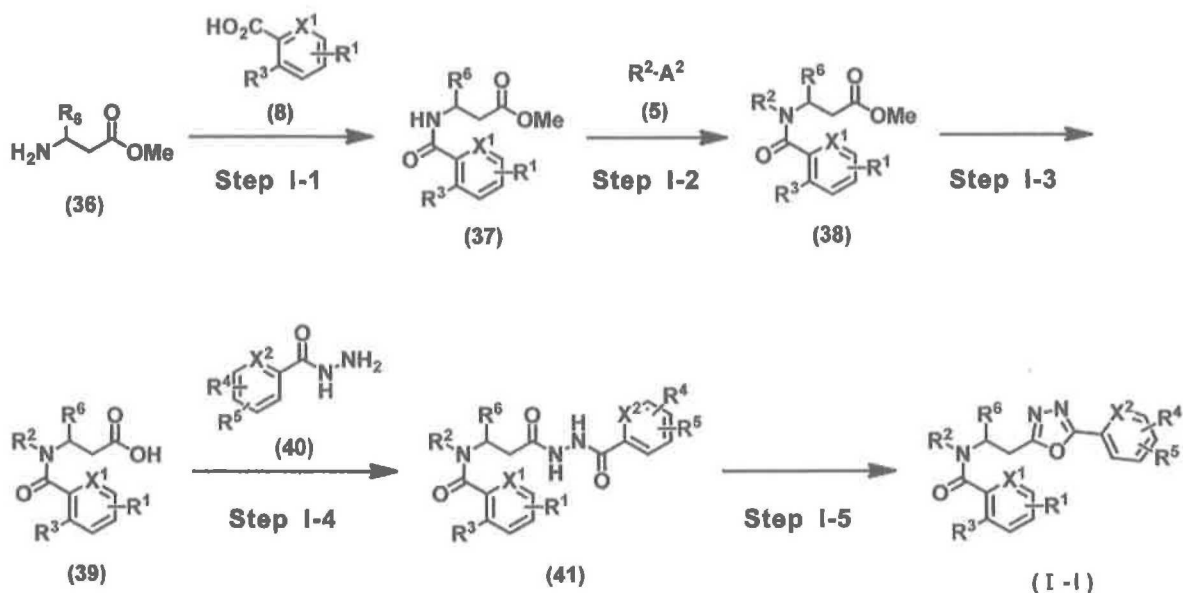
[0070]

Step H-7: The compound (I-h) of the present invention can be obtained by the alkylation reaction of the compound (35). The reaction in Step H-7 can be carried out in accordance with the same reaction conditions as in Step A-3.

Scheme I

[0071]

[Formula 23]



[0072]

wherein the symbols are as defined above.

- 5 The compound of the present invention represented by the formula (I-i) can be produced by the method shown in Scheme I.

Step I-1: The compound (37) can be obtained by the condensation reaction of the compound (36) and the compound (8). The reaction in Step I-1 can be carried out in accordance with the same reaction conditions as in Step A-5.

10 [0073]

Step I-2: The compound (38) can be obtained by the alkylation reaction of the compound (37). The reaction in Step I-2 can be carried out in accordance with the same reaction conditions as in Step A-3.

[0074]

- 15 Step I-3: The compound (39) can be obtained by the hydrolysis reaction of the compound (38). The reaction in Step I-3 can be carried out under the reaction conditions described in Protective Groups in Organic Chemistry, written by J. F. W. McOmie and Protective Groups in Organic Synthesis written by T. W. Greene and P. G. M. Wuts. Examples include hydrolysis methods which use a mineral acid such as hydrochloric acid or sulfuric acid, or an inorganic base such as
- 20 sodium hydroxide or potassium hydroxide. Examples of the solvent to be used in the present reaction include alcohol solvents such as methanol and ethanol, ether solvents such as tetrahydrofuran and 1,4-dioxane, water or mixed solvents thereof. The present reaction can be carried out at 0°C to 100°C .

[0075]

Step I-4: The compound (41) can be obtained by the condensation reaction of the compound (39) and the compound (40). The reaction in Step I-4 can be carried out in accordance with the same reaction conditions as in Step A-5.

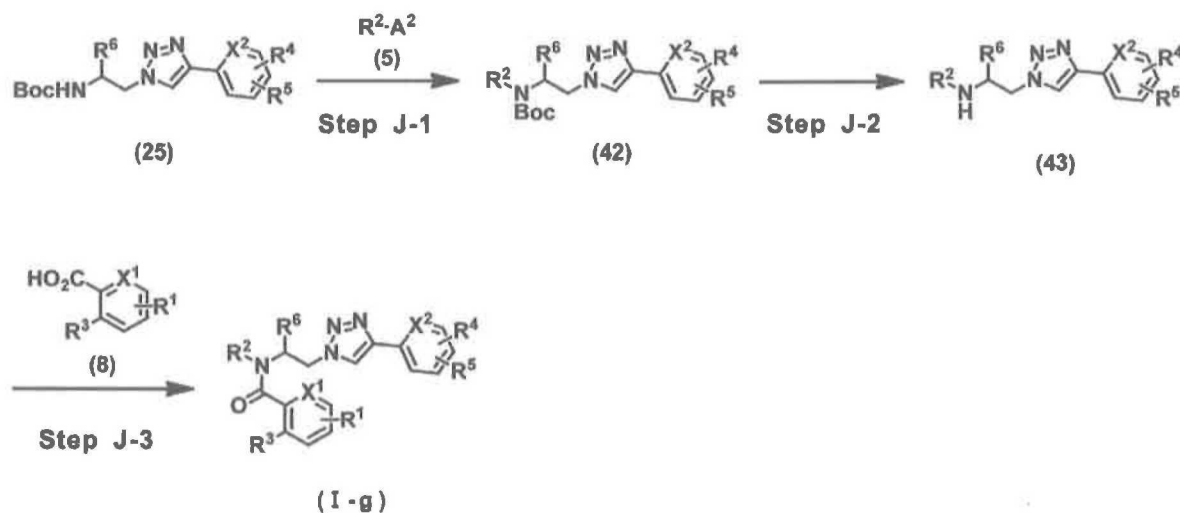
[0076]

- 5 Step I-5: The compound (I-i) of the present invention can be obtained by the cyclodehydration reaction of the compound (41). The reaction in Step I-5 can be carried out under the conditions in which the compound (41) is reacted with a dehydrating agent such as phosphorus oxychloride, sulfuric acid or Burgess reagent in an ether solvent such as tetrahydrofuran or 1,4-dioxane, an aprotic polar solvent such as N,N-dimethylformamide or acetonitrile or a mixed solvent thereof.
- 10 The present reaction can be carried out at 25°C to 100°C.

Scheme J

[0077]

[Formula 24]



[0078]

wherein the symbols are as defined above.

The compound of the present invention represented by the formula (I-g) can be produced by the method shown in Scheme J.

- 20 Step J-1: The compound (42) can be obtained by the alkylation reaction of the compound (25). The reaction in Step J-1 can be carried out in accordance with the same reaction conditions as in Step A-3.

[0079]

- Step J-2: The compound (43) can be obtained by reacting the compound (42) with an acid. The reaction in Step J-2 can be carried out in accordance with the same reaction conditions as in Step
- 25

A-4.

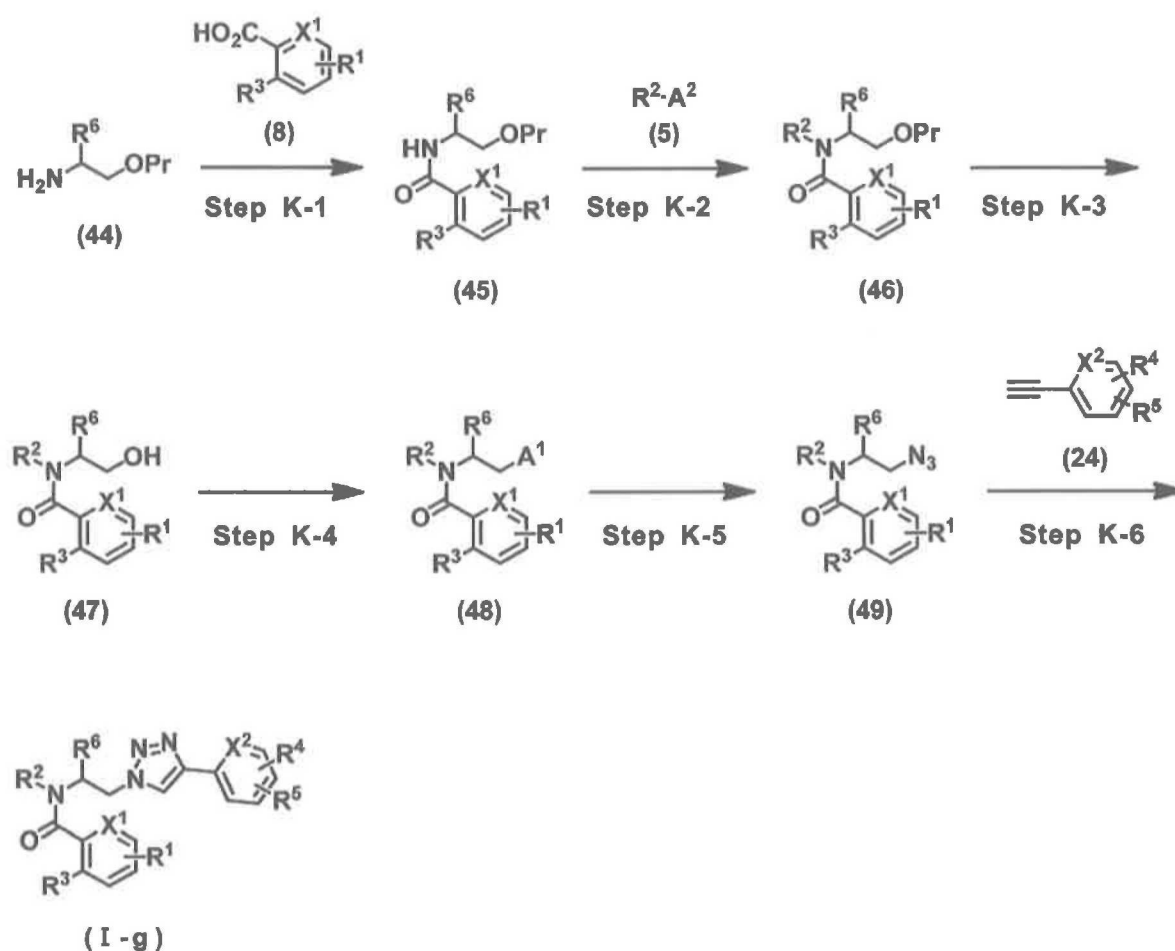
[0080]

Step J-3: The compound (I-g) of the present invention can be obtained by the condensation reaction of the compound (43) and the compound (8). The reaction in Step J-3 can be carried out in accordance with the same reaction condition as in Step A-5.

Scheme K

[0081]

[Formula 25]



[0082]

wherein Pr represents a commonly used protective group of a hydroxy group described in Protective Groups in Organic Chemistry, written by J. F. W. McOmie and Protective Groups in Organic Synthesis written by T. W. Greene and P. G. M. Wuts. Other symbols are as defined above.

The compound of the present invention represented by the formula (I-g) can be produced by the method shown in Scheme K.

Step K-1: The compound (45) can be obtained by the condensation reaction of the compound (44) and the compound (8). The reaction in Step K-1 can be carried out in accordance with the same reaction conditions as in Step A-5.

[0083]

- 5 Step K-2: The compound (46) can be obtained by the alkylation reaction of the compound (45). The reaction in Step K-2 can be carried out in accordance with the same reaction conditions as in Step A-3.

[0084]

- 10 Step K-3: The compound (47) can be obtained by removing the protective group of the hydroxy group of the compound (46). The comprehensive overview of the reaction in Step K-3 can be found in Protective Groups in Organic Chemistry, written by J. F. W. McOmie and Protective Groups in Organic Synthesis written by T. W. Greene and P. G. M. Wuts. When Pr of the compound (46) is an acetal protective group such as a methoxymethyl group, the compound (47) can be obtained by reacting the compound (46) with an acid such as hydrochloride.

15 [0085]

Step K-4: The compound (48) can be obtained by converting the hydroxy group of the compound (47) to a general leaving group. The reaction in Step K-4 can be carried out in accordance with the same reaction conditions as in Step A-1.

[0086]

- 20 Step K-5: The compound (49) can be obtained by substituting the leaving group of the compound (48) with an azide ion. The reaction in Step K-5 can use an aprotic polar solvent such as N,N-dimethylformamide or dimethyl sulfoxide, water, tetrahydrofuran or a mixed solvent thereof as a solvent. The reaction can be carried out at a reaction temperature of about 0°C to the boiling point of the reaction solvent, with a temperature from 50°C to 80°C being
25 preferable.

[0087]

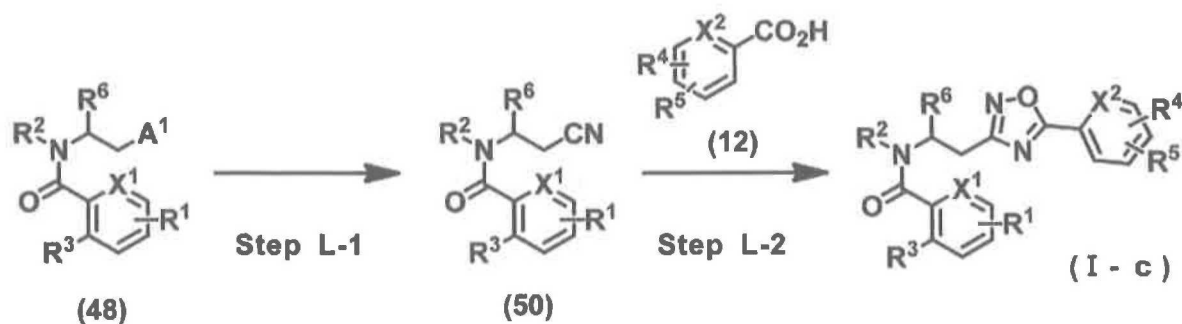
Step K-6: The compound (I-g) of the present invention can be obtained by the 1,3-dipolar cycloaddition reaction of the compound (49) and the compound (24). The reaction in Step K-6 can be carried out in accordance with the same reaction conditions as in Step G-1.

30

Scheme L

[0088]

[Formula 26]



[0089]

wherein the symbols are as defined above.

- 5 The compound of the present invention represented by the formula (I-c) can be produced by the method shown in Scheme L.

Step L-1: The compound (50) can be obtained by substituting the leaving group of the compound (48) with an inorganic cyanide. The reaction in Step L-1 can be carried out by using sodium cyanide or potassium cyanide in an aprotic polar solvent such as N,N-dimethylformamide, an alcohol such as MeOH, water, tetrahydrofuran or a mixed solvent thereof. The reaction is carried out at a reaction temperature of about room temperature to the boiling point of the reaction solvent, with a temperature from 50°C to 100°C being preferable.

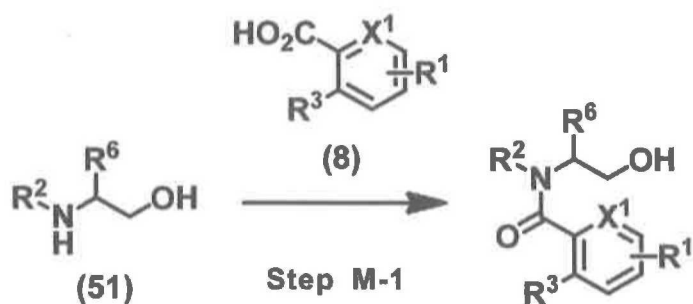
[0090]

Step L-2: The compound (I-c) of the present invention can be obtained by the amidoximation reaction of the compound (50), followed by the oxadiazole cyclization reaction. The reaction in Step L-2 can be carried out in accordance with the same reaction conditions as in Step C-1.

Scheme M

[0091]

20 [Formula 27]



[0092]

wherein the symbols are as defined above.

The intermediate (47) can alternatively be produced by the method shown in

Scheme M.

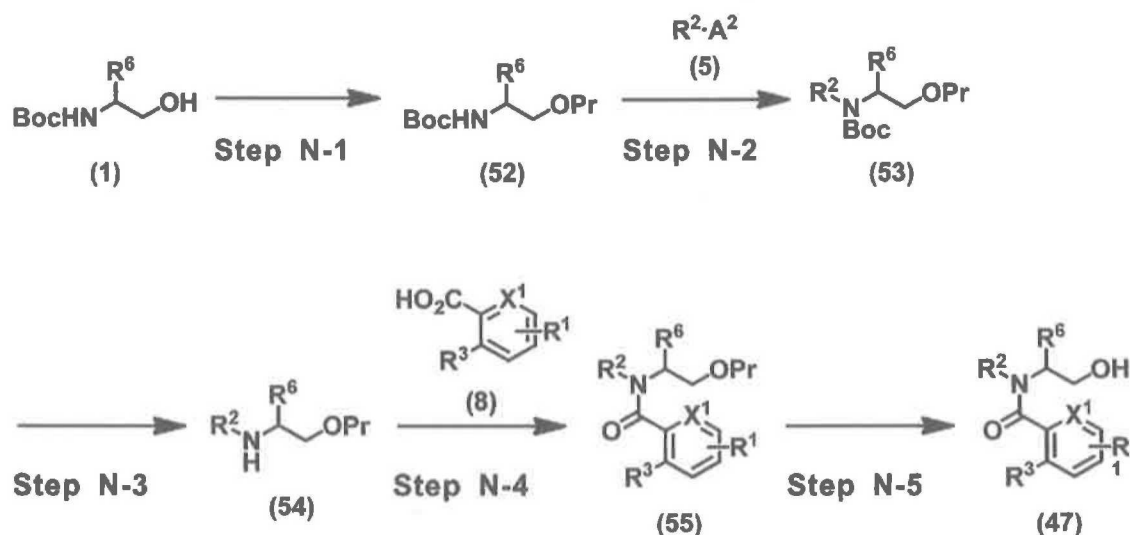
Step M-1: The compound (47) can be obtained by the condensation reaction of the compound (51) and the compound (8). The reactions in Step M-1 can be carried out in accordance with the same reaction conditions as in Step A-5.

5

Scheme N

[0093]

[Formula 28]



10 [0094]

wherein the symbols are as defined above.

The intermediate (47) can alternatively be produced by the method shown in Scheme N.

Step N-1: The compound (52) can be obtained by protecting the hydroxy group of the compound (1). The comprehensive overview of the reaction in Step N-1 can be found in Protective Groups in Organic Chemistry, written by J. F. W. McOmie and Protective Groups in Organic Synthesis written by T. W. Greene and P. G. M. Wuts. For example, when the protective group of the compound (52) is an acyl protective group such as a benzoyl group, the compound (52) can be obtained by reacting an acyl halide such as benzoyl chloride, benzoic anhydride or acetic anhydride with an organic base such as pyridine or triethylamine.

[0095]

Step N-2: The compound (53) can be obtained by the alkylation reaction of the compound (52).

The reaction in Step N-2 can be carried out in accordance with the same reaction conditions as in Step A-3.

25 [0096]

Step N-3: The compound (54) can be obtained by reacting the compound (53) with an acid.

The reaction in Step N-3 can be carried out in accordance with the same reaction conditions as in Step A-4.

[0097]

- 5 Step N-4: The compound (55) can be obtained by the condensation reaction of the compound (54) and the compound (8). The reaction in Step N-4 can be carried out in accordance with the same reaction conditions as in Step A-5.

[0098]

- Step N-5: The compound (47) can be obtained by removing the protective group of the hydroxy group of the compound (55). The comprehensive overview of the reaction in Step N-5 can be found in Protective Groups in Organic Chemistry, written by J. F. W. McOmie and Protective Groups in Organic Synthesis written by T. W. Greene and P. G. M. Wuts. For example, when Pr of the compound (55) is an acyl protective group such as a benzoyl group, the compound (47) can be obtained by reacting the compound (55) with a base such as potassium hydroxide or sodium hydroxide.
- 10
15

Examples

[0099]

- Hereinafter, the present invention is further described in details with reference to Reference Examples, Examples and Test Examples, but is not limited thereto, and changes may be made without departing from the scope of the present invention.
- 20

[0100]

- In Reference Examples and Examples below, the purification by column chromatography was performed using a Biotage SNAPCartridge KP-Sil for the "KP-Sil", a Biotage SNAPCartridge HP-Sil for the "HP-Sil", a Biotage SNAPCartridge SNAP Ultra for the "SNAP Ultra", a Biotage SNAPCartridge KP-NH for the "KP-NH", a Grace Reveleris Silica Flash Cartridge for the "Grace", and a Grace Reveleris Amino Flash Cartridge for the "Grace NH".
- 25

[0101]

- For the aftertreatment operation in the following Reference Examples and Examples, a Biotage ISOLUTE Phase Separator was used for the "ISOLUTE Phase Separator".
- 30

[0102]

In Reference Examples and Examples below, the purification by preparative high performance liquid chromatography (HPLC) was carried out under the following conditions.

However, for the case of a compound having a basic functional group and when trifluoroacetic acid is used in the present operation, a neutralization operation, or the like, may sometimes be carried out to obtain a free form.

Device: a Gilson preparative HPLC system

- 5 Column: Shiseido Capcelpak C18 MGII 5 μ m 20 x 150 mm
 Solvent: Liquid A; 0.1% trifluoroacetic acid containing water, Liquid B; 0.1% trifluoroacetic acid containing acetonitrile
 Gradient: 0 min. (Liquid A/Liquid B = 90/10), 22 min. (Liquid A/Liquid B = 20/80), 25 min. (Liquid A/Liquid B = 10/90)
 10 Flow rate: 20 mL/min., Detection method: UV 254 nm
 [0103]

In Reference Examples and Examples below, high performance liquid chromatography mass spectrum (HPLC) were measured by either one of the following 2 conditions.

