

DESCRIPTION

Title of the Invention: HETEROCYCLIC COMPOUND AND USE THEREOF
Technical Field

5 [0001]

The present invention relates to a heterocyclic compound, particularly, a heterocyclic compound having an orexin type 2 receptor agonist activity.

[0002]

10 (Background of the Invention)

Orexin is a neuropeptide specifically produced in particular neurons located sparsely in the lateral hypothalamus and its surrounding area, and consists of two subtypes, orexin A and orexin B. Both orexin A and orexin B are endogenous
15 ligands of the orexin receptors, which are G protein-coupled receptors mainly present in the brain, and two types of subtypes, type 1 and type 2, are known for the orexin receptors (non-patent document 1).

[0003]

20 Since orexin-producing neurons (orexin neurons) are localized in the vicinity of the feeding center, and intraventricular administration of orexin peptide results in an increase in food intake, orexin initially attracted attention as a neuropeptide having a feeding behavioral regulation.
25 Thereafter, however, it was reported that the cause of dog narcolepsy is genetic variation of orexin type 2 receptor (non-patent document 2), and the role of orexin in controlling sleep and wakefulness has been also attracted.

[0004]

30 From the studies using a transgenic mouse having denatured orexin neurons and a double transgenic mouse obtained by crossing this mouse with orexin overexpressing transgenic mouse, it was clarified that narcolepsy-like symptoms that appear by degeneration of orexin neurons disappear due to
35 sustained expression of orexin. Similarly, when orexin peptide

was intraventricularly administered to a transgenic mouse having denatured orexin neuron, improvement of narcolepsy-like symptoms was also observed (non-patent document 3). Studies of orexin type 2 receptor knockout mice have suggested that orexin type 2 receptor is important for maintaining arousal (non-patent document 4, non-patent document 5). Such background suggests that orexin type 2 receptor agonists become therapeutic drugs for narcolepsy or therapeutic drugs for other sleep disorders exhibiting excessive sleepiness (non-patent document 6).

[0005]

In addition, it is suggested that a peptidic agonist that selectively acts on the orexin type 2 receptor improves obesity due to high fat diet load in mice (non-patent document 7).

In addition, it is suggested that intraventricular administration of orexin peptide shortens the systemic anesthetic time of rat (non-patent document 8).

In addition, it is suggested that patients with sleep apnea syndrome show low orexin A concentration levels in plasma (non-patent document 9).

In addition, it is suggested that intraventricular administration of orexin peptide improves memory retention of senescence-accelerated model mouse (SAMP8) with cognitive dysfunction (non-patent document 10).

In addition, it is suggested that Orexin type 2 receptor agonist will be a therapeutic drug for cardiac failure (patent document 1, non-patent document 11).

In addition, it is suggested that the daytime sleepiness of Parkinson's disease patients is caused by orexin nerve fallout (non-patent document 12).

In addition, it is suggested that orexin regulates bone formation and bone loss, and orexin type 2 receptor agonist will be a therapeutic drug for diseases related to bone loss such as osteoporosis, rheumatoid arthritis and the like (patent document 2).

In addition, it is suggested that orexin receptor agonist is useful for the prophylaxis or treatment of sepsis, severe sepsis and septic shock, since the mortality was significantly improved by mere continuous administration of orexin from the periphery in septic shock model mouse (patent document 3).

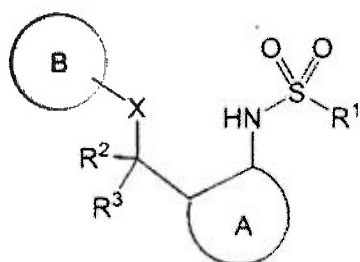
[0006]

Therefore, a compound having an orexin type 2 receptor agonist activity is expected to be useful as a novel therapeutic drug for narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, disturbance of consciousness such as coma and the like, narcolepsy syndrome accompanied by narcolepsy-like symptoms, hypersomnia syndrome accompanied by daytime hypersomnia (e.g., Parkinson's disease, Guillain-Barre syndrome and Kleine Levin syndrome), Alzheimer, obesity, insulin resistance syndrome, cardiac failure, diseases related to bone loss, sepsis and the like, further, anesthetic antagonist, a prophylactic or therapeutic drug for side effects

[0007]

As sulfonamide derivatives, a compound represented by the formula

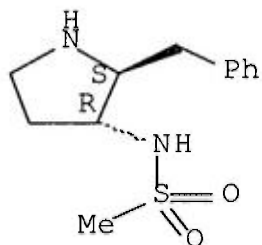
[0008]