- 15 Condition 1
 Measurement Instrument: a MicroMass Platform LC and an Agilent Agilent 1100
 Column: Waters SunFire C18 2.5 μ m 4.6 x 50 mm
 Solvent: 0.1% trifluoroacetic acid containing water, Liquid B; 0.1% trifluoroacetic acid containing acetonitrile
 20 Gradient: 0 min. (Liquid A/Liquid B = 90/10), 0.5 min. (Liquid A/Liquid B = 90/10), 5.5 min. (Liquid A/Liquid B = 20/80), 6.0 min. (Liquid A/Liquid B = 1/99), 6.3 min. (Liquid A/Liquid B = 1/99).
 Flow rate: 1 mL/min., Detection method: 254 nm
 Ionization method: Electron Spray method (ESI: Electron Spray Ionization)
 25 Condition 2
 Measurement Instrument: an Agilent Agilent 2900 and Agilent 6150
 Column: Waters Acquity CSH C18 1.7 μ m 2.1 x 50 mm
 Solvent: Liquid A; 0.1% formic acid containing water, Liquid B; 0.1% formic acid containing acetonitrile
 30 Gradient: 0 min. (Liquid A/Liquid B = 80/20), 1.2 to 1.4 min. (Liquid A/Liquid B = 1/99)
 Flow rate: 0.8 mL/min, Detection method: UV 254 nm
 Ionization method: Electron Spray method (ESI: Electron Spray Ionization)
 [0104]

In Reference Examples and Examples below, the mass spectrum (MS) was

measured under the following conditions.

MS Measurement Instrument: Shimadzu LCMS-2010EV or MicroMass Platform LC

In Reference Examples and Examples below, the compounds were named in accordance with ACD/Name (ACD/Labs 12.01, Advanced Chemistry Development Inc.).

5 [0105]

In Reference Examples and Examples, the following terms and reagents are shown as follows.

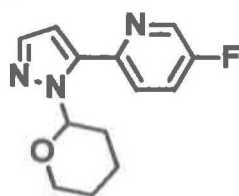
MgSO₄ (magnesium sulfate), Na₂SO₄ (anhydrous sodium sulfate), Na₂CO₃ (sodium carbonate), Cs₂CO₃ (cesium carbonate), KOH (potassium hydroxide), NaHCO₃ (sodium bicarbonate), NaOH
 10 (sodium hydroxide), NH₄Cl (ammonium chloride), DMF (N,N-dimethylformamide), EtOAc (ethyl acetate), CHCl₃ (chloroform), THF (tetrahydrofuran), Et₂O (diethyl ether), MeOH (methanol), EtOH (ethanol), H₂O (water), HATU [O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate], Pd(PPh₃)₄ [tetrakis(triphenylphosphine)palladium (O)], Pd/C (palladium on carbon), brine (saturated saline), Boc (tert-butoxycarbonyl), Ms
 15 (methanesulfonyl), DIPEA (N,N-diisopropylethylamine), MeI (methyl iodide), EtI (ethyl iodide), CuI (copper (I) iodide), NaH (sodium hydride), LAH (LiAlH₄, lithium aluminium hydride), NaBH₄ (sodium borohydride), HCl (hydrogen chloride).

[0106]

Reference Example 1: 5-Fluoro-2-[1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl]pyridine

20 [0107]

[Formula 29]



[0108]

To a mixed solution of 1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (100.5 g, 361.3 mmol), 2-bromo-5-fluoropyridine (56.5 g, 328.5
 25 mmol), and Pd(PPh₃)₄ (37.96 g, 32.85 mmol) in ethanol (300 mL) and toluene (300 mL), a 2M aqueous solution of Na₂CO₃ (492.7 mL, 985.4 mmol) was added, and the resulting mixture was heated to reflux for 2 hours. The reaction mixture was allowed to cool to room temperature, then water and EtOAc were added thereto, and the resulting mixture was stirred at room
 30 temperature for 30 minutes, followed by extraction with EtOAc. The organic layer was washed with brine and dried over MgSO₄, then the drying agent was filtered off, then NH silica gel (400

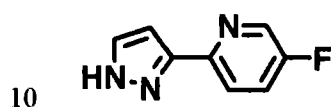
g) was added to the resulting organic layer, and the resulting mixture was stirred for 15 hours. The mixture was filtered through acid silica gel (eluted with n-hexane:EtOAc = 1:1 → EtOAc) and the solvent was distilled off under reduced pressure to obtain the title compound (100 g) (pale yellow oil).

5 MS (ESI pos.) m/z: 248 [M+H]⁺
[0109]

Reference Example 2: 5-Fluoro-2-(1H-pyrazol-3-yl)pyridine

[0110]

[Formula 30]



[0111]

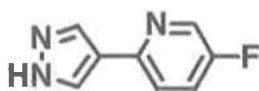
To a solution of 5-fluoro-2-[1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl]pyridine obtained in Reference Example 1 (81.2 g, 328.5 mmol) in methanol (250 mL), a 4M solution of HCl-EtOAc (246.3 mL, 985.4 mmol) was added, and the resulting mixture was stirred at room temperature for 16 hours. The solvent was distilled off under reduced pressure, then EtOAc (500 mL) was added to the residue, and the resulting mixture was heated to reflux for 1 hour. The reaction mixture was allowed to cool to room temperature, then ice-cooled, and then the precipitate was filtered out and dried to obtain a hydrochloride (colorless solid) of the title compound. Water (700 mL) and EtOAc (350 mL) were added to the obtained hydrochloride, and the resulting mixture was stirred for 30 minutes and then separated. The obtained organic layer was extracted with 1.2M hydrochloric acid (100 mL) three times. The aqueous layers were combined and the pH was adjusted to 12 with an 8M aqueous solution of NaOH, and then the organic layer was extracted with chloroform. The extracted organic layer was passed through an ISOLUTE Phase Separator, and the solvent was distilled off under reduced pressure. Diisopropyl ether (300 mL) was added to the obtained residue, and the resulting mixture was heated to reflux for 2 hours. The reaction mixture was allowed to cool to room temperature, then ice-cooled, and then the precipitate was filtered out and dried to obtain the title compound (44.9 g) (pale pink solid).

25 MS (ESI pos.) m/z: 164 [M+H]⁺
[0112]

Reference Example 3: 5-Fluoro-2-(1H-pyrazol-4-yl)pyridine

[0113]

[Formula 31]



[0114]

To a solution of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (15.4 g, 52.5 mmol) and 2-bromo-5-fluoropyridine (8.40 g, 47.7 mmol) in 1,4-dioxane (100 mL), Pd(PPh₃)₄ (5.52 g, 4.77 mmol) and a 2M aqueous solution of Na₂CO₃ (71.6 mL, 143.2 mmol) were added, then the resulting mixture was stirred at 100°C for 3 hours and then at room temperature for 72 hours. Water was added to the reaction mixture, followed by extraction with EtOAc. The organic layer was washed with brine, dried over MgSO₄, then the drying agent was filtered off, and then the solvent was distilled off under reduced pressure. A small amount of EtOAc was added to the obtained residue and the resulting mixture was filtered out and dried to obtain the title compound (4.9 g) (colorless solid).

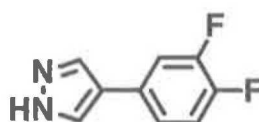
MS (ESI pos.) m/z: 164 [M+H]⁺

[0115]

15 Reference Example 4: 4-(3,4-Difluorophenyl)-1H-pyrazole

[0116]

[Formula 32]



[0117]

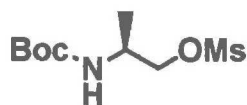
To a mixed solution of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (2.0 g, 6.80 mmol) and 4-bromo-1,2-difluorobenzene (1.19 g, 6.18 mmol) in ethanol (10 mL) and toluene (10 mL), Pd(PPh₃)₄ (0.71 g, 0.62 mmol) and a 2M aqueous solution of Na₂CO₃ (9.26 mL, 18.51 mmol) were added, and the resulting mixture was stirred at 100°C for 30 minutes and then at room temperature for 16 hours. Water was added to the reaction mixture, followed by extraction with EtOAc. The organic layer was washed with brine, dried over MgSO₄, then the drying agent was filtered off, and then the solvent was distilled off under reduced pressure. The obtained residue was purified by column chromatography (SNAP Ultra 100 g, hexane/EtOAc = 88/12 to 0/100) to obtain the title compound (0.55 g) (pale yellow solid).

30 MS (ESI neg.) m/z: 179 [M-H]⁻

[0118]

Reference Example 5: (2S)-2-[(tert-Butoxycarbonyl)amino]propyl methanesulfonate
[0119]

[Formula 33]



5 [0120]

To a solution of tert-butyl [(2S)-1-hydroxypropan-2-yl]carbamate (1.5 g, 8.6 mmol) in chloroform (20 mL), triethylamine (1.78 mL, 12.8 mmol) and methanesulfonyl chloride (0.80 mL, 10.3 mmol) were added under ice-cooling, and the resulting mixture was stirred for 1 hour. Water was added to the reaction mixture, followed by extraction with
10 chloroform. The organic layer was washed with brine, and then was passed through an ISOLUTE Phase Separator. The solvent was distilled off under reduced pressure to obtain the title compound (2.1 g) (yellow solid).

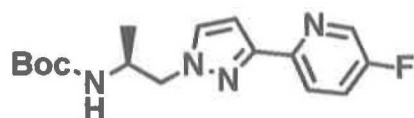
MS (ESI pos.) m/z: 276 [M+Na]⁺

[0121]

15 Reference Example 6: tert-Butyl {(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}carbamate

[0122]

[Formula 34]



20 [0123]

To a solution of 5-fluoro-2-(1H-pyrazol-3-yl)pyridine obtained in Reference Example 2 (0.30 g, 1.6 mmol) in DMF (10 mL), Cs₂CO₃ (1.20 g, 7.36 mmol) and a solution of (2S)-2-[(tert-butoxycarbonyl)amino]propyl methanesulfonate obtained in Reference Example 5 (0.93 g, 3.68 mmol) in DMF were added, and the resulting mixture was heated to 90°C and
25 stirred for 24 hours. The reaction mixture was allowed to cool, then water was added thereto, followed by extraction with EtOAc. The organic layer was washed with water and brine, dried over MgSO₄, then the drying agent was filtered off, and then the solvent was distilled off under reduced pressure. The obtained residue was purified by column chromatography (KP-NH 55g, hexane/EtOAc = 90/10 to 50/50) to obtain the title compound (0.2 g) (colorless solid).

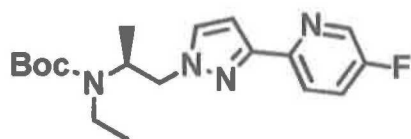
30 MS (ESI pos.) m/z: 321 [M+H]⁺

[0124]

Reference Example 7: tert-Butyl ethyl{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}carbamate

[0125]

[Formula 35]



[0126]

To a solution of tert-butyl {(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}carbamate obtained in Reference Example 6 (0.20 g, 0.62 mmol) in DMF (5 mL), 60% NaH (0.037 g, 0.94 mmol) was added, the resulting mixture was stirred for 30 minutes, then EtI (0.06 mL, 0.75 mmol) was added thereto, and the resulting mixture was stirred for 16 hours. Water was added to the reaction mixture, followed by extraction with EtOAc. The organic layer was washed with water and brine, dried over MgSO₄, then the drying agent was filtered off. The solvent was distilled off under reduced pressure to obtain the title compound (0.25 g) (yellow oil).

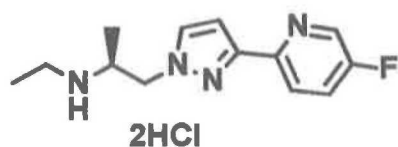
MS (ESI pos.) m/z: 349 [M+H]⁺

[0127]

Reference Example 8: (2S)-N-Ethyl-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-amine dihydrochloride

[0128]

[Formula 36]



[0129]

To a solution of tert-butyl ethyl{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}carbamate obtained in Reference Example 7 (0.22 g, 0.63 mmol) in chloroform (5 mL), a 4M solution of HCl-EtOAc (3.0 mL, 12.0 mmol) was added, and the resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure to obtain the title compound (0.14 g) (yellow solid).

MS (ESI pos.) m/z: 249 [M+H]⁺

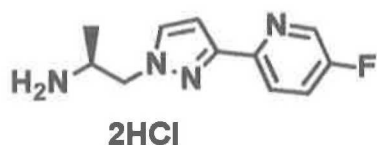
[0130]

Reference Example 9: (2S)-1-[3-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-amine

dihydrochloride

[0131]

[Formula 37]



5 [0132]

By using tert-butyl {(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl} carbamate obtained in Reference Example 6 (1.5 g, 4.68 mmol) as the raw material, the same procedure as in Reference Example 8 was carried out to obtain the title compound (1.2 g) (colorless and amorphous).

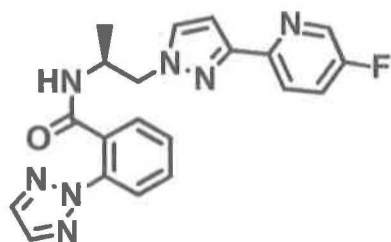
10 MS (ESI pos.) m/z: 221 [M+H]⁺

[0133]

Reference Example: 10 N-[(2S)-1-[3-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl]-2-(2H-1,2,3-triazol-2-yl)benzamide

[0134]

15 [Formula 38]



[0135]

To a solution of (2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-amine dihydrochloride obtained in Reference Example 9 (0.36 g, 1.23 mmol) and 2-(2H-1,2,3-triazol-2-yl)benzoic acid (0.28 g, 1.47 mmol) in DMF (5 mL), HATU (0.707 g, 1.84 mmol) and DIPEA (1.93 mL, 11.1 mmol) were added, and the resulting mixture was stirred for 24 hours. Water was added to the reaction mixture, followed by extraction with EtOAc. The organic layer was washed with water and brine, dried over MgSO₄, then the drying agent was filtered off, and then the solvent was distilled off under reduced pressure. The obtained residue was purified by column chromatography (KP-Sil 50 g, CHCl₃/MeOH = 100/0 to 90/10) to obtain the title compound (0.16 g) (colorless solid).

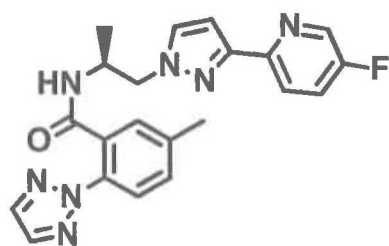
MS (ESI pos.) m/z: 392 [M+H]⁺

[0136]

Reference Example 11: N-{(2S)-1-[3-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0137]

[Formula 39]



[0138]

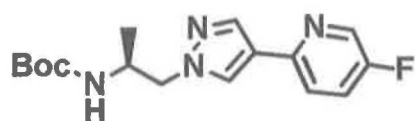
By using (2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-amine dihydrochloride obtained in Reference Example 9 (0.18 g, 0.61 mmol) and 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (0.15 g, 0.74 mmol) as the raw materials, the same procedure as in Reference Example 10 was carried out to obtain the title compound (0.13 g) (colorless solid). MS (ESI pos.) m/z: 406 [M+H]⁺

[0139]

Reference Example 12: tert-Butyl {(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}carbamate

[0140]

[Formula 40]



[0141]

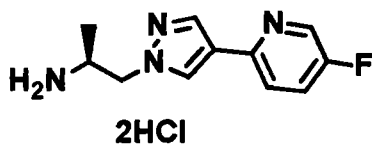
By using (2S)-2-[(tert-butoxycarbonyl)amino]propyl methane sulfonate obtained in Reference Example 5 (3.26 g, 12.87 mmol) and 5-fluoro-2-(1H-pyrazole-4-yl)pyridine (1.40 g, 8.58 mmol) obtained in Reference Example 3 as the raw materials, the same procedure as in Reference Example 6 was carried out to obtain the title compound (2.70 g) (pale yellow oil). MS (ESI pos.) m/z: 321 [M+H]⁺

[0142]

Reference Example 13: (2S)-1-[4-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-amine dihydrochloride

[0143]

[Formula 41]



[0144]

By using tert-butyl {(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl} carbamate obtained in Reference Example 12 (2.70 g, 8.43 mmol) as the raw material, the same procedure as in Reference Example 8 was carried out to obtain the title compound (1.6 g) (colorless solid).

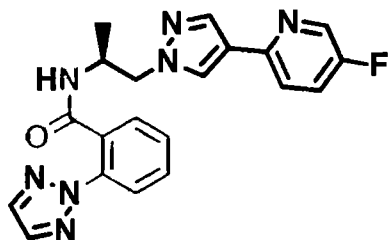
MS (ESI pos.) m/z: 221 [M+H]⁺

[0145]

- Reference Example 14: N-{(2S)-1-[4-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide

[0146]

[Formula 42]



- [0147]

By using (2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-amine dihydrochloride obtained in Reference Example 13 (0.30 g, 1.07 mmol) and 2-(2H-1,2,3-triazol-2-yl)benzoic acid (0.22 g, 1.18 mmol) as the raw materials, the same procedure as in Reference Example 10 was carried out to obtain the title compound (0.24 g) (colorless and amorphous).

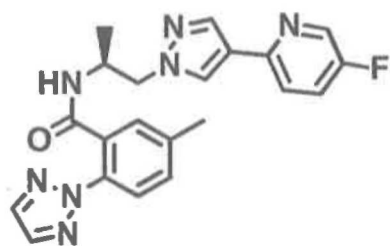
- MS (ESI pos.) m/z: 392 [M+H]⁺

[0148]

Reference Example 15: N-{(2S)-1-[4-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0149]

[Formula 43]



[0150]

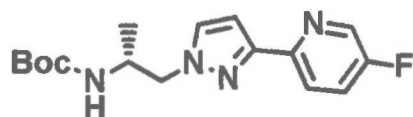
By using (2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-amine dihydrochloride obtained in Reference Example 13 (0.30 g, 1.07 mmol) and 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (0.24 g, 1.18 mmol) as the raw materials, the same procedure as in Reference Example 10 was carried out to obtain the title compound (0.28 g) (colorless solid). MS (ESI pos.) m/z: 406 [M+H]⁺

[0151]

Reference Example 16: tert-Butyl {(2R)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}carbamate

[0152]

[Formula 44]



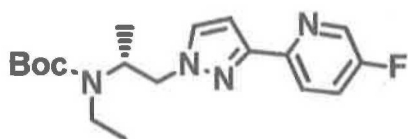
[0153]

To a solution of tert-butyl [(2R)-1-hydroxypropan-2-yl]carbamate (4.3 g, 24.5 mmol) in chloroform (50 mL), triethylamine (6.16 mL, 44.2 mmol) and methanesulfonyl chloride (2.28 mL, 29.5 mmol) were added under ice-cooling, and the resulting mixture was stirred for 1 hour. Water was added to the reaction mixture, followed by extraction with chloroform. The organic layer was washed with brine, then passed through an ISOLUTE Phase Separator, and the solvent was distilled off under reduced pressure. A solution of the obtained residue in DMF and Cs₂CO₃ (7.79 g, 23.9 mmol) were added to a solution of 5-fluoro-2-(1H-pyrazol-3-yl)pyridine obtained in Reference Example 2 (1.30 g, 7.97 mmol) in DMF (50 mL), then the resulting mixture was stirred at 90°C for 2 hours. The reaction mixture was allowed to cool to room temperature, then water was added thereto, followed by extraction with EtOAc. The organic layer was washed with water and brine, dried over MgSO₄, then the drying agent was filtered off, and then the solvent was distilled off under reduced pressure. The obtained residue was purified by column chromatography (HP-Sil 50 g, hexane/EtOAc = 90/10 to 50/50) to obtain the title compound (0.30 g) (colorless solid).

MS (ESI pos.) m/z: 321 [M+H]⁺

[0154]

[Formula 45]



5 [0155]

Reference Example 17: tert-Butyl ethyl{(2R)-1-[3-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}carbamate

[0156]

By using tert-butyl {(2R)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}carbamate obtained in Reference Example 16 (0.30 g, 0.94 mmol) as the raw material, the same procedure as in Reference Example 7 was carried out to obtain the title compound (0.26 g) (pale yellow oil).

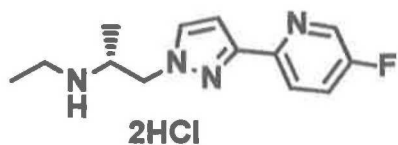
MS (ESI pos.) m/z: 349 [M+H]⁺

[0157]

15 Reference Example 18: (2R)-N-Ethyl-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-amine dihydrochloride

[0158]

[Formula 46]



20 [0159]

By using tert-butyl ethyl{(2R)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}carbamate obtained in Reference Example 17 (0.26 g, 0.75 mmol) as the raw material, the same procedure as in Reference Example 8 was carried out to obtain the title compound (0.17 g) (colorless solid).

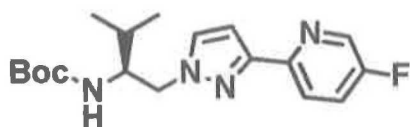
25 MS (ESI pos.) m/z: 249 [M+H]⁺

[0160]

Reference Example 19: tert-Butyl {(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]-3-methylbutan-2-yl}carbamate

[0161]

[Formula 47]



[0162]

By using tert-butyl [(2S)-1-hydroxy-3-methylbutan-2-yl]carbamate (0.5 g, 2.46 mmol) as the raw material, the same procedure as in Reference Example 16 was carried out to obtain the title compound (0.09 g) (colorless solid).

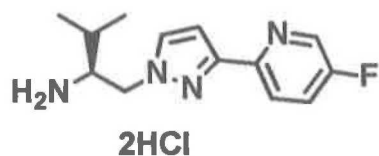
MS (ESI pos.) m/z: 349 [M+H]⁺

[0163]

Reference Example 20: (2S)-1-[3-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]-3-methylbutan-2-amine dihydrochloride

[0164]

[Formula 48]



[0165]

By using tert-butyl {(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]-3-methylbutan-2-yl}carbamate obtained in Reference Example 19 (0.09 g, 0.26 mmol) as the raw material, the same procedure as in Reference Example 8 was carried out to obtain the title compound (0.075 g) (colorless oil).

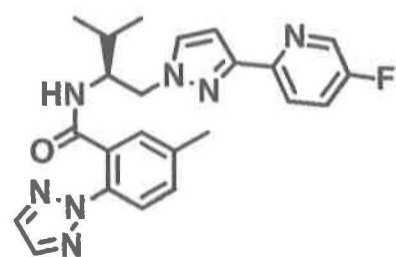
MS (ESI pos.) m/z: 249 [M+H]⁺

[0166]

Reference Example 21 N-{(2S)-1-[3-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]-3-methylbutan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0167]

[Formula 49]



[0168]

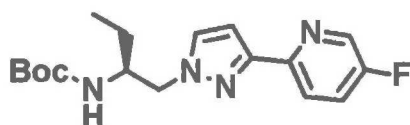
By using (2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]-3-methylbutan-2-amine dihydrochloride obtained in Reference Example 20 (0.075 g, 0.23 mmol) and 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (0.057 g, 0.28 mmol) as the raw materials, the same procedure as in Reference Example 10 was carried out to obtain the title compound (0.05 g) (colorless solid).

MS (ESI pos.) m/z: 434 [M+H]⁺
[0169]

Reference Example 22: tert-Butyl {(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]butan-2-yl}carbamate

[0170]

[Formula 50]



[0171]

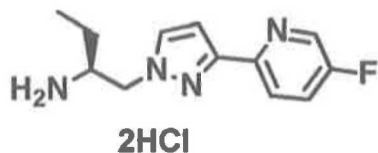
By using tert-butyl [(2S)-1-hydroxybutan-2-yl]carbamate (0.50 g, 2.64 mmol) as the raw material, the same procedure as in Reference Example 16 was carried out to obtain the title compound (0.14 g) (colorless solid).

MS (ESI pos.) m/z: 335 [M+H]⁺
[0172]

Reference Example 23: (2S)-1-[3-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]butan-2-amine dihydrochloride

[0173]

[Formula 51]



[0174]

By using tert-butyl {(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]butan-2-yl}carbamate obtained in Reference Example 22 (0.14 g, 0.42 mmol) as the raw material, the same procedure as in Reference Example 8 was carried out to obtain the title compound (0.06 g) (colorless oil).

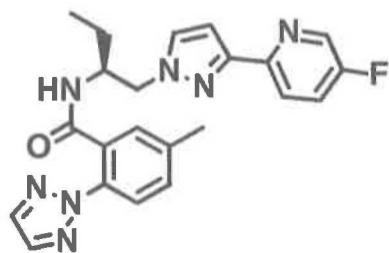
MS (ESI pos.) m/z: 235 [M+H]⁺

[0175]

Reference Example 24: N-{(2S)-1-[3-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]butan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0176]

[Formula 52]



[0177]

By using (2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]butan-2-amine dihydrochloride obtained in Reference Example 23 (0.06 g, 0.20 mmol) and 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (0.048 g, 0.23 mmol) as the raw materials, the same procedure as in Reference Example 10 was carried out to obtain the title compound (0.034 g) (colorless solid).

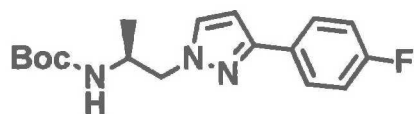
MS (ESI pos.) m/z: 420 [M+H]⁺

[0178]

Reference Example 25: tert-Butyl {(2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}carbamate

[0179]

[Formula 53]



[0180]

By using (2S)-2-[(tert-butoxycarbonyl)amino]propyl methane sulfonate obtained in Reference Example 5 (3.62 g, 14.3 mmol) and 3-(4-fluorophenyl)-1H-pyrazole (1.17 g, 7.2 mmol) as the raw materials, the same procedure as in Reference Example 6 was carried out to obtain the title compound (0.67 g) (colorless solid).

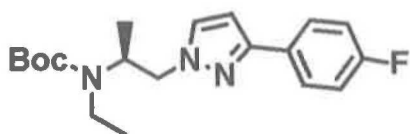
MS (ESI pos.) m/z: 320 [M+H]⁺

[0181]

Reference Example 26: tert-Butyl ethyl{(2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}carbamate

[0182]

[Formula 54]



[0183]

By using tert-butyl {(2S)-1-[3-(4-Fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl} carbamate obtained in Reference Example 25 (0.67 g, 2.10 mmol) as the raw material, the same procedure as in Reference Example 7 was carried out to obtain the title compound (0.35 g) (colorless oil).

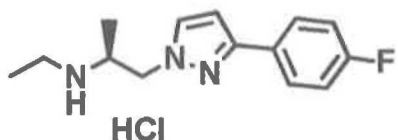
MS (ESI pos.) m/z: 348 [M+H]⁺

[0184]

- 10 Reference Example 27: (2S)-N-Ethyl-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-amine hydrochloride

[0185]

[Formula 55]



- 15 [0186]

By using tert-butyl ethyl{(2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl} carbamate obtained in Reference Example 26 (0.35 g, 1.01 mmol) as the raw material, the same procedure as in Reference Example 8 was carried out to obtain the title compound (0.26 g) (colorless solid).

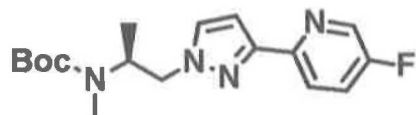
- 20 MS (ESI pos.) m/z: 248 [M+H]⁺

[0187]

Reference Example 28: tert-Butyl {(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl} methyl carbamate

[0188]

- 25 [Formula 56]



[0189]

By using tert-butyl {(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl} carbamate obtained in Reference Example 6 (0.63 g, 1.97 mmol) as the raw material, the

same procedure as in Reference Example 7 was carried out by using MeI (0.19 mL, 2.94 mmol) to obtain the title compound (0.74 g) (pale yellow oil).

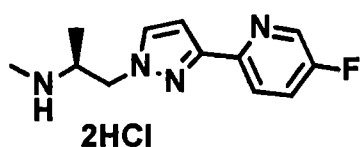
MS (ESI pos.) m/z: 335 [M+H]⁺

[0190]

- 5 Reference Example 29: (2S)-1-[3-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]-N-methylpropan-2-amine dihydrochloride

[0191]

[Formula 57]



- 10 [0192]

By using tert-butyl {(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}methyl carbamate obtained in Reference Example 28 (0.66 g, 1.97 mmol) as the raw material, the same procedure as in Reference Example 8 was carried out to obtain the title compound (0.46 g) (yellow oil).

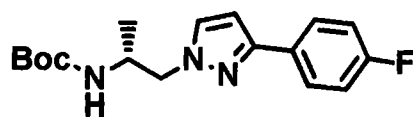
- 15 MS (ESI pos.) m/z: 235 [M+H]⁺

[0193]

Reference Example 30: tert-Butyl {(2R)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}carbamate

[0194]

- 20 [Formula 58]



[0195]

By using tert-butyl [(2R)-1-hydroxypropan-2-yl]carbamate (4.3 g, 24.5 mmol) as the raw material, the same procedure as in Reference Example 16 was carried out to obtain the title compound (1.0 g) (colorless solid).

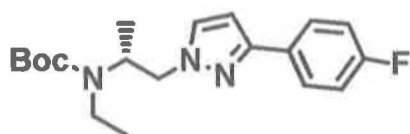
- 25 MS (ESI pos.) m/z: 320 [M+H]⁺

[0196]

Reference Example 31: tert-Butyl ethyl{(2R)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}carbamate

- 30 [0197]

[Formula 59]



[0198]

- By using tert-butyl {(2R)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl} carbamate obtained in Reference Example 30 (1.0 g, 3.13 mmol) as the raw material, the same procedure as in Reference Example 7 was carried out to obtain the title compound (0.65 g) (colorless oil).

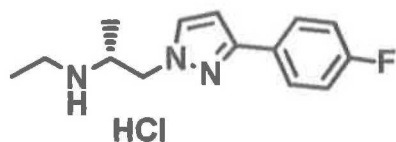
MS (ESI pos.) m/z: 348 [M+H]⁺

[0199]

- 10 Reference Example 32: (2R)-N-Ethyl-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-amine hydrochloride

[0200]

[Formula 60]



- 15 [0201]

By using tert-butyl ethyl{(2R)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl} carbamate obtained in Reference Example 31 (0.65 g, 1.87 mmol) as the raw material, the same procedure as in Reference Example 8 was carried out to obtain the title compound (0.5 g) (colorless solid).

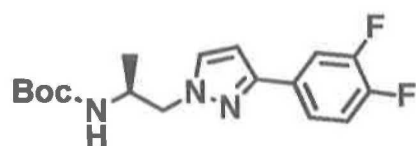
- 20 MS (ESI pos.) m/z: 248 [M+H]⁺

[0202]

Reference Example 33: tert-Butyl {(2S)-1-[3-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl} carbamate

[0203]

- 25 [Formula 61]



[0204]

By using (2S)-2-[(tert-butoxycarbonyl)amino]propyl methane sulfonate obtained

in Reference Example 5 (0.45 g, 1.77 mmol) and 3-(3,4-difluorophenyl)-1H-pyrazole (0.35 g, 1.95 mmol) as the raw materials, the same procedure as in Reference Example 6 was carried out to obtain the title compound (0.30 g) (colorless solid).

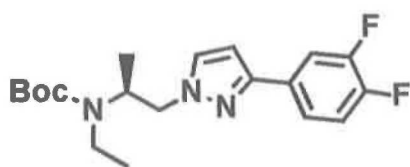
MS (ESI pos.) m/z: 338 [M+H]⁺

5 [0205]

Reference Example 34: tert-Butyl {(2S)-1-[3-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}ethyl carbamate

[0206]

[Formula 62]



10

[0207]

By using tert-butyl {(2S)-1-[3-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}carbamate obtained in Reference Example 33 (0.30 g, 0.89 mmol) as the raw material, the same procedure as in Reference Example 7 was carried out to obtain the title compound (0.34 g) (colorless oil).

15

MS (ESI pos.) m/z: 366 [M+H]⁺

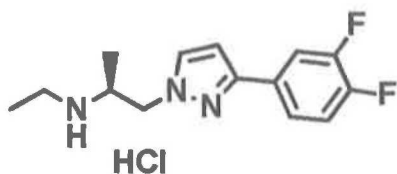
[0208]

Reference Example 35: (2S)-1-[3-(3,4-Difluorophenyl)-1H-pyrazol-1-yl]-N-ethylpropan-2-amine hydrochloride

20

[0209]

[Formula 63]



[0210]

By using tert-butyl {(2S)-1-[3-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}ethyl carbamate obtained in Reference Example 34 (0.33 g, 0.89 mmol) as the raw material, the same procedure as in Reference Example 8 was carried out to obtain the title compound (0.19 g) (colorless solid).

25

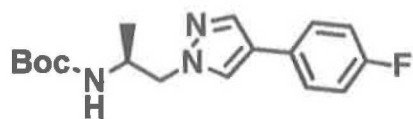
MS (ESI pos.) m/z: 266 [M+H]⁺

[0211]

Reference Example 36: tert-Butyl {(2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}carbamate

[0212]

[Formula 64]



[0213]

By using (2S)-2-[(tert-butoxycarbonyl)amino]propyl methane sulfonate obtained in Reference Example 5 (0.41 g, 2.54 mmol) and 4-(4-fluorophenyl)-1H-pyrazole (0.97 g, 3.81 mmol) as the raw materials, the same procedure as in Reference Example 6 was carried out to obtain the title compound (0.68 g) (colorless solid).

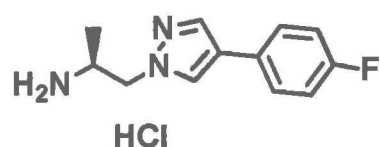
MS (ESI pos.) m/z: 320 [M+H]⁺

[0214]

Reference Example 37: (2S)-1-[4-(4-Fluorophenyl)-1H-pyrazol-1-yl]propan-2-amine hydrochloride

15 [0215]

[Formula 65]



[0216]

By using tert-butyl {(2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}carbamate obtained in Reference Example 36 (0.68 g, 2.11 mmol) as the raw material, the same procedure as in Reference Example 8 was carried out to obtain the title compound (0.54 g) (pale yellow and amorphous).

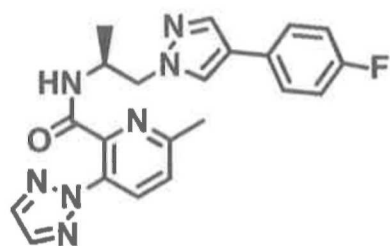
MS (ESI pos.) m/z: 220 [M+H]⁺

[0217]

Reference Example 38: N-{(2S)-1-[4-(4-Fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide

25 [0218]

[Formula 66]



[0219]

By using (2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-amine

- 5 hydrochloride obtained in Reference Example 37 (0.27 g, 1.05 mmol) and 6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxylic acid (0.21 g, 1.05 mmol) as the raw material, the same procedure as in Reference Example 10 was carried out to obtain the title compound (0.26 g) (pale yellow solid).

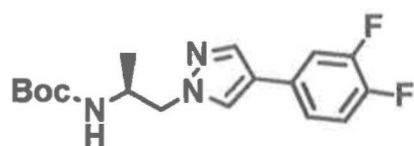
MS (ESI pos.) m/z: 406 [M+H]⁺

[0220]

Reference Example 39: *tert*-Butyl {(2S)-1-[4-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}carbamate

[0221]

[Formula 67]



15

[0222]

By using (2S)-2-[(*tert*-butoxycarbonyl)amino]propyl methane sulfonate obtained in Reference Example 5 (1.16 g, 4.59 mmol) and 4-(3,4-difluorophenyl)-1H-pyrazole obtained in Reference Example 4 (0.55 g, 3.06 mmol) as the raw materials, the same procedure as in

- 20 Reference Example 6 was carried out to obtain the title compound (0.91 g) (colorless solid).

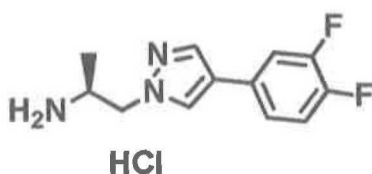
MS (ESI pos.) m/z: 338 [M+H]⁺

[0223]

Reference Example 40: (2S)-1-[4-(3,4-Difluorophenyl)-1H-pyrazol-1-yl]propan-2-amine hydrochloride

25 [0224]

[Formula 68]



[0225]

By using tert-butyl {(2S)-1-[4-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl} carbamate obtained in Reference Example 39 (0.91 g, 2.69 mmol) as the raw material, the same procedure as in Reference Example 8 was carried out to obtain the title compound (0.73 g) (colorless and amorphous).

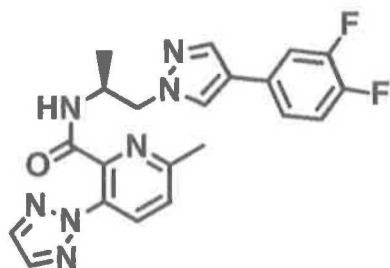
MS (ESI pos.) m/z: 238 [M+H]⁺

[0226]

Reference Example 41: N-{(2S)-1-[4-(3,4-Difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide

[0227]

[Formula 69]



15 [0228]

By using (2S)-1-[4-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-amine hydrochloride obtained in Reference Example 40 (0.37 g, 1.34 mmol) and 6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxylic acid (0.27 g, 1.34 mmol) as the raw materials, the same procedure as in Reference Example 10 was carried out to obtain the title compound (0.35 g) (pale yellow solid).

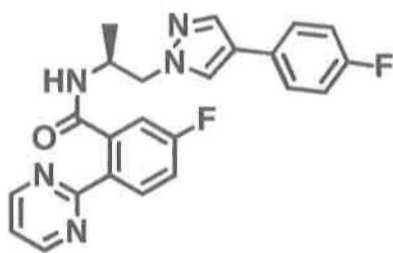
MS (ESI pos.) m/z: 424 [M+H]⁺

[0229]

Reference Example 42: 5-Fluoro-N-{(2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide

25 [0230]

[Formula 70]



[0231]

By using (2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-amine

- 5 hydrochloride obtained in Reference Example 37 (0.27 g, 1.05 mmol) and 5-fluoro-2-(pyrimidin-2-yl)benzoic acid (0.29 g, 1.33 mmol) as the raw materials, the same procedure as in Reference Example 10 was carried out to obtain the title compound (0.30 g) (brown and amorphous).

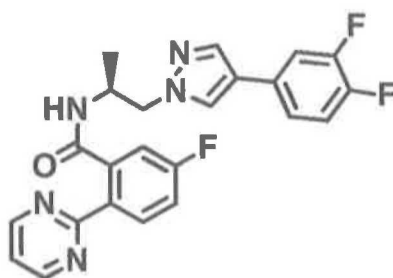
MS (ESI pos.) m/z: 420 [M+H]⁺

[0232]

- 10 Reference Example 43: N-{(2S)-1-[4-(3,4-Difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-5-fluoro-2-(pyrimidin-2-yl)benzamide

[0233]

[Formula 71]



- 15 [0234]

By using (2S)-1-[4-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-amine

hydrochloride obtained in Reference Example 40 (0.37 g, 1.34 mmol) and 5-fluoro-2-(pyrimidin-2-yl)benzoic acid (0.37 g, 1.70 mmol) as the raw materials, the same procedure as in Reference Example 10 was carried out to obtain the title compound (0.43 g) (brown and amorphous).

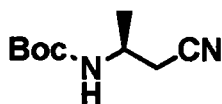
- 20 MS (ESI pos.) m/z: 460 [M+Na]⁺

[0235]

Reference Example 44 tert-Butyl [(2S)-1-cyanopropan-2-yl]carbamate

[0236]

[Formula 72]



[0237]

A solution of sodium cyanide (0.54 g, 11.05 mmol) in DMF (10 mL) was stirred at 35°C for 30 minutes, then tetrabutylammonium bromide (0.28 g, 8.56 mmol) was added, and then the resulting mixture was stirred for 2 hours. To the reaction mixture, a solution of (2S)-2-[(tert-butoxycarbonyl)amino]propyl methane sulfonate obtained in Reference Example 5 (2.17 g, 8.56 mmol) in DMF (2 mL) was added, then the resulting mixture was stirred at 35°C for 4 hours and then at room temperature for 12 hours. Water was added to the reaction mixture, followed by extraction with EtOAc. The organic layer was washed with brine, and then the solvent was distilled off under reduced pressure. The obtained residue was purified by column chromatography (SNAP Ultra 50g, hexane/EtOAc = 95/5 to 60/40) to obtain the title compound (0.91 g) (colorless solid).

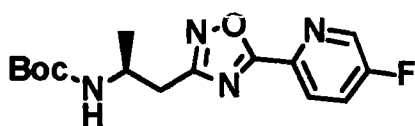
MS (ESI pos.) m/z: 207 [M+Na]⁺

[0238]

Reference Example 45: tert-Butyl {(2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl}carbamate

[0239]

[Formula 73]



20

[0240]

To a solution of tert-butyl [(2S)-1-cyanopropan-2-yl]carbamate obtained in Reference Example 44 (0.91 g, 4.95 mmol) in EtOH (5 mL), a 50% aqueous solution of hydroxylamine (0.65 mL, 9.90 mmol) was added, then the mixture was heated to 90°C and stirred for 14 hours. Water was added to the reaction mixture, followed by extraction with EtOAc, then the organic layer was dried over MgSO₄, then the drying agent was filtered off, and the solvent was distilled off under reduced pressure. To a solution of 5-fluoropyridine-2-carboxylic acid hydrochloride (0.97 g, 5.45 mmol) in DMF (10 mL), 1,1'-carbonyldiimidazole (0.96 g, 5.94 mmol) was added, then the resulting mixture was stirred at room temperature for 1 hour. To the reaction solution, a solution of the residue obtained in the previous process in DMF (3 mL) was added, then the mixture was heated to 90°C and stirred for 7 hours and then at

room temperature for 60 hours. Water was added to the reaction mixture, followed by extraction with EtOAc. The solvent was distilled off under reduced pressure, and the obtained residue was purified by column chromatography (SNAP Ultra 50g, hexane/EtOAc = 98/2 to 30/70) to obtain the title compound (1.16 g) (colorless solid).

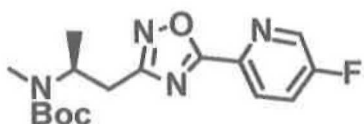
5 MS (ESI pos.) m/z: 345 [M+Na]⁺

[0241]

Reference Example 46: tert-Butyl {(2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl}methyl carbamate

[0242]

10 [Formula 74]



[0243]

By using tert-butyl {(2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl}carbamate obtained in Reference Example 45 (0.58 g, 1.80 mmol) as the raw material, the same procedure as in Reference Example 7 was carried out by using MeI (0.134 mL, 2.16 mmol) to obtain the title compound (0.34 g) (light brown oil).

15 MS (ESI pos.) m/z: 359 [M+Na]⁺

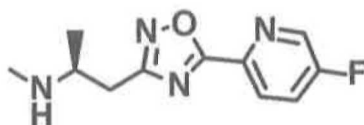
[0244]

Reference Example 47: (2S)-1-[5-(5-Fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]-N-methylpropan-2-amine

20 [0245]

[0245]

[Formula 75]



[0246]

To a solution of tert-butyl {(2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl}methyl carbamate obtained in Reference Example 46 (0.34 g, 1.00 mmol) in chloroform (3 mL), trifluoroacetic acid (1.2 mL, 16.2 mmol) was added, then the resulting mixture was stirred at room temperature for 16 hours. A saturated aqueous solution of NaHCO₃ was added to the reaction mixture, followed by extraction with CHCl₃ and a 10% solution of MeOH/CHCl₃. The solvent was distilled off under reduced pressure to obtain the title compound (0.24 g) (yellow solid).

30 [0246]

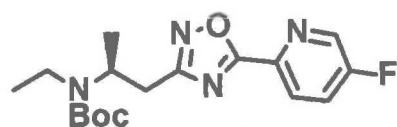
MS (ESI pos.) m/z : 237 $[M+H]^+$

[0247]

Reference Example 48: tert-Butyl ethyl{(2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl}carbamate

5 [0248]

[Formula 76]



[0249]

By using tert-butyl {(2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl}carbamate obtained in Reference Example 45 (0.58 g, 1.80 mmol) as the raw material, the same procedure as in Reference Example 7 was carried out to obtain the title compound (0.22 g) (yellow and amorphous).