[0009]

wherein each symbol is as described in the document (Patent Document 4), a compound represented by the formula

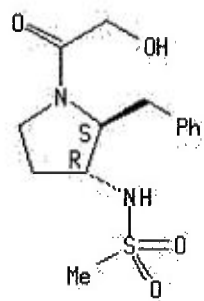
[0010]



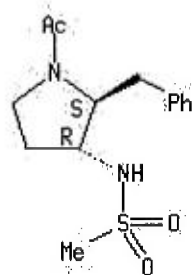
[0011]

(RN 1422063-50-0) have been reported. The latter compound is an optically active form of "N-(2-benzylpyrrolidin-3-yl)methanesulfonamide" which is excluded from the compound (I) of the present invention. Additionally, compounds represented by the formula

[0012]

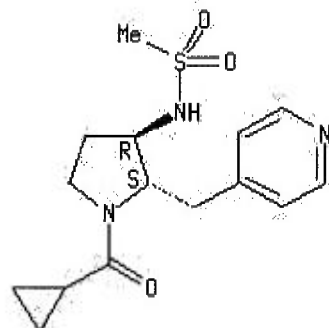


(RN 2184459-04-7),

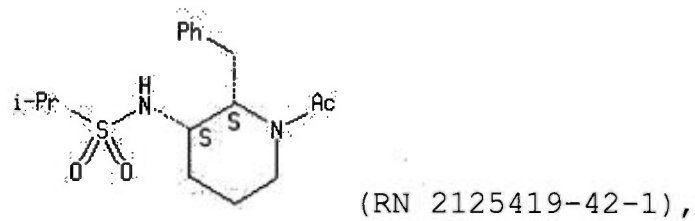
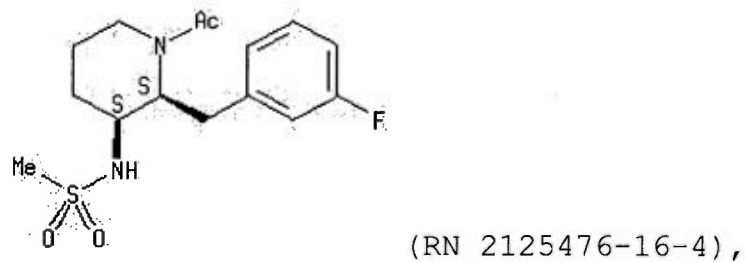
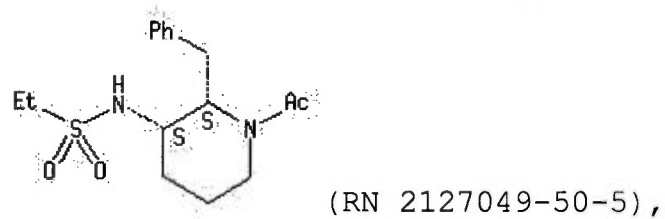
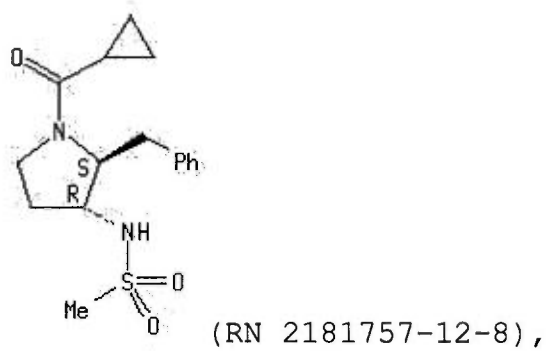
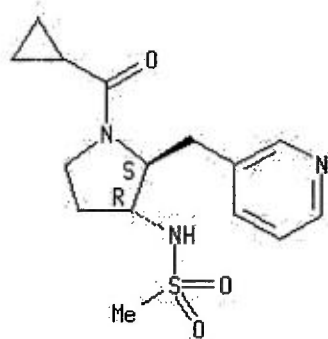