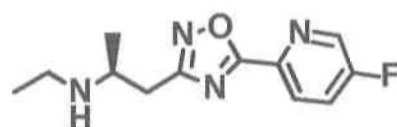
MS (ESI pos.) m/z : 373 $[M+Na]^+$

[0250]

15 Reference Example 49: tert-Butyl {(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}carbamate

[0251]

[Formula 77]



20 [0252]

By using tert-butyl ethyl{(2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl}carbamate obtained in Reference Example 48 (0.22 g, 0.63 mmol) as the raw material, the same procedure as in Reference Example 47 was carried out to obtain the title compound (0.075 g) (yellow solid).

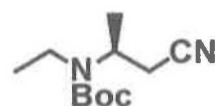
25 MS (ESI pos.) m/z : 251 $[M+H]^+$

[0253]

Reference Example 50: tert-Butyl [(2S)-1-cyanopropan-2-yl]ethyl carbamate

[0254]

[Formula 78]



30

[0255]

By using tert-butyl [(2S)-1-cyanopropan-2-yl]carbamate obtained in Reference Example 44 (1.7 g, 9.23 mmol) as the raw material, the same procedure as in Reference Example 7 was carried out to obtain the title compound (0.94 g) (pale yellow oil).

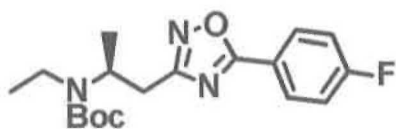
5 MS (ESI pos.) m/z: 213 [M+H]⁺

[0256]

Reference Example 51: (tert-Butyl ethyl{(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl}carbamate

[0257]

10 [Formula 79]



[0258]

By using tert-butyl [(2S)-1-cyanopropan-2-yl]ethyl carbamate obtained in Reference Example 50 (0.45 g, 2.12 mmol) and 4-fluorobenzoic acid (0.33 g, 2.33 mmol) as the raw materials, the same procedure as in Reference Example 45 was carried out to obtain the title compound (0.35 g) (colorless oil).

15 MS (ESI pos.) m/z: 372 [M+Na]⁺

MS (ESI pos.) m/z: 372 [M+Na]⁺

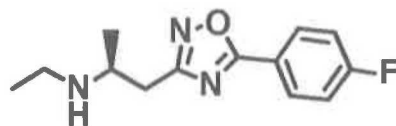
[0259]

Reference Example 52: (2S)-N-Ethyl-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-

20 amine

[0260]

[Formula 80]



[0261]

25 By using (tert-butyl ethyl{(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl}carbamate obtained in Reference Example 51 (0.35 g, 0.99 mmol) as the raw material, the same procedure as in Reference Example 47 was carried out to obtain the title compound (0.24 g) (yellow oil).

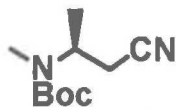
MS (ESI pos.) m/z: 250 [M+H]⁺

30 [0262]

Reference Example 53: tert-Butyl [(2S)-1-cyanopropan-2-yl]methyl carbamate

[0263]

[Formula 81]



[0264]

- 5 By using tert-butyl [(2S)-1-cyanopropan-2-yl]carbamate obtained in Reference Example 44 (0.35 g, 1.90 mmol) as the raw material, the same procedure as in Reference Example 7 was carried out by using MeI (0.142 mL, 2.28 mmol) to obtain the title compound (0.12 g) (pale yellow oil).

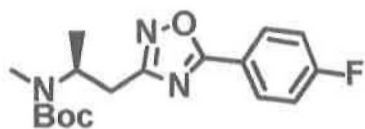
MS (ESI pos.) m/z: 221 [M+Na]⁺

10 [0265]

Reference Example 54: tert-Butyl {(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl}methyl carbamate

[0266]

[Formula 82]



15

[0267]

- By using tert-butyl [(2S)-1-cyanopropan-2-yl]methyl carbamate obtained in Reference Example 53 (0.12 g, 0.59 mmol) and 4-fluorobenzoic acid (0.091 g, 0.65 mmol) as the raw materials, the same procedure as in Reference Example 45 was carried out to obtain the title compound (0.076 g) (colorless oil).

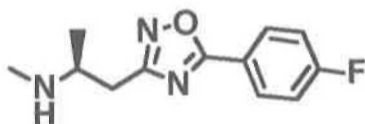
MS (ESI pos.) m/z: 358 [M+Na]⁺

[0268]

Reference Example 55: (2S)-1-[5-(4-Fluorophenyl)-1,2,4-oxadiazol-3-yl]-N-methylpropan-2-amine

25 [0269]

[Formula 83]



[0270]

By using tert-butyl {(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-

yl}methyl carbamate obtained in Reference Example 54 (0.076 g, 0.23 mmol) as the raw material, the same procedure as in Reference Example 47 was carried out to obtain the title compound (0.039 g) (colorless oil).

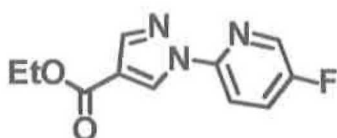
MS (ESI pos.) m/z: 236 [M+H]⁺

5 [0271]

Reference Example 56: Ethyl 1-(5-fluoropyridin-2-yl)-1H-pyrazole-4-carboxylate

[0272]

[Formula 84]



10 [0273]

To a solution of ethyl 1H-pyrazole-4-carboxylate (1.0 g, 7.14 mmol) in DMF (10 mL), 60% NaH (0.29 g, 7.13 mmol) was gradually added under ice-cooling, and the resulting mixture was returned to room temperature and stirred for 1 hour. The resulting mixture was ice-cooled again, then 2,5-difluoropyridine (0.68 g, 5.94 mmol) was added dropwise thereto, then the resulting mixture was stirred at room temperature for 66 hours and then heated to 80°C and stirred for 5 hours. Water (80 mL) was added to the reaction mixture, and the precipitate was filtered out. The obtained precipitate was purified by column chromatography (Grace 12g, hexane/EtOAc = 92/8 to 35/65) to obtain the title compound (0.58 g) (colorless solid).

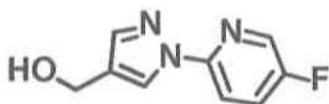
MS (ESI pos.) m/z: 258 [M+Na]⁺

20 [0274]

Reference Example 57: [1-(5-Fluoropyridin-2-yl)-1H-pyrazol-4-yl]methanol

[0275]

[Formula 85]



25 [0276]

To a solution of ethyl 1-(5-fluoropyridin-2-yl)-1H-pyrazole-4-carboxylate obtained in Reference Example 56 (0.67 g, 2.83 mmol) in toluene (12 mL), a 1.02M solution of diisobutylaluminium hydride-hexane (6.10 mL, 6.22 mmol) was added dropwise at -60°C or below, and then the resulting mixture was gradually heated. The resulting mixture was stirred for 3 hours, and then a 1M aqueous solution of HCl (20 mL) was added thereto at -48°C. After extraction with EtOAc, the solvent was distilled off under reduced pressure. The obtained

residue was purified by column chromatography (Grace 12g, hexane/EtOAc = 92/8 to 35/65) to obtain the title compound (0.40 g) (colorless solid).

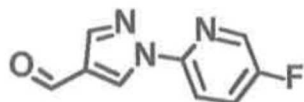
MS (ESI pos.) m/z : 216 $[M+Na]^+$

[0277]

5 Reference Example 58: 1-(5-Fluoropyridin-2-yl)-1H-pyrazole-4-carbaldehyde

[0278]

[Formula 86]



[0279]

10 A solution of [1-(5-fluoropyridin-2-yl)-1H-pyrazol-4-yl]methanol obtained in Reference Example 57 (0.40 g, 2.07 mmol) and MnO_2 (1.80 g, 20.7 mmol) in chloroform (10 mL) was stirred at room temperature for 5.5 hours and then at 60°C for 5 hours. The reaction mixture was filtered through Celite® and washed with chloroform, and then the filtrate was concentrated under reduced pressure to obtain the title compound (0.36 g) (colorless solid).

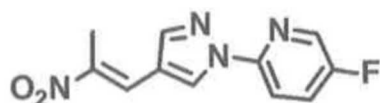
15 MS (ESI pos.) m/z : 192 $[M+H]^+$

[0280]

Reference Example 59: 5-Fluoro-2-{4-[(1E)-2-nitropropan-1-en-1-yl]-1H-pyrazol-1-yl}pyridine

[0281]

[Formula 87]



20

[0282]

A suspension of 1-(5-fluoropyridin-2-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 58 (0.26 g, 1.34 mmol), nitroethane (0.16 g, 2.13 mmol), and formic acid:2-aminoethanol (1:1) (2.0 g, 18.7 mmol) was stirred at room temperature for 19 hours. Water was added to the reaction mixture, followed by extraction with EtOAc. The organic layer was concentrated under reduced pressure and then purified by column chromatography (Grace 12g, hexane/EtOAc = 92/8 to 35/65) to obtain the title compound (0.32 g) (light brown solid).

25

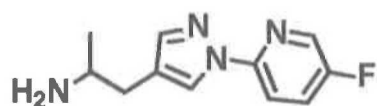
MS (ESI pos.) m/z : 249 $[M+H]^+$

[0283]

30 Reference Example 60: 1-[1-(5-Fluoropyridin-2-yl)-1H-pyrazol-4-yl]propan-2-amine

[0284]

[Formula 88]



[0285]

A solution of 5-fluoro-2-{4-[(1E)-2-nitropropan-1-en-1-yl]-1H-pyrazol-1-yl}pyridine obtained in Reference Example 59 (0.15 g, 0.60 mmol) and 10% Pd/C (0.15 g) in THF-MeOH (10 mL - 5 mL) was stirred at room temperature for 14 hours under a hydrogen atmosphere. The reaction mixture was filtered through Celite® and then the obtained filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography (SNAP KP-NH 28g, hexane/EtOAc = 75/25 to 0/100) to obtain the title compound (0.04 g) (pale yellow oil).

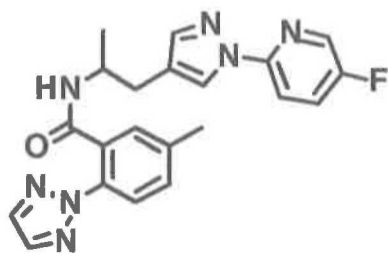
MS (ESI pos.) m/z: 221 [M+H]⁺

[0286]

Reference Example 61: N-{1-[1-(5-Fluoropyridin-2-yl)-1H-pyrazol-4-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0287]

[Formula 89]



[0288]

By using 1-[1-(5-fluoropyridin-2-yl)-1H-pyrazol-4-yl]propan-2-amine obtained in Reference Example 60 (0.043 g, 0.21 mmol) and 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (0.039 g, 0.18 mmol) as the raw materials, the same procedure as in Reference Example 10 was carried out to obtain the title compound (0.005 g) (colorless solid).

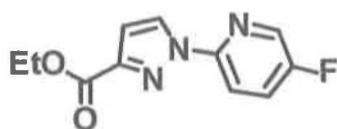
MS (ESI pos.) m/z: 406 [M+H]⁺

[0289]

Reference Example 62: Ethyl 1-(5-fluoropyridin-2-yl)-1H-pyrazole-3-carboxylate

[0290]

[Formula 90]



[0291]

By using ethyl 1H-pyrazole-3-carboxylate (0.50 g, 3.57 mmol) and 2,5-difluoropyridine (0.49 g, 4.28 mmol) as the raw materials, the same procedure as in Reference Example 56 was carried out to obtain the title compound (0.15 g) (colorless solid).

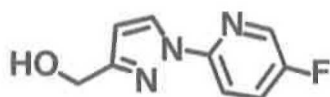
MS (ESI pos.) m/z: 236 [M+H]⁺

[0292]

Reference Example 63: [1-(5-Fluoropyridin-2-yl)-1H-pyrazol-3-yl]methanol

10 [0293]

[Formula 91]



[0294]

By using ethyl 1-(5-fluoropyridin-2-yl)-1H-pyrazole-3-carboxylate obtained in Reference Example 62 (10.0 g, 42.5 mmol) as the raw material, the same procedure as in Reference Example 57 was carried out to obtain the title compound (8.0 g) (pale yellow solid).

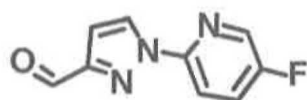
MS (ESI pos.) m/z: 194 [M+H]⁺

[0295]

Reference Example 64: 1-(5-Fluoropyridin-2-yl)-1H-pyrazole-3-carbaldehyde

20 [0296]

[Formula 92]



[0297]

By using [1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl]methanol obtained in Reference Example 63 (8.0 g, 34.0 mmol) as the raw material, the same procedure as in Reference Example 58 was carried out to obtain the title compound (5.3 g) (light brown solid).

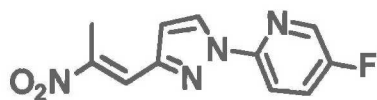
MS (ESI pos.) m/z: 192 [M+H]⁺

[0298]

Reference Example 65: 5-Fluoro-2-{3-[(1E)-2-nitropropan-1-en-1-yl]-1H-pyrazol-1-yl}pyridine

30 [0299]

[Formula 93]



[0300]

By using 1-(5-fluoropyridin-2-yl)-1H-pyrazole-3-carbaldehyde obtained in

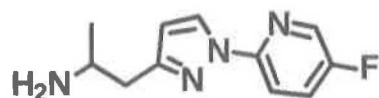
- 5 Reference Example 64 (0.10 g, 0.52 mmol) as the raw material, the same procedure as in Reference Example 59 was carried out to obtain the title compound (0.13 g) (yellow solid). MS (ESI pos.) m/z: 249 [M+H]⁺

[0301]

Reference Example 66: 1-[1-(5-Fluoropyridin-2-yl)-1H-pyrazol-3-yl]propan-2-amine

- 10 [0302]

[Formula 94]



[0303]

A solution of 5-fluoro-2-{3-[(1E)-2-nitropropan-1-en-1-yl]-1H-pyrazol-1-

- 15 yl}pyridine obtained in Reference Example 65 (0.13 g, 0.54 mmol) in THF (2 mL) was added dropwise to a solution of LAH (0.12 g, 3.22 mmol) in THF (3 mL) under ice-cooling. The resulting mixture was stirred per se for 1 hour under ice-cooling, and then heated to room temperature and stirred for 1 hour. Na₂SO₄•10H₂O was added to the reaction mixture, then the reaction was stopped, Na₂SO₄ was added thereto, and then the resulting mixture was stirred.
- 20 Insolubles were separated by filtration through Celite®, then the filtrate was concentrated under reduced pressure. The obtained residue was purified by HPLC to obtain the title compound (0.0068 g) (colorless oil).

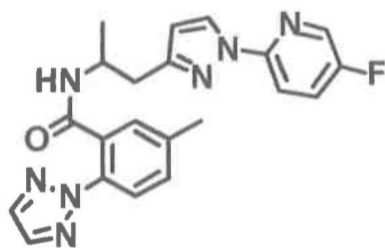
MS (ESI pos.) m/z: 221 [M+H]⁺

[0304]

- 25 Reference Example 67: N-{1-[1-(5-Fluoropyridin-2-yl)-1H-pyrazol-3-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0305]

[Formula 95]



[0306]

By using 1-[1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl]propan-2-amine obtained in

- 5 Reference Example 66 (0.0068 g, 0.031 mmol) and 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (0.0069 g, 0.034 mmol) as the raw materials, the same procedure as in Reference Example 10 was carried out to obtain the title compound (0.0054 g) (colorless and amorphous).

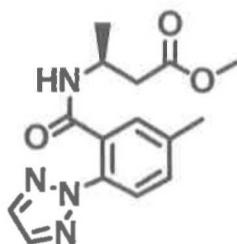
MS (ESI pos.) m/z: 428 [M+Na]⁺

[0307]

- 10 Reference Example 68: Methyl (3S)-3-{[5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoyl]amino}butanoate

[0308]

[Formula 96]



- 15 [0309]

To a suspension of (3S)-3-aminobutanoic acid (0.20 g, 1.94 mmol) in MeOH (1 mL)-THF (1 mL), a solution of 2.0M (diazomethyl)(trimethyl)silane-Et₂O (1.0 mL, 2.0 mmol) was added dropwise, and the mixture was stirred at room temperature for 3 hours. The solvent was distilled off under reduced pressure, then by using the obtained residue and 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (0.26 g, 1.29 mmol) as the raw materials, the same procedure as in Reference Example 10 was carried out to obtain the title compound (0.029 g) (colorless solid).

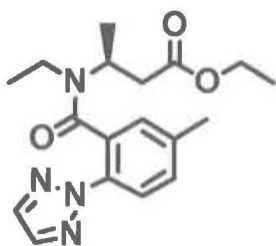
MS (ESI pos.) m/z: 303 [M+H]⁺

[0310]

- Reference Example 69: Ethyl (3S)-3-{ethyl[5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoyl]amino}butanoate

- 25 [0311]

[Formula 97]



[0312]

By using methyl (3S)-3-{{5-methyl-2-(2H-1,2,3-triazol-2-

- 5 yl)benzoyl]amino}butanoate obtained in Reference Example 68 (0.067 g, 0.22 mmol) as the raw material, the same procedure as in Reference Example 7 was carried out to obtain the title compound (0.047 g).

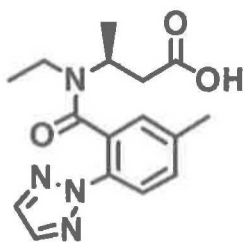
MS (ESI pos.) m/z: 345 [M+H]⁺

[0313]

- 10 Reference Example 70: (3S)-3-{Ethyl[5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoyl]amino}butanoic acid

[0314]

[Formula 98]



- 15 [0315]

A solution of ethyl (3S)-3-{ethyl[5-methyl-2-(2H-1,2,3-triazol-2-

- yl)benzoyl]amino}butanoate obtained in Reference Example 69 (0.044 g, 0.13 mmol) and a 2M aqueous solution of NaOH (0.32 mL, 0.64 mmol) in EtOH (2 mL) was stirred at 60°C for 2 hours. EtOAc (30 mL) was added to the reaction mixture, and the resulting mixture was
- 20 washed with water (30 mL) twice. A 1M aqueous solution of HCl was added to the aqueous layer for adjustment of pH to about 1, and then the resulting mixture was extracted with CHCl₃ (40 mL) three times. The obtained organic layer was allowed to pass through an ISOLUTE Phase Separator, and then the solvent was distilled off under reduced pressure to obtain the title compound (0.029 g) (colorless oil).

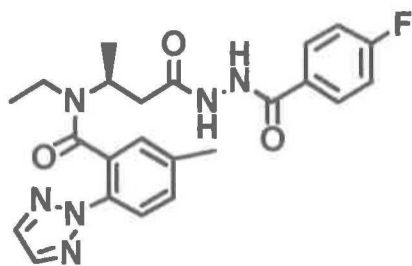
- 25 MS (ESI pos.) m/z: 317 [M+H]⁺

[0316]

Reference Example 71: N-Ethyl-N-{(2S)-4-[2-(4-fluorobenzoyl)hydrazinyl]-4-oxobutan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0317]

[Formula 99]



5

[0318]

By using (3S)-3-{ethyl[5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoyl]amino}butanoic acid obtained in Reference Example 70 (0.028 g, 0.089 mmol) and 4-fluorobenzohydrazide (0.022 g, 0.14 mmol) as the raw materials, the same procedure as in Reference Example 10 was carried out to obtain the title compound (0.027 g) (colorless solid). MS (ESI pos.) m/z: 475 [M+Na]⁺

10

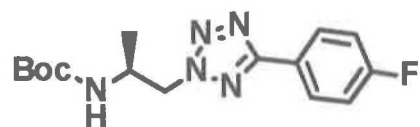
[0319]

Reference Example 72: tert-Butyl {(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}carbamate

15

[0320]

[Formula 100]



[0321]

By using (2S)-2-[(tert-butoxycarbonyl)amino]propyl methane sulfonate obtained in Reference Example 5 (2.89 g, 11.4 mmol) and 5-(4-fluorophenyl)-2H-tetrazole (1.86 g, 11.4 mmol) as the raw materials, the same procedure as in Reference Example 6 was carried out to obtain the title compound (0.54 g) (pale yellow oil).

20

MS (ESI pos.) m/z: 322 [M+H]⁺

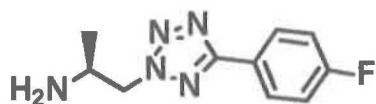
[0322]

25

Reference Example 73: (2S)-1-[5-(4-Fluorophenyl)-2H-tetrazol-2-yl]propan-2-amine

[0323]

[Formula 101]



[0324]

To tert-butyl {(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}carbamate
 5 obtained in Reference Example 72 (0.5 g, 1.6 mmol), a 4M solution of HCl-dioxane (2.0 mL, 8.0 mmol) was added, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure, then chloroform and a saturated aqueous solution of NaHCO₃ were added to the obtained residue for extraction. The obtained organic layer was washed with water and then dried over Na₂SO₄. The drying agent was filtered off,
 10 then the solvent was distilled off under reduced pressure to obtain the title compound (0.34 g) (pale yellow oil).

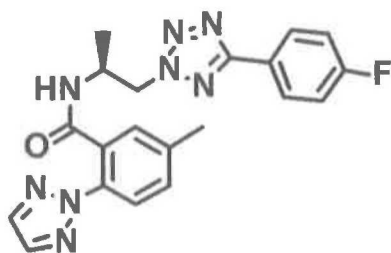
MS (ESI pos.) m/z: 222 [M+H]⁺

[0325]

Reference Example 74: N-{(2S)-1-[5-(4-Fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-5-methyl-
 15 2-(2H-1,2,3-triazol-2-yl)benzamide

[0326]

[Formula 102]



[0327]

20 By using (2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-amine obtained in Reference Example 73 (0.11 g, 0.49 mmol) and 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (0.10 g, 0.49 mmol) as the raw materials, the same procedure as in Reference Example 10 was carried out to obtain the title compound (0.18 g) (pale yellow oil).

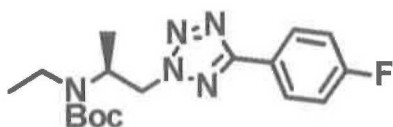
MS (ESI pos.) m/z: 407 [M+H]⁺

25 [0328]

Reference Example 75: tert-Butyl ethyl{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}carbamate

[0329]

[Formula 103]



[0330]

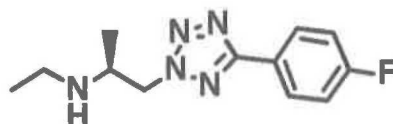
By using tert-butyl {(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}carbamate obtained in Reference Example 72 (0.50 g, 1.56 mmol) as the raw material, the same procedure as in Reference Example 7 was carried out to obtain the title compound (0.26 g) (pale yellow solid).

MS (ESI pos.) m/z: 350 [M+H]⁺

[0331]

Reference Example 76: (2S)-N-Ethyl-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-amine

[Formula 104]



[0333]

By using tert-butyl ethyl{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}carbamate obtained in Reference Example 75 (0.26 g, 0.74 mmol) as the raw material, the same procedure as in Reference Example 73 was carried out to obtain the title compound (0.17 g) (pale yellow oil).

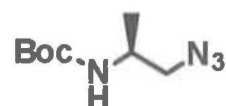
MS (ESI pos.) m/z: 250 [M+H]⁺

[0334]

Reference Example 77: tert-Butyl [(2S)-1-azidepropan-2-yl]carbamate

[0335]

[Formula 105]



[0336]

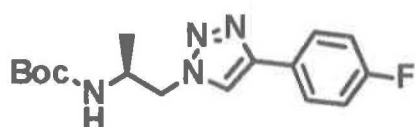
A solution of (2S)-2-[(tert-butoxycarbonyl)amino]propyl methane sulfonate obtained in Reference Example 5 (4.3 g, 17.1 mmol) and sodium azide (3.34 g, 51.4 mmol) in DMF (20 mL) was stirred at 80°C for 3 hours. The reaction mixture was allowed to cool to room temperature, then water was added thereto, followed by extraction with EtOAc. The

obtained organic layer was washed with water, and then dried over Na₂SO₄. The drying agent was filtered off, then the solvent was distilled off under reduced pressure, and then the obtained residue was purified by column chromatography (SNAP Ultra 50g, hexane/EtOAc = 100/0 to 0/100) to obtain the title compound (1.8 g) (pale yellow oil).

- 5 ¹H NMR (600 MHz, CHLOROFORM-d) δ ppm : 1.04 - 1.27 (m, 3 H), 1.44 (s, 9 H), 3.14 - 3.50 (m, 2 H), 3.84 (br. s., 1 H), 4.53 (br. s., 1 H)
[0337]

Reference Example 78: tert-Butyl {(2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}carbamate

- 10 [0338]
[Formula 106]



[0339]

To a solution of tert-butyl [(2S)-1-azidepropan-2-yl]carbamate obtained in

- 15 Reference Example 77 (0.80 g, 4.00 mmol) in DMF/4-methylpiperidine (5 mL/5 mL), 1-ethynyl-4-fluorobenzene (0.48 g, 4.00 mmol), CuI (0.038 g, 0.20 mmol), and L-ascorbic acid (0.14 g, 0.80 mmol) were added, and the resulting mixture was stirred at 80°C for 3 hours. The reaction mixture was allowed to cool to room temperature, and then filtered through Celite®. Water was added to the filtrate, followed by extraction with EtOAc, and the organic layer was washed with
20 water and then dried over Na₂SO₄. The drying agent was filtered off, and then the residue obtained by concentration under reduced pressure was purified by column chromatography (SNAP Ultra 50g, hexane/EtOAc = 100/0 to 0/100) to obtain the title compound (0.82 g) (pale yellow oil).

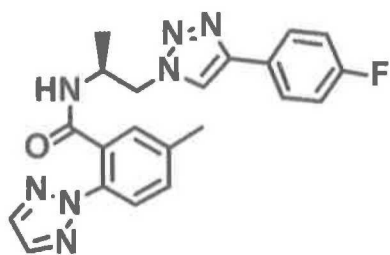
MS (ESI pos.) m/z: 321 [M+H]⁺

- 25 [0340]

Reference Example 79: N-{(2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0341]

[Formula 107]



[0342]

The Boc group was eliminated from tert-butyl {(2S)-1-[4-(4-fluorophenyl)-1H-
 5 1,2,3-triazol-1-yl]propan-2-yl}carbamate obtained in Reference Example 78 (0.79 g, 2.46 mmol)
 by carrying out the same procedure as in Reference Example 73 to obtain pale yellow oil. By
 using the obtained pale yellow oil and 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (0.50 g,
 2.46 mmol) as the raw materials, the same procedure as in Reference Example 10 was carried
 out to obtain the title compound (0.65 g) (pale yellow oil).

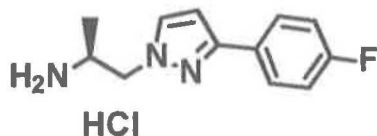
10 MS (ESI pos.) m/z: 406 [M+H]⁺

[0343]

Reference Example 80: (2S)-1-[3-(4-Fluorophenyl)-1H-pyrazol-1-yl]propan-2-amine
 hydrochloride

[0344]

15 [Formula 108]



[0345]

By using tert-butyl {(2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-
 yl}carbamate obtained in Reference Example 25 (3.21 g, 10.1 mmol) as the raw material, the
 20 same procedure as in Reference Example 8 was carried out to obtain the title compound (2.58 g)
 (pale yellow and amorphous).

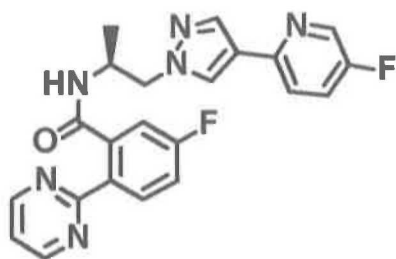
MS (ESI pos.) m/z: 220 [M+H]⁺

[0346]

Reference Example 81: 5-Fluoro-N-{(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-
 25 yl}-2-(pyrimidin-2-yl)benzamide

[0347]

[Formula 109]



[0348]

By using (2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-amine dihydrochloride obtained in Reference Example 13 (0.10 g, 0.36 mmol) and 5-fluoro-2-(pyrimidin-2-yl)benzoic acid (0.099 g, 0.46 mmol) as the raw materials, the same procedure as in Reference Example 10 was carried out to obtain the title compound (0.028 g) (colorless and amorphous).

MS (ESI pos.) m/z: 421 [M+H]⁺

10 [0349]

Reference Examples 82 to 86 were obtained by the same procedure as in Reference Example 81. The structural formula, the names, and MS data of the obtained compounds are shown in Table 1.

[0350]

[Table 1]

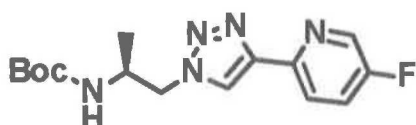
Reference Example No.	Structural formula	Compound name	MS (ESI pos.) m/z
Reference Example 82		N-[(2S)-1-[4-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl]-5-methyl-2-(pyrimidin-2-yl)benzamide	417(M+H)+
Reference Example 83		5-Fluoro-N-[(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl]-2-(2H-1,2,3-triazol-2-yl)benzamide	410(M+H)+
Reference Example 84		5-Chloro-N-[(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl]-2-(pyrimidin-2-yl)benzamide	459(M+Na)+
Reference Example 85		N-[(2S)-1-[3-(4-Fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	405(M+H)+
Reference Example 86		N-[(2S)-1-[4-(4-Fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	405(M+H)+

[0351]

Reference Example 87: tert-Butyl {(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-yl}carbamic acid

[0352]

[Formula 110]



[0353]

By using tert-butyl [(2S)-1-azidepropan-2-yl]carbamate obtained in Reference Example 77 (0.50 g, 2.48 mmol) and 2-ethynyl-5-fluoropyridine (0.30 g, 2.48 mmol) as the raw materials, the same procedure as in Reference Example 78 was carried out to obtain the title

compound (0.58 g) (colorless solid).

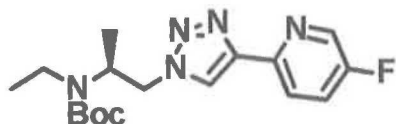
MS (ESI pos.) m/z: 322 [M+H]⁺

[0354]

Reference Example 88: tert-Butyl ethyl{(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-yl}carbamate

[0355]

[Formula 111]



[0356]

By using tert-butyl {(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-yl}carbamic acid obtained in Reference Example 87 (0.30 g, 0.93 mmol) as the raw material, the same procedure as in Reference Example 7 was carried out to obtain the title compound (0.33 g) (colorless oil).

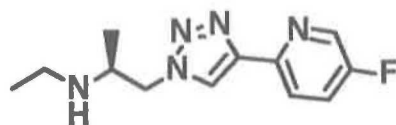
MS (ESI pos.) m/z: 350 [M+H]⁺

[0357]

Reference Example 89: (2S)-N-Ethyl-1-[4-(5-fluoropyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-amine

[0358]

[Formula 112]



[0359]

By using tert-butyl ethyl{(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-yl}carbamate obtained in Reference Example 88 (0.33 g, 0.93 mmol) as the raw material, the same procedure as in Reference Example 73 was carried out to obtain the title compound (0.19 g) (colorless oil).

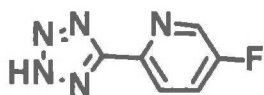
MS (ESI pos.) m/z: 250 [M+H]⁺

[0360]

Reference Example 90: 5-Fluoro-2-(2H-tetrazol-5-yl)pyridine

[0361]

[Formula 113]



[0362]

An aqueous solution (16 mL) of 5-fluoropyridine-2-carbonitrile (1.0 g, 8.19 mmol), zinc dibromide (1.84 g, 8.19 mmol), and sodium azide (0.59 g, 9.01 mmol) was stirred at 110°C for 15 hours. A 2M aqueous solution of HCl (20 mL) and EtOAc (70 mL) were added to the reaction solution, and the resulting mixture was intensely stirred at room temperature for 1 hour until the solid dissolved. After extraction with EtOAc, the organic layer was washed with brine and dried over Na₂SO₄. The drying agent was filtered off, and then the solvent was distilled off under reduced pressure. The obtained solid was washed with Et₂O and filtered out to obtain the title compound (1.17 g) (colorless solid).

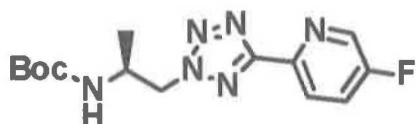
MS (ESI pos.) m/z: 166 [M+H]⁺

[0363]

Reference Example 91: tert-Butyl {(2S)-1-[5-(5-fluoropyridin-2-yl)-2H-tetrazol-2-yl]propan-2-yl}carbamic acid

[0364]

[Formula 114]



[0365]

By using (2S)-2-[(tert-butoxycarbonyl)amino]propyl methane sulfonate obtained in Reference Example 5 (1.30 g, 5.14 mmol) and 5-fluoro-2-(2H-tetrazol-5-yl)pyridine obtained in Reference Example 90 (0.85 g, 5.14 mmol) as the raw materials, the same procedure as in Reference Example 6 was carried out to obtain the title compound (0.42 g) (colorless solid).

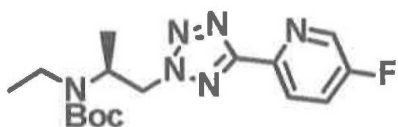
MS (ESI pos.) m/z: 345 [M+Na]⁺

[0366]

Reference Example 92: tert-Butyl ethyl{(2S)-1-[5-(5-fluoropyridin-2-yl)-2H-tetrazol-2-yl]propan-2-yl}carbamate

[0367]

[Formula 115]



30

[0368]

By using tert-butyl {(2S)-1-[5-(5-fluoropyridin-2-yl)-2H-tetrazol-2-yl]propan-2-yl}carbamic acid obtained in Reference Example 91 (0.42 g, 1.32 mmol) as the raw material, the same procedure as in Reference Example 7 was carried out to obtain the title compound (0.45 g) (colorless oil).

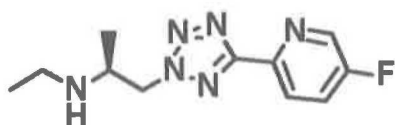
MS (ESI pos.) m/z: 373 [M+Na]⁺

[0369]

Reference Example 93: (2S)-N-Ethyl-1-[4-(5-fluoropyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-amine

[0370]

[Formula 116]



[0371]

By using tert-butyl ethyl{(2S)-1-[5-(5-fluoropyridin-2-yl)-2H-tetrazol-2-yl]propan-2-yl}carbamate obtained in Reference Example 92 (0.45 g, 1.29 mmol) as the raw material, the same procedure as in Reference Example 73 was carried out to obtain the title compound (0.31 g) (colorless oil).

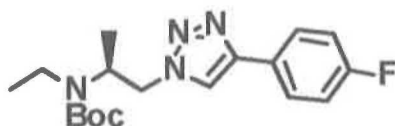
MS (ESI pos.) m/z: 251 [M+H]⁺

[0372]

Reference Example 94: tert-Butyl ethyl{(2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}carbamate

[0373]

[Formula 117]



[0374]

By using tert-butyl {(2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}carbamate obtained in Reference Example 78 (0.50 g, 1.56 mmol) as the raw material, the same procedure as in Reference Example 7 was carried out to obtain the title compound (0.54 g) (colorless oil).

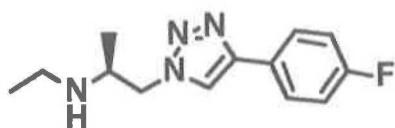
MS (ESI pos.) m/z: 349 [M+H]⁺

[0375]

Reference Example 95: ((2S))-N-Ethyl-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-amine

[0376]

[Formula 118]



[0377]

By using tert-butyl ethyl{(2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}carbamate obtained in Reference Example 94 (0.54 g, 1.56 mmol) as the raw material, the same procedure as in Reference Example 73 was carried out to obtain the title

10 compound (0.39 g) (colorless oil).

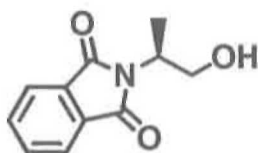
MS (ESI pos.) m/z: 249 [M+H]⁺

[0378]

Reference Example 96: 2-[(2S)-1-Hydroxypropan-2-yl]-1H-isindole-1,3(2H)-dione

[0379]

15 [Formula 119]



[0380]

A solution of (2S)-2-aminopropan-1-ol (10 g, 133 mmol) and 2-benzofuran-1,3-dione (19.7 g, 133 mmol) in toluene (100 mL) was heated to reflux for 6 hours. A saturated aqueous solution of NaHCO₃ was added to the reaction mixture, followed by extraction with EtOAc. The organic layer was washed with water, dried over Na₂SO₄, and then the drying agent was filtered off. The solvent was distilled off under reduced pressure to obtain the title compound (24.3 g) (pale yellow solid).

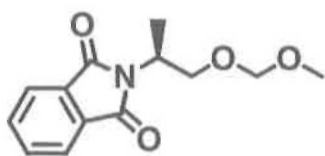
MS (ESI pos.) m/z: 206 [M+H]⁺

25 [0381]

Reference Example 97: 2-[(2S)-1-(Methoxymethoxy)propan-2-yl]-1H-isindole-1,3(2H)-dione

[0382]

[Formula 120]



[0383]

To a solution of 2-[(2S)-1-hydroxypropan-2-yl]-1H-isindole-1,3(2H)-dione
 5 obtained in Reference Example 96 (16.7 g, 81.4 mmol) and DIPEA (21.3 mL, 122 mmol) in
 chloroform (50 mL), chloro(methoxy)methane (8.52 g, 106 mmol) was added at 0°C, and the
 mixture was heated to room temperature and stirred for 3 hours. Water was added to the
 reaction mixture, followed by extraction with EtOAc. The organic layer was washed with
 water, dried over Na₂SO₄, and then the drying agent was filtered off. The obtained residue was
 10 purified by column chromatography (SNAP Ultra 50g, hexane/EtOAc = 100/0 to 0/100) to
 obtain the title compound (9.3 g) (pale yellow oil).

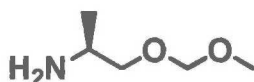
MS (ESI pos.) m/z: 250 [M+H]⁺

[0384]

Reference Example 98: (2S)-1-(Methoxymethoxy)propan-2-amine

15 [0385]

[Formula 121]



[0386]

A solution of 2-[(2S)-1-(methoxymethoxy)propan-2-yl]-1H-isindole-1,3(2H)-
 20 dione obtained in Reference Example 97 (9.7 g, 38.9 mmol) and hydrazine monohydrate (1.95 g,
 38.9 mmol) in EtOH (50 mL) was stirred at 80°C for 2 hours. The reaction mixture was
 allowed to cool to room temperature, then the solvent was distilled off under reduced pressure to
 obtain pale yellow solid. Chloroform was added thereto, then the resulting mixture was stirred
 and filtered. The filtrate was concentrated under reduced pressure to obtain the title compound
 25 (2.3 g) (pale yellow oil).

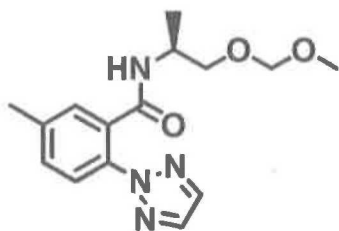
¹H NMR (200 MHz, CHLOROFORM-d) δ ppm 1.07 (d, J=6.15 Hz, 3 H) 3.01 - 3.54 (m, 6 H)
 4.65 (s, 2 H)

[0387]

Reference Example 99: N-[(2S)-1-(Methoxymethoxy)propan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-
 30 2-yl)benzamide

[0388]

[Formula 122]



[0389]

By using (2S)-1-(methoxymethoxy)propan-2-amine obtained in Reference

- 5 Example 98 (0.92 g, 7.7 mmol) and 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (1.57 g, 7.7 mmol) as the raw materials, the same procedure as in Reference Example 10 was carried out to obtain the title compound (2.3 g) (pale yellow oil).

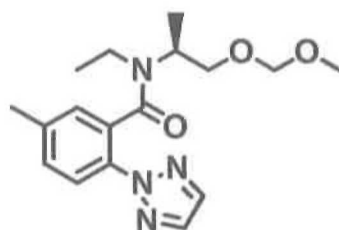
MS (ESI pos.) m/z: 305 [M+H]⁺

[0390]

- 10 Reference Example 100: N-Ethyl-N-[(2S)-1-(methoxymethoxy)propan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0391]

[Formula 123]



- 15 [0392]

By using N-[(2S)-1-(methoxymethoxy)propan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide obtained in Reference Example 99 (2.28 g, 7.5 mmol) as the raw material, the same procedure as in Reference Example 7 was carried out by using EtI (0.90 mL, 11.3 mmol) to obtain the title compound (1.34 g) (pale yellow solid).

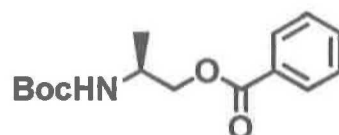
- 20 MS (ESI pos.) m/z: 333 [M+H]⁺

[0393]

Reference Example 101: (2S)-2-[(tert-Butoxycarbonyl)amino]propyl benzoate

[0394]

[Formula 124]



[0395]

To a solution of tert-butyl [(2S)-1-hydroxypropan-2-yl]carbamate (2.0 g, 11.4 mmol) in chloroform (24 mL), triethylamine (2.1 mL, 14.8 mmol) and benzoyl chloride (1.6 mL, 13.7 mmol) were added under ice-cooling, and the resulting mixture was stirred for 4.5 hours under continuous ice-cooling. The reaction solution was washed with water twice after dilution with chloroform, and then the resultant was dried over MgSO_4 . The drying agent was filtered off, the solvent was distilled off under reduced pressure, then the obtained solid was washed with hexane under stirring, and then filtered out and dried under reduced pressure to obtain the title compound (3.11 g) (colorless solid).

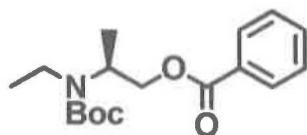
10 MS (ESI pos.) m/z: 302[M+Na]⁺

[0396]

Reference Example 102: (2S)-2-[(tert-Butoxycarbonyl)(ethyl)amino]propyl benzoate

[0397]

[Formula 125]



15

[0398]

By using (2S)-2-[(tert-butoxycarbonyl)amino]propyl benzoate obtained in Reference Example 101 (1.50 g, 5.37 mmol) as the raw material, the same procedure as in Reference Example 7 was carried out by using EtI (0.48 mL, 5.91 mmol) to obtain the title compound (1.56 g) (colorless oil).

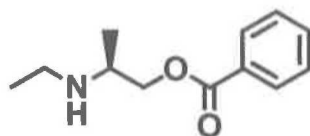
20

MS (ESI pos.) m/z: 330[M+Na]⁺

Reference Example 103: (2S)-2-(Ethylamino)propyl benzoate

[0399]

25 [Formula 126]



[0400]

By using (2S)-2-[(tert-butoxycarbonyl)(ethyl)amino]propyl benzoate obtained in Reference Example 102 (0.50 g, 1.63 mmol) as the raw material, the same procedure as in Reference Example 73 was carried out to obtain the title compound (0.20 g) (colorless oil).

30

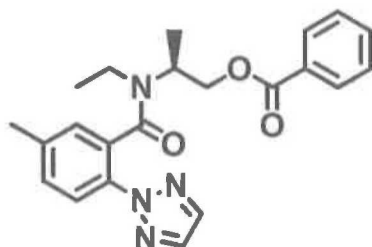
MS (ESI pos.) m/z: 208[M+H]⁺

[0401]

Reference Example 104: (2S)-2-{Ethyl[5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoyl]amino}propyl benzoate

5 [0402]

[Formula 127]



[0403]

By using (2S)-2-(ethylamino)propyl benzoate obtained in Reference Example 103

- 10 (0.39 g, 1.94 mmol) and 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (0.44 g, 2.13 mmol) as the raw materials, the same procedure as in Reference Example 10 was carried out to obtain the title compound (0.56 g) (pale yellow solid).

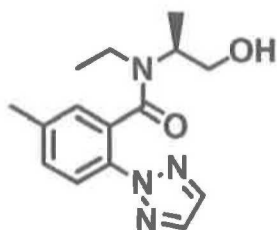
MS (ESI pos.) m/z: 393 [M+H]⁺

[0404]

- 15 Reference Example 105-1: N-Ethyl-N-[(2S)-1-hydroxypropan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0405]

[Formula 128]



20 [0406]

To N-ethyl-N-[(2S)-1-(methoxymethoxy)propan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide obtained in Reference Example 100 (1.34 g, 4.0 mmol), a 4M solution of HCl-dioxane (5.0 mL, 20.0 mmol) was added, and the resulting mixture was stirred at room temperature for 2 hours. The solvent was distilled off under reduced pressure, then a saturated aqueous solution of NaHCO₃ was added to the obtained residue, followed by extraction with chloroform. The organic layer was washed with water and then dried over MgSO₄. The drying agent was filtered off, the solvent was distilled off under reduced pressure, and the

obtained residue was purified by column chromatography (SNAP Ultra 50g, hexane/EtOAc = 80/20 to 0/100) to obtain the title compound (0.89 g) (colorless solid).

MS (ESI pos.) m/z: 289 [M+H]⁺

[0407]

- 5 Reference Example 105-2: N-Ethyl-N-[(2S)-1-hydroxypropan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

The title compound can also be obtained by the following procedure. A solution of (2S)-2-{ethyl[5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoyl]amino}propyl benzoate obtained in Reference Example 104 (0.40 g, 1.02 mmol) and a 3M aqueous solution of KOH (0.51 mL, 1.53 mmol) in MeOH (4 mL) was stirred at room temperature for 12 hours. EtOAc was added to the reaction solution, then the resulting mixture was washed with a saturated aqueous solution of NaHCO₃, water, and brine, and then the solvent was distilled off under reduced pressure. The obtained residue was purified by column chromatography (Grace NH 12g, hexane/EtOAc = 84/16 to 0/100) to obtain the title compound (0.29 g) (colorless oil).

15 [0408]

Reference Example 105-3: N-Ethyl-N-[(2S)-1-hydroxypropan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

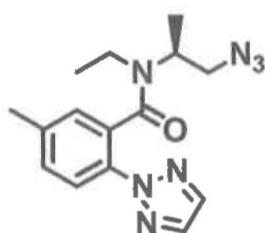
The title compound can also be obtained by the following procedure. By using (2S)-2-(ethylamino)propan-1-ol (0.14 g, 1.35 mmol) and 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (0.25 g, 1.23 mmol) as the raw materials, the same procedure as in Reference Example 10 was carried out to obtain the title compound (0.31 g) (colorless oil).

20 [0409]

Reference Example 106: N-[(2S)-1-Azidepropan-2-yl]-N-ethyl-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

25 [0410]

[Formula 129]



[0411]

To a solution of N-ethyl-N-[(2S)-1-hydroxypropan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide obtained in Reference Example 105 (0.51 g, 1.77 mmol) in chloroform

30

(10 mL), triethylamine (0.49 mL, 3.54 mmol) and methanesulfonyl chloride (0.21 mL, 2.65 mmol) were added, and then the resulting mixture was stirred at room temperature for 1 hour. A saturated aqueous solution of NaHCO₃ was added to the reaction mixture at 0°C, then the resulting mixture was extracted with chloroform, and then the solvent was distilled off under reduced pressure. Sodium azide (0.13 g, 1.95 mmol) was added to a solution of the obtained residue in DMF (10 mL), and the resulting mixture was heated to 80°C and stirred for 3 hours. The reaction mixture was allowed to cool to room temperature, then water was added thereto, followed by extraction with EtOAc. The organic layer was dried over Na₂SO₄, the drying agent was filtered off, and the solvent was distilled off under reduced pressure to obtain the title compound (0.48 g) (pale yellow oil).

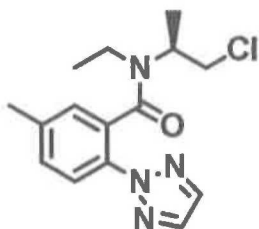
MS (ESI pos.) m/z: 314 [M+H]⁺

[0412]

Reference Example 107: N-[(2S)-1-Chloropropan-2-yl]-N-ethyl-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0413]

[Formula 130]



[0414]

Thionyl chloride (0.03 mL, 0.42 mmol) was added to a solution of N-ethyl-N-[(2S)-1-hydroxypropan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide obtained in Reference Example 105 (0.10 g, 0.35 mmol) in chloroform (1.5 mL), and the resulting mixture was heated to reflux for 5 hours. The solvent was distilled off under reduced pressure before dissolution of the obtained residue in EtOAc. NH silica gel (about 1 g) was added thereto, then the resulting mixture was stirred at room temperature for 10 minutes, then insolubles were filtered off, and then the solvent was concentrated under reduced pressure to obtain the title compound (0.11 g) (colorless oil).

MS (ESI pos.) m/z: 307 [M+H]⁺

[0415]

Reference Example 108: N-[(2S)-1-Cyanopropan-2-yl]-N-ethyl-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0416]

[Formula 131]



[0417]

- 5 By using N-[(2S)-1-chloropropan-2-yl]-N-ethyl-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide obtained in Reference Example 107 (0.11 g, 0.35 mmol) as the raw material, the same procedure as in Reference Example 44 was carried out to obtain the title compound (0.10 g) (colorless oil).

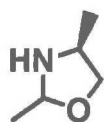
MS (ESI pos.) m/z: 298 [M+H]⁺

10 [0418]

Reference Example 109: (4S)-2,4-Dimethyl-1,3-oxazolidine

[0419]

[Formula 132]



15 [0420]

- MgSO₄ (12.0 g, 99.9 mmol) was added to a solution of (2S)-2-aminopropan-1-ol (5.0 g, 66.6 mmol) in chloroform (67 mL) under ice-cooling. A 90% aqueous solution of acetaldehyde (3.91 mL, 79.9 mmol) was added dropwise to the obtained suspension, then the resulting mixture was stirred for 30 minutes and then at room temperature overnight. The reaction solution was filtered, and then the filtrate was concentrated under reduced pressure to obtain the title compound (4.0 g) (colorless oil).

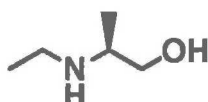
MS (ESI pos.) m/z: 102 [M+H]⁺

[0421]

Reference Example 110: (2S)-2-(Ethylamino)propan-1-ol

25 [0422]

[Formula 133]



[0423]

NaBH₄ (0.38 g, 10.1 mmol) was added to a solution of (4S)-2,4-dimethyl-1,3-oxazolidine obtained in Reference Example 109 (1.0 g, 5.07 mmol) in EtOH (5 mL) under ice-cooling, and the resulting mixture was stirred at room temperature for 18 hours. H₂O (1 mL) was added to the reaction solution, then the resulting mixture was filtered, and then the filtrate was concentrated under reduced pressure. The obtained residue was poured into H₂O, followed by extraction with Et₂O, and then the extract was dried over MgSO₄. The drying agent was filtered off, then the solvent was distilled off under reduced pressure to obtain the title compound (0.6 g) (colorless oil).

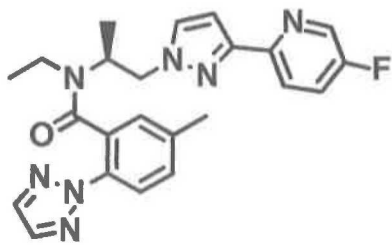
MS (ESI pos.) m/z: 104 [M+H]⁺

[0424]

Example 1: N-Ethyl-N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0425]

[Formula 134]



[0426]

To a solution of (2S)-N-ethyl-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-amine dihydrochloride obtained in Reference Example 8 (0.14 g, 0.44 mmol) in DMF (5.0 mL), 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (0.11 g, 0.52 mmol), HATU (0.25 g, 0.65 mmol), and DIPEA (0.68 mL, 3.92 mmol) were added, and the resulting mixture was stirred at room temperature for 24 hours. Water was added to the reaction solution, followed by extraction with EtOAc. The organic layer was washed with a saturated aqueous solution of NaHCO₃ and brine and dried over MgSO₄, then the drying agent was filtered off, and then the solvent was distilled off under reduced pressure. The obtained residue was purified by column chromatography (KP-OH 25g, hexane/EtOAc = 80/20 to 20/80) and HPLC to obtain the title compound (0.027 g) (colorless and amorphous).

LCMS retention time 5.07 min.

MS (ESI pos.) m/z: 434 [M+H]⁺

[0427]

Examples 2 to 17 were obtained by the same procedure as in Example 1. The

structural formula, the names, and LCMS data of the obtained compounds are shown in Tables 2-1 and 2-2.

[0428]

[Table 2-1]

Example No.	Structural formula	Compound name	MS (ESI pos.) m/z	LCMS measurement condition Retention time (min)
Example 2		N-Ethyl-N-((2R)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	434(M+H)+	Condition 1 5.08
Example 3		N-Ethyl-N-((2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide	434(M+H)+	Condition 2 0.974, 1.053
Example 4		N-((2S)-1-[3-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N-methyl-2-(pyrimidin-2-yl)benzamide	417(M+H)+	Condition 2 0.819
Example 5		5-Fluoro-N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N-methyl-2-(pyrimidin-2-yl)benzamide	435(M+H)+	Condition 2 0.733, 0.828, 0.868
Example 6		N-((2S)-1-[3-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N,5-dimethyl-2-(pyrimidin-2-yl)benzamide	431 (M+H)+	Condition 2 0.781, 0.830, 0.881
Example 7		N-Ethyl-N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide	431 (M+H)+	Condition 2 0.86
Example 8		N-Ethyl-5-fluoro-N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide	449 (M+H)+	Condition 2 0.814, 0.973
Example 9		N-Ethyl-5-fluoro-N-((2R)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide	449 (M+H)+	Condition 2 0.98

[0429]

[Table 2-2]

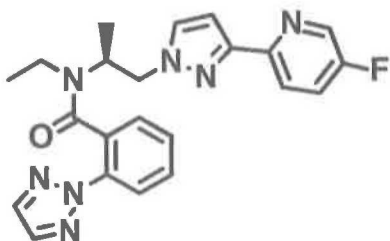
Example No.	Structural formula	Compound name	MS (ESI pos.) m/z	LCMS measurement condition Retention time (min)
Example 10		N-Ethyl-N-((2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide	430 (M+H) +	Condition 2 1.007
Example 11		N-Ethyl-5-fluoro-N-((2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide	448 (M+H) +	Condition 2 0.962, 1.087
Example 12		N-Ethyl-5-fluoro-N-((2R)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide	448 (M+H) +	Condition 2 1.1
Example 13		N-Ethyl-2-fluoro-N-((2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-6-(pyrimidin-2-yl)benzamide	448 (M+H) +	Condition 2 0.981, 1.038, 1.096
Example 14		N-Ethyl-4-fluoro-N-((2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide	448 (M+H) +	Condition 2 1.052
Example 15		N-Ethyl-N-((2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-6-methyl-3-(pyrimidin-2-yl)pyridine-2-carboxamide	445 (M+H) +	Condition 2 0.943, 1.036
Example 16		N-((2S)-1-[3-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-ethyl-8-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide	452 (M+H) +	Condition 2 1.04, 1.12
Example 17		N-((2S)-1-[3-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-ethyl-5-fluoro-2-(pyrimidin-2-yl)benzamide	466 (M+H) +	Condition 2 1.13

[0430]

Example 18: N-Ethyl-N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide

[0431]

5 [Formula 135]



[0432]

To a solution of N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide obtained in Reference Example 10 (0.13 g, 0.33 mmol) in DMF (5.0 mL), 60% NaH (0.020 g, 0.50 mmol) was added, and the resulting mixture was stirred at room temperature for 30 minutes. EtI (0.032 mL, 0.40 mmol) was added to the reaction solution, then the resulting mixture was stirred at room temperature for 24 hours. Water was added to the reaction solution, followed by extraction with EtOAc. The organic layer was washed with a saturated aqueous solution of NaHCO₃ and brine and dried over MgSO₄, then the drying agent was filtered off, and then the solvent was distilled off under reduced pressure. The obtained residue was purified by column chromatography (KP-NH 28g, hexane/EtOAc = 80/20 to 40/60) to obtain the title compound (0.058 g) (colorless and amorphous).

LCMS retention time 4.82 min.

MS (ESI pos.) m/z: 420 [M+H]⁺

[0433]

Examples 19 to 33 were obtained by the same procedure as in Example 18. The structural formula, the names, and LCMS data of the obtained compounds are shown in Tables 3-1 and 3-2.

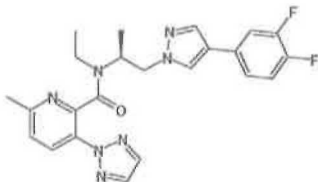
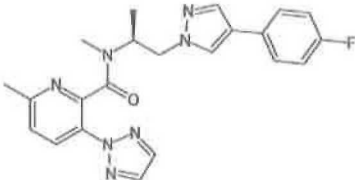
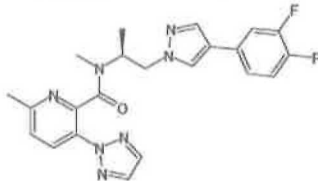
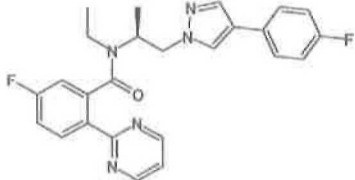
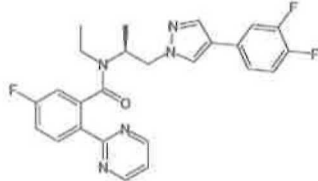
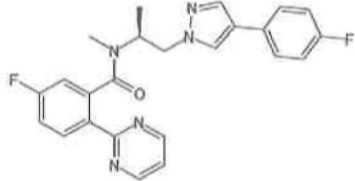
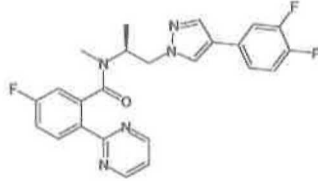
25 [0434]

[Table 3-1]

Example No.	Structural formula	Compound name	MS (ESI pos.) m/z	LCMS measurement condition Retention time (min)
Example 19		N-((2S)-1-[3-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide	420(M+H)+	Condition 1 4.78
Example 20		N-((2S)-1-[3-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	408(M+H)+	Condition 1 4.63
Example 21		N-Ethyl-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide	420(M+H)+	Condition 1 4.65
Example 22		N-((2S)-1-[4-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide	420(M+H)+	Condition 1 4.56
Example 23		N-((2S)-1-[3-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]-3-methylbutan-2-yl)-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide	448(M+H)+	Condition 2 1.03
Example 24		N-((2S)-1-[3-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]butan-2-yl)-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide	434(M+H)+	Condition 2 0.98
Example 25		N-Ethyl-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	434(M+H)+	Condition 2 0.91
Example 26		N-Ethyl-N-((2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide	434(M+H)+	Condition 2 0.958, 1.039

[0435]

[Table 3-2]

Example No.	Structural formula	Compound name	MS (ESI pos.) m/z	LCMS measurement condition Retention time (min)
Example 27		N-((2S)-1-[4-(3,4-Difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-ethyl-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide	452(M+H)+	Condition 2 0.984, 1.070
Example 28		N-((2S)-1-[4-(4-Fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N,6-dimethyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide	420(M+H)+	Condition 2 0.885, 0.927
Example 29		N-((2S)-1-[4-(3,4-Difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N,6-dimethyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide	438(M+H)+	Condition 2 0.921, 0.963
Example 30		N-Ethyl-5-fluoro-N-((2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide	448(M+H)+	Condition 2 1.027
Example 31		N-((2S)-1-[4-(3,4-Difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-ethyl-5-fluoro-2-(pyrimidin-2-yl)benzamide	466(M+H)+	Condition 2 1.062
Example 32		5-Fluoro-N-((2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-methyl-2-(pyrimidin-2-yl)benzamide	434(M+H)+	Condition 2 0.967
Example 33		N-((2S)-1-[4-(3,4-Difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-5-fluoro-N-methyl-2-(pyrimidin-2-yl)benzamide	452(M+H)+	Condition 2 0.995

[0436]

5

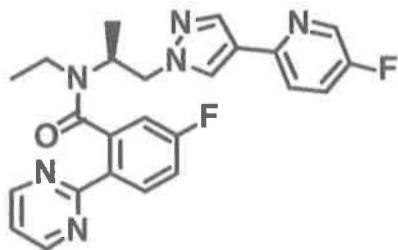
All of the LCMS measurement operations shown below were carried out under condition 2.

[0437]

Example 34: N-Ethyl-5-fluoro-N-{(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide

[0438]

5 [Formula 136]



[0439]

To a solution of 5-fluoro-N-{(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide obtained in Reference Example 81 (0.028 g, 0.067 mmol) in DMF (1.5 mL), 60% NaH (0.0039 g, 0.10 mmol) was added, and the resulting mixture was stirred at room temperature for 10 minutes. EtI (0.0064 mL, 0.080 mmol) was added to the reaction solution, and the resulting mixture was stirred at room temperature for 1.5 hours. 60% NaH (0.0039 g, 0.10 mmol) was added to the reaction solution, the mixture was stirred at room temperature for 10 minutes, then EtI (0.0064 mL, 0.080 mmol) was added thereto, and the resulting mixture was stirred at room temperature for 16 hours. A saturated aqueous solution of NH₄Cl was added to the reaction solution, followed by extraction with chloroform. The organic layer was concentrated under reduced pressure, and the obtained residue was purified by column chromatography (KP-NH 11g, hexane/EtOAc = 88/12 to 0/100). The obtained oil was freeze-dried to obtain the title compound (0.019 g) (colorless and amorphous).

20 LCMS retention time 0.94 min.

MS (ESI pos.) m/z: 449 [M+H]⁺

[0440]

Examples 35 to 40 were obtained by the same procedure as in Example 34. The structural formula, the names, and LCMS data of the obtained compounds are shown in Table 4.

25 [0441]

[Table 4]

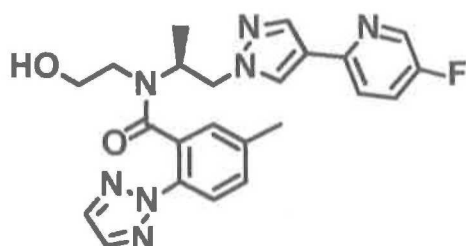
Example No.	Structural formula	Compound name	MS (ESI pos.) m/z	Retention time (min)
Example 35		N-Ethyl-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-5-methyl-2-(pyrimidin-2-yl)benzamide	445(M+H)+	0.960
Example 36		N-Ethyl-5-fluoro-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide	438(M+H)+	0.894
Example 37		5-Chloro-N-ethyl-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide	465(M+H)+	1.004
Example 38		N-((2S)-1-[4-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N-(2-methoxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	464(M+H)+	0.896
Example 39		N-((2S)-1-[3-(4-Fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-(2-methoxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	463(M+H)+	1.071
Example 40		N-((2S)-1-[3-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N-(2-methoxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	464(M+H)+	0.928

[0442]

Example 41: N-((2S)-1-[4-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0443]

[Formula 137]



[0444]

To a solution of N-{(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide obtained in Reference Example 15 (0.080 g, 0.20 mmol) in DMF (2.0 mL), 60% NaH (0.009 g, 0.22 mmol) was added, and the resulting mixture was stirred at room temperature for 30 minutes. To the reaction solution, 2-(2-bromoethoxy)tetrahydro-2H-pyran (0.0036 ml, 0.24 mmol) was added, and the resulting mixture was stirred at room temperature for 60 hours. To the reaction solution, 60% NaH (0.044 g, 1.10 mmol) and 2-(2-bromoethoxy)tetrahydro-2H-pyran (0.182 ml, 1.20 mmol) were added, and the resulting mixture was stirred at room temperature for 16 hours. Water was added to the reaction solution, followed by extraction with EtOAc. The organic layer was washed with brine and then dried over Na₂SO₄. The drying agent was filtered off, and then the solvent was distilled off under reduced pressure. The obtained residue was purified by column chromatography (SNAP Ultra 10g, hexane/EtOAc = 80/20 to 0/100) to obtain the title compound (0.067 g) (colorless and amorphous). The obtained amorphous was dissolved in MeOH (0.31 mL), then a 4M solution of HCl-EtOAc (0.047 mL, 0.19 mmol) was added thereto, and the resulting mixture was stirred at room temperature for 2 hours. The solvent was distilled off under reduced pressure, followed by extraction with EtOAc. The organic layer was washed with brine and then dried over Na₂SO₄. The drying agent was filtered off, and then the solvent was distilled off under reduced pressure. The obtained residue was purified by column chromatography (SNAP Ultra 10g, hexane/EtOAc = 80/20 to 0/100). Et₂O was added to the obtained oil for precipitation of a solid, and the precipitated solid was filtered out to obtain the title compound (0.045 g) (colorless solid).

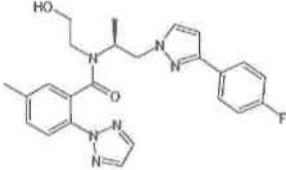
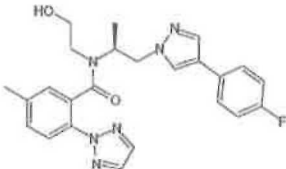
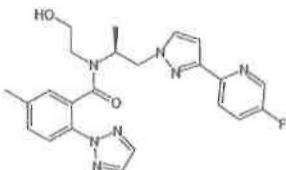
LCMS retention time 0.758 min.

MS (ESI pos.) m/z: 450 [M+H]⁺
[0445]

Examples 42 to 44 were obtained by the same procedure as in Example 41. The structural formula, the names, and LCMS data of the obtained compounds are shown in Table 5.

[0446]

[Table 5]

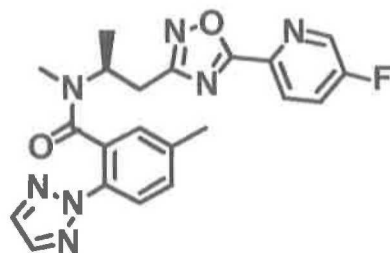
Example No.	Structural formula	Compound name	MS (ESI pos.) m/z	Retention time (min)
Example 42		N-((2S)-1-[3-(4-Fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	449(M+H)+	0.926
Example 43		N-((2S)-1-[4-(4-Fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	449(M+H)+	0.908
Example 44		N-((2S)-1-[3-(5-Fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	450(M+H)+	0.787

[0447]

Example 45: N-((2S)-1-[5-(5-Fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0448]

[Formula 138]



[0449]

To a solution of (2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]-N-methylpropan-2-amine obtained in Reference Example 47 (0.037 g, 0.16 mmol) in DMF (1.5 mL), 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (0.032 g, 0.16 mmol), HATU (0.071 g, 0.19 mmol), and DIPEA (0.082 ml, 0.47 mmol) were added, and the resulting mixture was stirred at room temperature for 60 hours. Water was added to the reaction solution, followed by extraction with chloroform. The solvent was distilled off under reduced pressure, and the obtained residue was purified by HPLC and PLC (NH silica 1.0 mm, hexane/EtOAc = 1/1). The obtained oil was freeze-dried to obtain the title compound (0.023 g) (colorless and amorphous).

LCMS retention time 0.841, 0.925 min.

MS (ESI pos.) m/z: 422 [M+H]⁺

[0450]

Examples 46 to 61 were obtained by the same procedure as in Example 45. The structural formula, the names, and LCMS data of the obtained compounds are shown in Tables 6-1 to 6-3.

[0451]

[Table 6-1]

Example No.	Structural formula	Compound name	MS (ESI pos.) m/z	Retention time (min)
Example 46		N-((2S)-1-[5-(5-Fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-N,5-dimethyl-2-(pyrimidin-2-yl)benzamide	433(M+H) ⁺	0.799, 0.826, 0.901
Example 47		N-Ethyl-N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	436(M+H) ⁺	0.940
Example 48		N-Ethyl-N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-5-methyl-2-(pyrimidin-2-yl)benzamide	447(M+H) ⁺	0.902
Example 49		N-Ethyl-N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide	436(M+H) ⁺	0.988, 1.046
Example 50		N-Ethyl-5-fluoro-N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide	439(M+H) ⁺	1.069
Example 51		N-Ethyl-N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide	421(M+H) ⁺	1.038

10 [0452]

[Table 6-2]

Example No.	Structural formula	Compound name	MS (ESI pos.) m/z	Retention time (min)
Example 52		N-Ethyl-N-[(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl]-6-methyl-3-(pyrimidin-2-yl)pyridine-2-carboxamide	447(M+H)+	0.946, 1.021
Example 53		N-Ethyl-5-fluoro-N-[(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl]-2-(pyrimidin-2-yl)benzamide	450(M+H)+	1.054
Example 54		N-Ethyl-N-[(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl]-2-(pyrimidin-2-yl)benzamide	432(M+H)+	1.007
Example 55		N-Ethyl-N-[(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl]-5-methyl-2-(pyrimidin-2-yl)benzamide	446(M+H)+	1.065
Example 56		N-Ethyl-N-[(2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl]-2-(2H-1,2,3-triazol-2-yl)benzamide	422(M+H)+	0.883
Example 57		N-Ethyl-5-fluoro-N-[(2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl]-2-(2H-1,2,3-triazol-2-yl)benzamide	440(M+H)+	0.917

[0453]

[Table 6-3]

Example No.	Structural formula	Compound name	MS (ESI pos.) m/z	Retention time (min)
Example 58		N-Ethyl-N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide	437(M+H)+	0.805, 0.878
Example 59		N-[(2S)-1-[5-(4-Fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl]-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide	421(M+H)+	1.064
Example 60		N-[(2S)-1-[5-(4-Fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl]-N,5-dimethyl-2-(pyrimidin-2-yl)benzamide	432(M+H)+	1.037
Example 61		N-Ethyl-N-[(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	435(M+H)+	1.098

[0454]

Example 47-2: N-Ethyl-N-[(2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

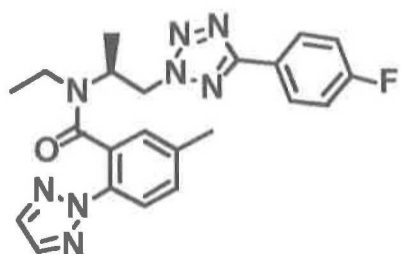
The title compound can also be obtained by the following procedure. By using N-[(2S)-1-cyanopropan-2-yl]-N-ethyl-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide obtained in Reference Example 108 (0.099 g, 0.33 mmol) and 5-fluoropyridine-2-carboxylic acid (0.064 g, 0.36 mmol) as the raw materials, the same procedure as in Reference Example 45 was carried out to obtain the title compound (0.070 g) (colorless oil).

[0455]

Example 62: N-Ethyl-N-[(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0456]

15 [Formula 139]



[0457]

By using N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide obtained in Reference Example 74 (0.040 g, 0.098 mmol) as the raw material, the same procedure as in Example 34 was carried out to obtain the title

5 compound (0.025 g) (pale yellow solid).

LCMS retention time 0.710 min.

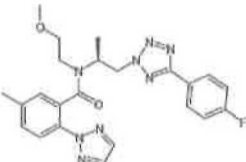
MS (ESI pos.) m/z: 435 [M+H]⁺

[0458]

Example 63 was obtained by the same procedure as in Example 62. The
10 structural formula, the name, and LCMS data of the obtained compound are shown in Table 7.

[0459]

[Table 7]

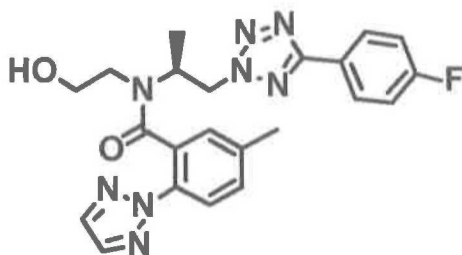
Example No.	Structural formula	Compound name	MS (ESI pos.) m/z	Retention time (min)
Example 63		N-((2S)-1-[5-(4-Fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl)-N-(2-methoxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	465(M+H) ⁺	1.084

[0460]

15 Example 64: N-{(2S)-1-[5-(4-Fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0461]

[Formula 140]



20 [0462]

By using N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide obtained in Reference Example 74 (0.070 g, 0.17 mmol) as the raw material, the same procedure as in Example 41 was carried out to obtain the title compound (0.008 g) (pale yellow oil).

25 LCMS retention time 0.914 min.

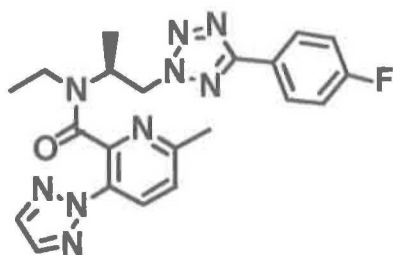
MS (ESI pos.) m/z: 451 [M+H]⁺

[0463]

Example 65: N-Ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide

[0464]

5 [Formula 141]



[0465]

By using (2S)-N-ethyl-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-amine obtained in Reference Example 76 (0.050 g, 0.20 mmol) and 6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxylic acid (0.045 g, 0.22 mmol) as the raw materials, the same procedure as

10 in Example 45 was carried out to obtain the title compound (0.0042 g) (colorless solid).

LCMS retention time 0.500, 0.545 min.

MS (ESI pos.) m/z: 436 [M+H]⁺

[0466]

15 Examples 66 to 70 were obtained by the same procedure as in Example 65. The structural formula, the names, and LCMS data of the obtained compounds are shown in Table 8.

[0467]

[Table 8]

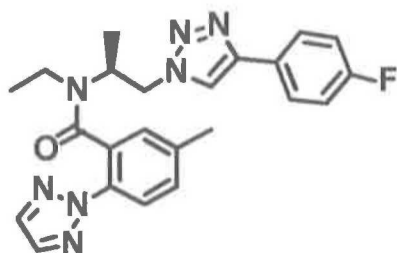
Example No.	Structural formula	Compound name	MS (ESI pos.) m/z	Retention time (min)
Example 66		N-Ethyl-5-fluoro-N-((2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide	439(M+H)+	0.560, 0.577
Example 67		N-Ethyl-N-((2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide	421(M+H)+	0.564
Example 68		N-Ethyl-N-((2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl)-5-methyl-2-(pyrimidin-2-yl)benzamide	446(M+H)+	0.583
Example 69		N-Ethyl-N-((2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl)-6-methyl-3-(pyrimidin-2-yl)pyridine-2-carboxamide	447(M+H)+	0.480, 0.533
Example 70		N-Ethyl-5-fluoro-N-((2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide	450(M+H)+	0.556

[0468]

Example 71: N-Ethyl-N-((2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0469]

[Formula 142]



[0470]

10

By using N-((2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide obtained in Reference Example 79 (0.10 g, 0.25 mmol) as the raw material, the same procedure as in Example 34 was carried out to obtain the

title compound (0.042 g) (pale yellow solid).

LCMS retention time 0.989 min.

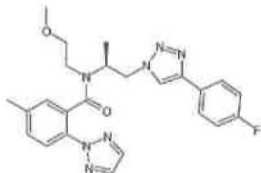
MS (ESI pos.) m/z: 434 [M+H]⁺

[0471]

- 5 Example 72 was obtained by the same procedure as in Example 71. The structural formula, the name, and LCMS data of the obtained compound are shown in Table 9.

[0472]

[Table 9]

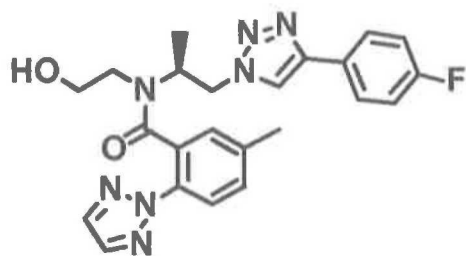
Example No.	Structural formula	Compound name	MS (ESI pos.) m/z	Retention time (min)
Example 72		N-((2S)-1-[4-(4-Fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-N-(2-methoxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	464(M+H) ⁺	0.971

- 10 [0473]

Example 73: N-((2S)-1-[4-(4-Fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0474]

[Formula 143]



- 15

[0475]

By using N-((2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide obtained in Reference Example 79 (0.18 g, 0.44 mmol) as the raw material, the same procedure as in Example 41 was carried out to obtain the

- 20 title compound (0.10 g) (colorless solid).

LCMS retention time 0.823 min.

MS (ESI pos.) m/z: 450 [M+H]⁺

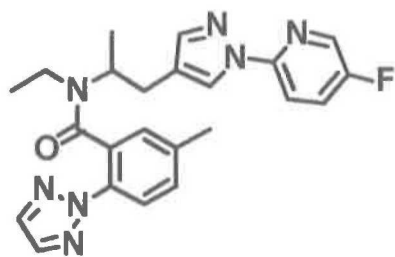
[0476]

Example 74: N-Ethyl-N-((1-[1-(5-fluoropyridin-2-yl)-1H-pyrazol-4-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

- 25

[0477]

[Formula 144]



[0478]

By using N-{1-[1-(5-fluoropyridin-2-yl)-1H-pyrazol-4-yl]propan-2-yl}-5-methyl-
 5 2-(2H-1,2,3-triazol-2-yl)benzamide obtained in Reference Example 61 (0.005 g, 0.012 mmol) as
 the raw material, the same procedure as in Example 34 was carried out to obtain the title
 compound (0.003 g) (colorless and amorphous).

LCMS retention time 1.173 min.

MS (ESI pos.) m/z: 434 [M+H]⁺

10 [0479]

Example 75 was obtained by the same procedure as in Example 74. The
 structural formula, the name, and LCMS data of the obtained compound are shown in Table 10.

[0480]

[Table 10]

Example No.	Structural formula	Compound name	MS (ESI pos.) m/z	Retention time (min)
Example 75		N-Ethyl-N-{1-[1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	434(M+H) ⁺	1.072

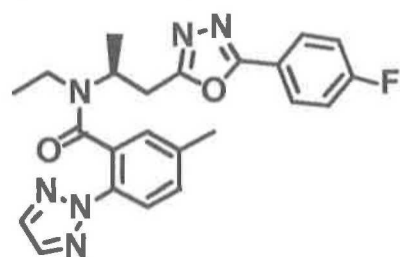
15

[0481]

Example 76: N-Ethyl-N-[(2S)-1-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]propan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0482]

20 [Formula 145]



[0483]

A solution of N-ethyl-N-{(2S)-4-[2-(4-fluorobenzoyl)hydrazinyl]-4-oxobutan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide obtained in Reference Example 71 (0.026 g, 0.057 mmol) and 3,3,3-triethyl-1-(methoxycarbonyl)diazathian-3-ium-1-ide 2,2-dioxide (0.041 g, 0.17 mmol) in THF (1 mL) was stirred at 50°C for 1.5 hours. To the reaction solution, 3,3,3-triethyl-1-(methoxycarbonyl)diazathian-3-ium-1-ide 2,2-dioxide (0.041 g, 0.17 mmol) was added, and the resulting mixture was stirred at 50°C for 1.5 hours. The reaction mixture was allowed to cool to room temperature, then the solvent was distilled off under reduced pressure, and then the obtained residue was purified by column chromatography (SNAP Ultra 10g, hexane/EtOAc = 75/25 to 0/100). The obtained oil was freeze-dried to obtain the title compound (0.025 g) (colorless and amorphous).

LCMS retention time 1.059 min.

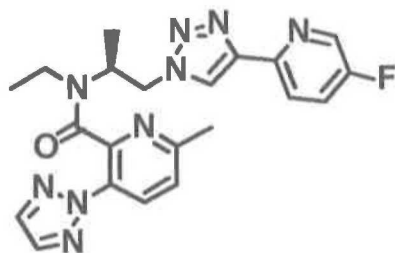
MS (ESI pos.) m/z: 435 [M+H]⁺

[0484]

Example 77: N-Ethyl-N-{(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide

[0485]

[Formula 146]



[0486]

By using (2S)-N-ethyl-1-[4-(5-fluoropyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-amine obtained in Reference Example 89 (0.030 g, 0.12 mmol) as the raw material, the same procedure as in Example 45 was carried out to obtain the title compound (0.028 g) (colorless solid).

LCMS retention time 0.374, 0.438 min.

MS (ESI pos.) m/z: 436 [M+H]⁺

[0487]

Examples 78 to 84 were obtained by the same procedure as in Example 77. The structural formula, the names, and LCMS data of the obtained compounds are shown in Table 11.

[0488]

[Table 11]

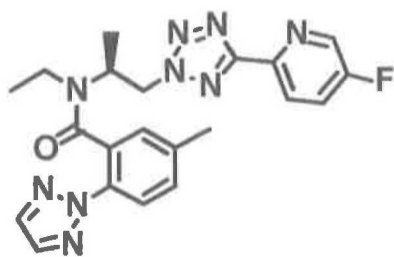
Example No.	Structural formula	Compound name	MS (ESI pos.) m/z	Retention time (min)
Example 78		N-Ethyl-5-fluoro-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide	461(M+Na)+	0.358
Example 79		N-Ethyl-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-5-methyl-2-(pyrimidin-2-yl)benzamide	446(M+H)+	0.344
Example 80		N-Ethyl-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-6-methyl-3-(pyrimidin-2-yl)pyridine-2-carboxamide	447(M+H)+	0.338
Example 81		N-Ethyl-5-fluoro-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide	472(M+Na)+	0.338
Example 82		N-Ethyl-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	435(M+H)+	0.535
Example 83		N-Ethyl-N-((2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide	435(M+H)+	0.518, 0.573
Example 84		N-Ethyl-5-fluoro-N-((2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide	438(M+H)+	0.566

[0489]

Example 85: N-Ethyl-N-((2S)-1-[5-(5-fluoropyridin-2-yl)-2H-tetrazol-2-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0490]

[Formula 147]



[0491]

By using (2S)-N-ethyl-1-[4-(5-fluoropyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-amine obtained in Reference Example 93 (0.050 g, 0.20 mmol) as the raw material, the same procedure as in Example 45 was carried out to obtain the title compound (0.033 g) (colorless solid).

LCMS retention time 0.556 min.

MS (ESI pos.) m/z: 436 [M+H]⁺

[0492]

Examples 86 to 88 were obtained by the same procedure as in Example 85. The structural formula, the names, and LCMS data of the obtained compounds are shown in Table 12.

[0493]

[Table 12]

Example No.	Structural formula	Compound name	MS (ESI pos.) m/z	Retention time (min)
Example 86		N-Ethyl-N-[(2S)-1-[5-(5-fluoropyridin-2-yl)-2H-tetrazol-2-yl]propan-2-yl]-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide	437(M+H) ⁺	0.471, 0.520
Example 87		N-Ethyl-5-fluoro-N-[(2S)-1-[5-(5-fluoropyridin-2-yl)-2H-tetrazol-2-yl]propan-2-yl]-2-(2H-1,2,3-triazol-2-yl)benzamide	440(M+H) ⁺	0.547
Example 88		N-Ethyl-N-[(2S)-1-[5-(5-fluoropyridin-2-yl)-2H-tetrazol-2-yl]propan-2-yl]-5-methyl-2-(pyrimidin-2-yl)benzamide	447(M+H) ⁺	0.536

[0494]

Examples 89 to 91 were obtained by the same procedure as in Example 71. The structural formula, the names, and LCMS data of the obtained compounds are shown in Table 13.

[0495]

[Table 13]

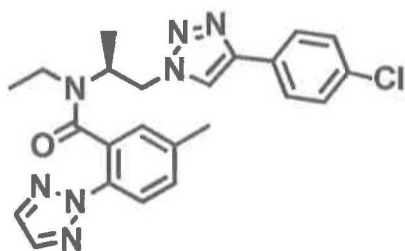
Example No.	Structural formula	Compound name	MS (ESI pos.) m/z	Retention time (min)
Example 89		N-[2-(Dimethylamino)ethyl]-N-((2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	477(M+H)+	0.56
Example 90		N-((2S)-1-[4-(4-Fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-5-methyl-N-[2-(methylsulfonyl)ethyl]-2-(2H-1,2,3-triazol-2-yl)benzamide	512(M+H)+	0.878
Example 91		N-(2-Cyanoethyl)-N-((2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	459(M+H)+	0.929

[0496]

Example 92: N-((2S)-1-[4-(4-Chlorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-N-ethyl-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0497]

[Formula 148]



[0498]

- 10 To a solution of N-[(2S)-1-azidepropan-2-yl]-N-ethyl-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide obtained in Reference Example 106 (0.064 g, 0.21 mmol) and 1-chloro-4-ethynylbenzene (0.028 g, 0.21 mmol) in DMF/4-methylpiperidine (1.6 mL/0.4 mL), CuI (0.002 g, 0.010 mmol) and L-ascorbic acid (0.007 g, 0.041 mmol) were added, and the resulting mixture was stirred at 80°C for 2 hours. The reaction mixture was allowed to cool to room
- 15 temperature, then water was added at 0°C, followed by extraction with EtOAc. The obtained organic layer was washed with brine and then dried over Na₂SO₄. The drying agent was filtered off, the reaction mixture was concentrated under reduced pressure, and then the obtained residue was purified by column chromatography (SNAP Ultra 10g, hexane/EtOAc = 88/12 to 0/100) to obtain the title compound (0.065 g) (colorless solid).

LCMS retention time 1.064 min.

MS (ESI pos.) m/z: 450 [M+H]⁺

[0499]

Examples 93 to 99 were obtained by the same procedure as in Example 92. The structural formula, the names, and LCMS data of the obtained compounds are shown in Table 14.

[0500]

[Table 14]

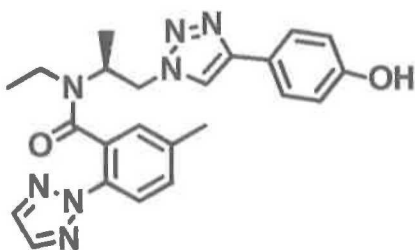
Example No.	Structural formula	Compound name	MS (ESI pos.) m/z	Retention time (min)
Example 93		N-Ethyl-N-[(2S)-1-[4-(3-hydroxyphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	432(M+H) ⁺	0.838
Example 94		N-Ethyl-5-methyl-N-[(2S)-1-[4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-yl]-2-(2H-1,2,3-triazol-2-yl)benzamide	417(M+H) ⁺	0.787
Example 95		N-Ethyl-5-methyl-N-[(2S)-1-[4-phenyl-1H-1,2,3-triazol-1-yl]propan-2-yl]-2-(2H-1,2,3-triazol-2-yl)benzamide	416(M+H) ⁺	0.96
Example 96		N-Ethyl-N-[(2S)-1-[4-(4-methoxyphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	446(M+H) ⁺	0.95
Example 97		N-Ethyl-5-methyl-N-[(2S)-1-[4-(3-methylphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl]-2-(2H-1,2,3-triazol-2-yl)benzamide	430(M+H) ⁺	1.04
Example 98		N-Ethyl-N-[(2S)-1-[4-(3-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	434(M+H) ⁺	1.006
Example 99		N-Ethyl-N-[(2S)-1-[4-(4-fluoro-3-methoxyphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide	464(M+H) ⁺	0.987

[0501]

Example 100: N-Ethyl-N-[(2S)-1-[4-(4-hydroxyphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0502]

[Formula 149]



[0503]

By using N-[(2S)-1-azidepropan-2-yl]-N-ethyl-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide obtained in Reference Example 106 (0.044 g, 0.14 mmol) and benzyl 4-ethynylphenyl ether (0.029 g, 0.14 mmol) as the raw materials, the same procedure as in

Example 92 was carried out to obtain colorless oil (0.006 g). The obtained oil was dissolved in MeOH (1 mL), then 10% Pd/C (0.01 g) was added thereto, and the resulting mixture was stirred at room temperature for 15 hours under hydrogen atmosphere. The reaction mixture was filtered through Celite®, then the obtained filtrate was concentrated under reduced pressure to obtain the title compound (0.0045 g) (pale yellow oil).

LCMS retention time 0.784 min.

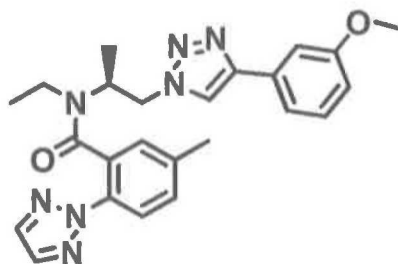
MS (ESI pos.) m/z: 432 [M+H]⁺

[0504]

Example 101: N-Ethyl-N-[(2S)-1-[4-(3-methoxyphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0505]

[Formula 150]



[0506]

By using N-ethyl-N-[(2S)-1-[4-(3-hydroxyphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl]-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide obtained in Example 93 (0.020 g, 0.046 mmol) and MeI (0.004 ml, 0.070 mmol) as the raw materials, the same procedure as in Example

34 was carried out to obtain the title compound (0.004 g) (colorless solid).

LCMS retention time 0.964 min.

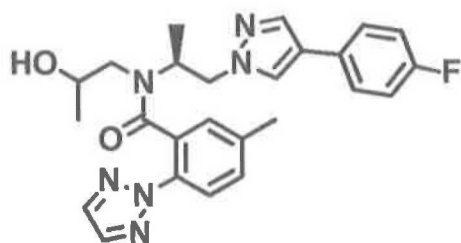
MS (ESI pos.) m/z: 446 [M+H]⁺

[0507]

- 5 Example 102: N-{(2S)-1-[4-(4-Fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-N-(2-hydroxypropyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide

[0508]

[Formula 151]



- 10 [0509]

By using N-{(2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide obtained in Reference Example 86 (0.10 g, 0.25 mmol) and 2-[(1-bromopropan-2-yl)oxy]tetrahydro-2H-pyran (1.3 g, 5.9 mmol) as the raw materials, the same procedure as in Example 41 was carried out to obtain the title compound (0.019 g)

- 15 (colorless and amorphous).

LCMS retention time 0.981 min.

MS (ESI pos.) m/z: 463 [M+H]⁺

[0510]

Test Example (measurement of orexin antagonistic activity)

- 20 The antagonistic activities of the test compounds on human orexin-1 receptor (hOX1R) and orexin-2 receptor (hOX2R) were measured by modifying from the method described in literature (Toshikatsu Okumura et al., Biochemical and Biophysical Research Communications, 280, 976-981, 2001). Chinese hamster ovary (CHO) cells forcibly expressing the hOX1R and hOX2R were seeded into a 96 well Black clear bottom plate (Nunc)
- 25 at 20,000 cells per well, which were cultured in Ham's F-12 medium containing 0.1 mM MEM non-essential amino acids, 0.5 mg/mL G418, 10% fetal bovine serum (all by Invitrogen) for 16 hours under the conditions of 37°C, 5% CO₂. After removing the medium, 100 µL of 0.5 µM Fluo-4AM ester (Dojin) in an assay buffer (25 mM HEPES (Dojin), Hank's balanced salt solution (Invitrogen), 0.1% bovine serum albumin, 2.5 mM probenecid, 200 µg/mL Amaranth
- 30 (all by Sigma-Aldrich), pH 7.4) was added and the cells were incubated for 60 minutes at 37°C,

5% CO₂. After removing the assay buffer containing fluo-4AM ester, the test compound was dissolved in dimethyl sulfoxide to be 10 mM and diluted with the assay buffer, 150 µL of which was added and incubated for 30 minutes.

[0511]

5 The ligand peptide, in which 2 amino acids of human orexin-A are substituted (Pyr-Pro-Leu-Pro-Asp-Ala-Cys-Arg-Gln-Lys-Thr-Ala-Ser-Cys-Arg-Leu-Tyr-Glu-Leu-Leu-His-Gly-Ala-Gly-Asn-His-Ala-Ala-Gly-Ile-Leu-Thr-Leu-NH₂; Peptide Institute, Inc.), were diluted with an assay buffer to give the final concentration of 300 pM for hOX1R and 3 nM for hOX2R, and 50 µL of the ligand solution was added to start the reaction. The reaction was measured for
10 the fluorescence intensity of each well every second for 3 minutes using Functional Drug Screening System (FDSS; Hamamatsu Photonics K.K.), and the antagonistic activity was determined using the maximum fluorescence intensity as the indicator of intracellular Ca²⁺ concentration. The antagonistic activity of test compound was calculated when the
15 fluorescence intensity of wells to which only the dilution buffer was added is 100% and the fluorescence intensity of wells to which the buffer containing no ligand or compound was added is 0%, and the 50% inhibition concentration (IC₅₀ value) was determined from the fluorescence intensities when the several concentrations of compounds were added.

The IC₅₀ values of the compounds of the present invention are shown in Table 15.

[0512]

[Table 15]

Example No.	IC ₅₀ Value		Example No.	IC ₅₀ Value		Example No.	IC ₅₀ Value	
	OX1 (nM)	OX2 (nM)		OX1 (nM)	OX2 (nM)		OX1 (nM)	OX2 (nM)
1	1.0	1.1	35	3.4	62.8	69	1.6	1896.4
2	17.4	185.9	36	6.8	214.2	70	1.1	452.2
3	1.0	4.5	37	7.1	83.1	71	1.3	21.8
4	1.7	67.0	38	25.5	350.6	72	101.5	401.2
5	0.5	75.5	39	1.2	5.5	73	80.3	5.7
6	1.2	8.4	40	1.4	12.4	74	1.3	13.1
7	6.8	43.1	41	30.9	86.3	75	1.4	1.7
8	1.5	35.3	42	1.1	21.8	76	1.0	59.7
9	988.3	1423.7	43	3.5	13.6	77	48.8	1448.5
10	0.2	12.8	44	1.3	25.9	78	20.9	592.8
11	0.2	14.4	45	3.3	75.5	79	63.6	426.9
12	364.2	579.9	46	21.6	390.3	80	686.9	7807.1
13	1.9	53.9	47	0.8	9.5	81	176.7	3151.0
14	1.3	7.0	48	0.9	28.2	82	2.2	13.3
15	1.2	18.0	49	1.1	32.2	83	9.9	308.2
16	1.8	9.7	50	0.8	16.8	84	3.1	51.4
17	2.1	10.1	51	0.2	9.3	85	1.3	27.5
18	0.7	7.7	52	9.2	375.7	86	37.7	1025.4
19	1.1	5.8	53	6.6	75.6	87	9.8	282.7
20	3.4	55.9	54	2.0	75.7	88	13.4	41.2
21	8.1	188.1	55	1.4	9.4	89	228.5	6934.0
22	3.8	52.9	56	5.0	602.4	90	23.7	2069.8
23	133.9	1892.0	57	5.1	1082.4	91	202.9	279.5
24	9.8	41.4	58	22.2	1621.5	92	2.5	64.6
25	0.7	6.4	59	0.5	10.1	93	1.4	7.4
26	1.7	55.9	60	1.3	45.0	94	9.3	108.5
27	1.4	13.8	61	0.7	3.3	95	0.6	17.7
28	18.6	89.3	62	0.7	2.3	96	159.7	8365.5
29	10.1	25.6	63	2.2	66.9	97	2.4	21.3
30	1.2	35.7	64	1.0	47.9	98	6.3	9.8
31	1.0	10.2	65	1.3	144.3	99	1.8	1.5
32	20.7	96.9	66	1.6	129.2	100	10.4	774.3
33	11.9	20.8	67	1.8	75.9	101	0.9	1.5
34	9.8	334.1	68	0.8	33.7	102	1.4	27.9

Industrial Applicability

[0513]

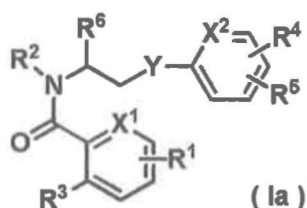
- 5 The compounds of the present invention are verified to have the OX receptor antagonistic activities. Thus, the compounds of the present invention or the pharmaceutically acceptable salts thereof can be used as a therapeutic or preventive drug for diseases regulated by OX receptor antagonistic activities such as sleep disorder, depression, anxiety disorder, panic disorder, schizophrenia, drug dependence, Alzheimer's disease, Parkinson's disease, Huntington's
- 10 disease, eating disorder, headache, migraine, pain, gastrointestinal disease, epilepsy, inflammation, immunological diseases, endocrine related disease and hypertension.

CLAIMS

[Claim 1]

A compound represented by formula (Ia):

[Formula 1]

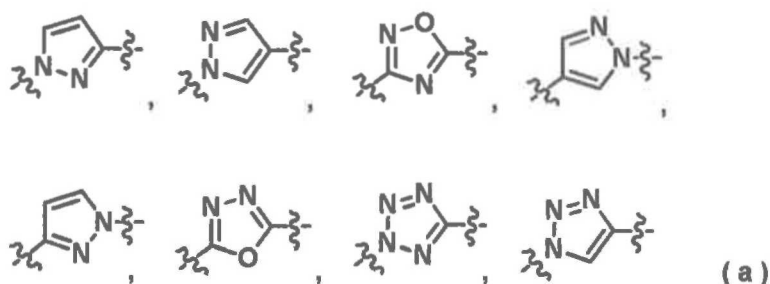


wherein,

 X^1 and X^2 are the same or different and represent a nitrogen atom or a formula CH;

Y represents any of the structures in a following formula group (a):

[Formula 2]

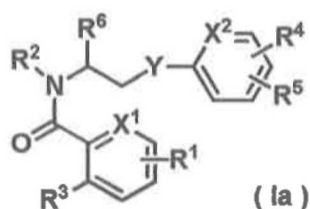
 R^1 represents a hydrogen atom, a halogen atom or a C_{1-6} alkyl group; R^2 represents a C_{1-6} alkyl group (the C_{1-6} alkyl group may optionally be substituted with one substituent selected from the group consisting of a hydroxy group, a C_{1-6} alkoxy group, a C_{1-6} alkylsulfonyl group, a diC_{1-6} alkylamino group and a cyano group); R^3 represents a triazolyl group or a pyrimidinyl group; R^4 and R^5 are the same or different and represent a hydrogen atom, a halogen atom, a C_{1-6} alkyl group, a hydroxyl group or a C_{1-6} alkoxy group; and R^6 represents a C_{1-6} alkyl group;

or a pharmaceutically acceptable salt thereof.

[Claim 2]

A compound represented by formula (Ia):

[Formula 3]

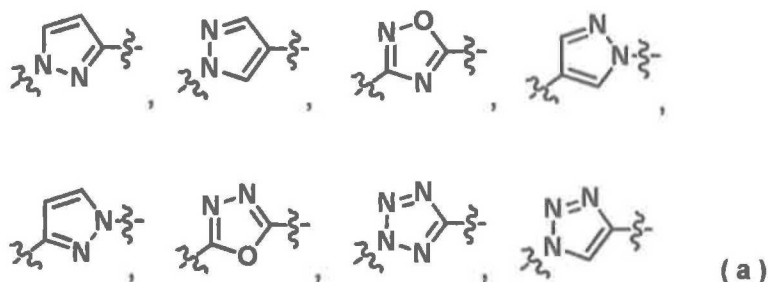


wherein,

X^1 and X^2 are the same or different and represent a nitrogen atom or a formula CH;

Y represents any of the structures in a following formula group (a):

[Formula 4]



R^1 represents a hydrogen atom, a halogen atom or a C_{1-6} alkyl group;

R^2 represents a C_{1-6} alkyl group (the C_{1-6} alkyl group may optionally be substituted with one substituent selected from the group consisting of a hydroxy group and a C_{1-6} alkoxy group);

R^3 represents a triazolyl group or a pyrimidinyl group;

R^4 represents a halogen atom;

R^5 represents a hydrogen atom or a halogen atom; and

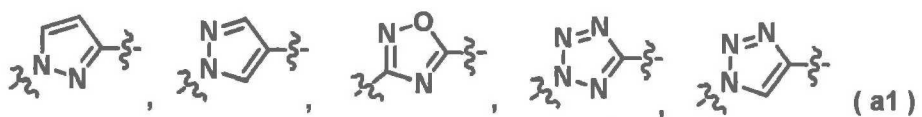
R^6 represents a C_{1-6} alkyl group;

or a pharmaceutically acceptable salt thereof.

[Claim 3]

The compound or a pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein Y in the above formula (Ia) is any of the structures in a following formula group (a1):

[Formula 5]



[Claim 4]

The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 3, wherein R^1 in the above formula (Ia) is a hydrogen atom, a fluorine atom or a methyl group.

[Claim 5]

The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, wherein R^2 in the above formula (Ia) is a methyl group or an ethyl group (the ethyl group may optionally be substituted with one substituent selected from the group consisting of a hydroxyl group and a methoxy group).

[Claim 6]

The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein R^4 in the above formula (Ia) is a fluorine atom.

[Claim 7]

The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 6, wherein R^5 in the above formula (Ia) is a hydrogen atom or a fluorine atom.

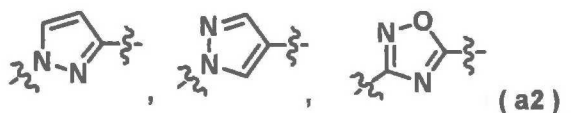
[Claim 8]

The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 7, wherein R^6 in the above formula (Ia) is a C_{1-3} alkyl group.

[Claim 9]

The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 8, wherein Y in the above formula (Ia) is any of the structures in a following formula group (a2):

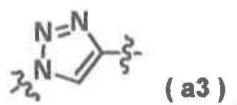
[Formula 6]



[Claim 10]

The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 8, wherein Y in the above formula (Ia) is a following formula (a3):

[Formula 7]



[Claim 11]

The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 10, wherein R^2 in the above formula (Ia) is an ethyl group.

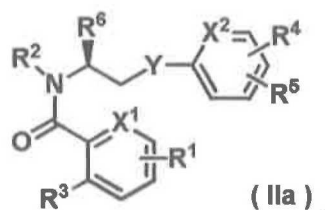
[Claim 12]

The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 11, wherein R^6 in the above formula (Ia) is a methyl group.

[Claim 13]

The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 12, wherein the above formula (Ia) is represented by formula (IIa):

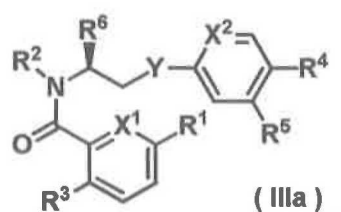
[Formula 8]



[Claim 14]

The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, wherein the above formula (Ia) is represented by formula (IIIa):

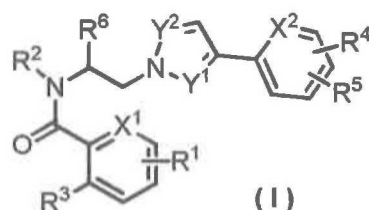
[Formula 9]



[Claim 15]

A compound represented by formula (I):

[Formula 10]



wherein,

X^1 and X^2 are the same or different and represent a nitrogen atom or a formula CH;

either one of Y^1 and Y^2 represents a nitrogen atom, and the other represents CH;

R^1 represents a hydrogen atom, a halogen atom or a C_{1-6} alkyl group;

R^2 represents a C_{1-6} alkyl group;

R^3 represents a triazolyl group or a pyrimidinyl group;

R^4 represents a halogen atom;

R^5 represents a hydrogen atom or a halogen atom; and

R^6 represents a C_{1-6} alkyl group;

or a pharmaceutically acceptable salt thereof.

[Claim 16]

The compound or a pharmaceutically acceptable salt thereof according to claim 15, wherein R^1 in the above formula (I) is a hydrogen atom, a fluorine atom or a methyl group.

[Claim 17]

The compound or a pharmaceutically acceptable salt thereof according to any of claim 15 or 16, wherein R^2 in the above formula (I) is a methyl group or an ethyl group.

[Claim 18]

The compound or a pharmaceutically acceptable salt thereof according to any one of claims 15 to 17, wherein R^4 in the above formula (I) is a fluorine atom.

[Claim 19]

The compound or a pharmaceutically acceptable salt thereof according to any one of claims 15 to 18, wherein R^5 in the above formula (I) is a hydrogen atom or a fluorine atom.

[Claim 20]

The compound or a pharmaceutically acceptable salt thereof according to any one of claims 15 to 19, wherein R^6 in the above formula (I) is a C_{1-3} alkyl group.

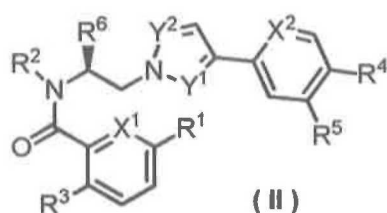
[Claim 21]

The compound or a pharmaceutically acceptable salt thereof according to any one of claims 15 to 20, wherein R^6 in the above formula (I) is a methyl group.

[Claim 22]

The compound or a pharmaceutically acceptable salt thereof according to any one of claims 15 to 21, wherein the above formula (I) is represented by formula (II):

[Formula 11]



[Claim 23]

The compound or a pharmaceutically acceptable salt thereof according to claim 1, which is a species or a mixture of two or more species selected from:

N-ethyl-N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{(2R)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,

N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-N-methyl-2-(pyrimidin-2-yl)benzamide,

5-fluoro-N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-N-methyl-2-(pyrimidin-2-yl)benzamide,

N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-N,5-dimethyl-2-(pyrimidin-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide,

N-ethyl-5-fluoro-N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide,

N-ethyl-5-fluoro-N-{(2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide,

N-ethyl-2-fluoro-N-{(2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-6-(pyrimidin-2-yl)benzamide,

N-ethyl-4-fluoro-N-{(2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-6-methyl-3-(pyrimidin-2-yl)pyridine-2-carboxamide,

N-{(2S)-1-[3-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-N-ethyl-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,

N-{(2S)-1-[3-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-N-ethyl-5-fluoro-2-(pyrimidin-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-N-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-{(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]butan-2-yl}-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,

N-{(2S)-1-[4-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-N-ethyl-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,

N-{(2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-N,6-dimethyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,

N-{(2S)-1-[4-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-N,6-dimethyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,

N-ethyl-5-fluoro-N-{(2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide,

N-{(2S)-1-[4-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-N-ethyl-5-fluoro-2-(pyrimidin-2-yl)benzamide,

5-fluoro-N-{(2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-N-methyl-2-(pyrimidin-2-yl)benzamide,

N-{(2S)-1-[4-(3,4-difluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-5-fluoro-N-methyl-2-(pyrimidin-2-yl)benzamide,

N-ethyl-5-fluoro-N-{(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-5-methyl-2-(pyrimidin-2-yl)benzamide,

N-ethyl-5-fluoro-N-{(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,

5-chloro-N-ethyl-N-{(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide,

N-{(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-N-(2-methoxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-{(2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-N-(2-methoxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-{(2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-N-(2-methoxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-{(2S)-1-[4-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl}-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-((2S)-1-[3-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-((2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl)-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-((2S)-1-[3-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl]propan-2-yl)-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-N,5-dimethyl-2-(pyrimidin-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-5-methyl-2-(pyrimidin-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,
 N-ethyl-5-fluoro-N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-6-methyl-3-(pyrimidin-2-yl)pyridine-2-carboxamide,
 N-ethyl-5-fluoro-N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-2-(pyrimidin-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-5-methyl-2-(pyrimidin-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-5-fluoro-N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl)-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,

N-{(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-N,5-dimethyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-{(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-N,5-dimethyl-2-(pyrimidin-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-1,2,4-oxadiazol-3-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-N-(2-methoxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,

N-ethyl-5-fluoro-N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-5-methyl-2-(pyrimidin-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-6-methyl-3-(pyrimidin-2-yl)pyridine-2-carboxamide,

N-ethyl-5-fluoro-N-{(2S)-1-[5-(4-fluorophenyl)-2H-tetrazol-2-yl]propan-2-yl}-2-(pyrimidin-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-{(2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-N-(2-hydroxyethyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{1-[1-(5-fluoropyridin-2-yl)-1H-pyrazol-4-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{1-[1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-{(2S)-1-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,

N-ethyl-N-((2S)-1-[4-(5-fluoropyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridine-2-carboxamide,
 N-ethyl-5-fluoro-N-((2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(5-fluoropyridin-2-yl)-2H-tetrazol-2-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-5-fluoro-N-((2S)-1-[5-(5-fluoropyridin-2-yl)-2H-tetrazol-2-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[5-(5-fluoropyridin-2-yl)-2H-tetrazol-2-yl]propan-2-yl}-5-methyl-2-(pyrimidin-2-yl)benzamide,
 N-[2-(dimethylamino)ethyl]-N-((2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-((2S)-1-[4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-N-[2-(methylsulfonyl)ethyl]-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-((2S)-1-[4-(4-chlorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-N-ethyl-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[4-(3-hydroxyphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-5-methyl-N-((2S)-1-[4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-5-methyl-N-((2S)-1-(4-phenyl-1H-1,2,3-triazol-1-yl)propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-5-methyl-N-((2S)-1-[4-(3-methylphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl)-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[4-(3-fluorophenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[4-(4-fluoro-3-methoxyphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[4-(4-hydroxyphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide,
 N-ethyl-N-((2S)-1-[4-(3-methoxyphenyl)-1H-1,2,3-triazol-1-yl]propan-2-yl}-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide, and

N-{(2S)-1-[4-(4-fluorophenyl)-1H-pyrazol-1-yl]propan-2-yl}-N-(2-hydroxypropyl)-5-methyl-2-(2H-1,2,3-triazol-2-yl)benzamide.

[Claim 24]

A pharmaceutical composition containing the compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 23, as an active ingredient.

[Claim 25]

A therapeutic or preventive drug for sleep disorder, depression, anxiety disorder, panic disorder, schizophrenia, drug dependence, Alzheimer's disease, Parkinson's disease, Huntington's disease, eating disorder, headache, migraine, pain, gastrointestinal disease, epilepsy, inflammation, immunological diseases, endocrine related disease or hypertension, containing the compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 23, as an active ingredient.