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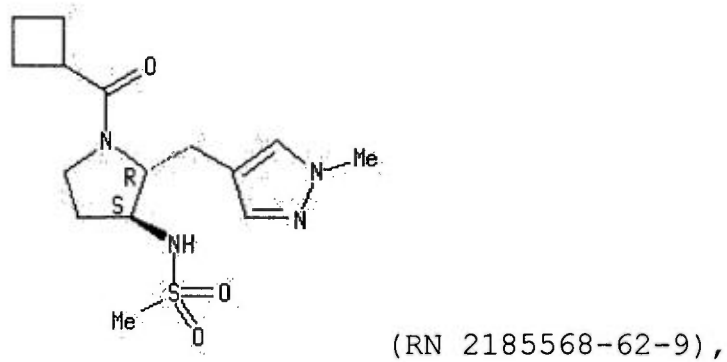
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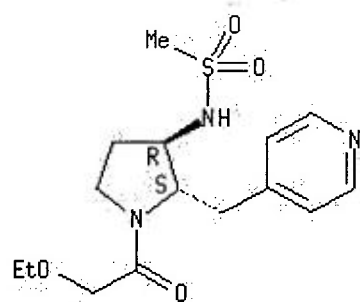


(RN 2183690-03-9),

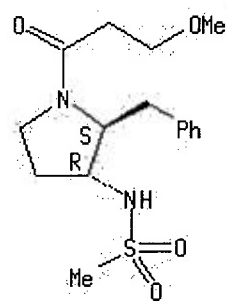


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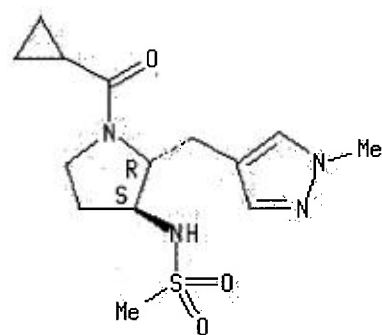




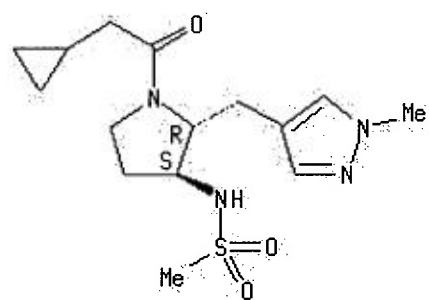
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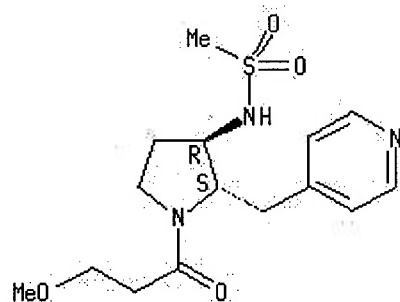
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(RN 2185369-35-9),

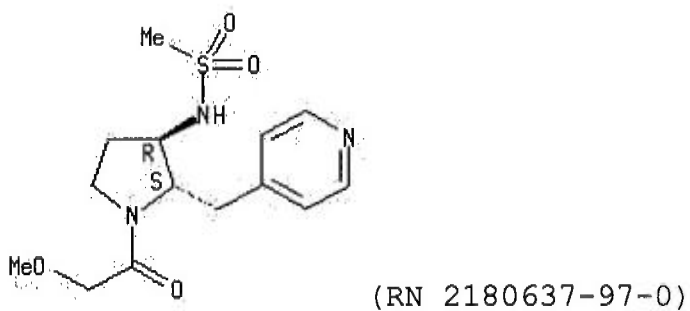
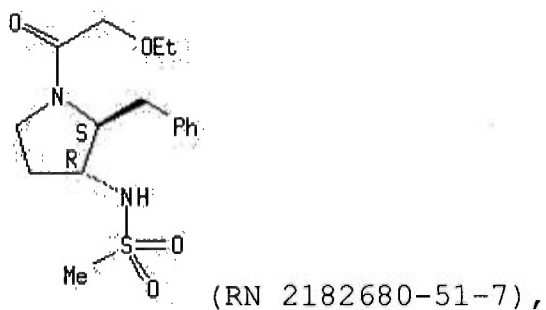
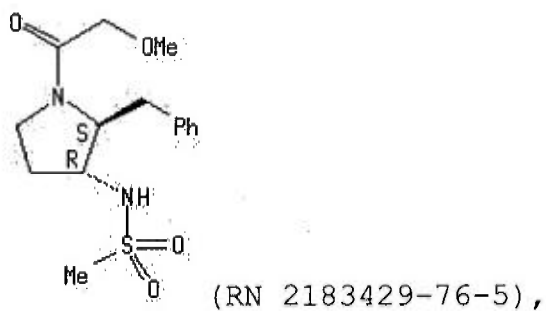
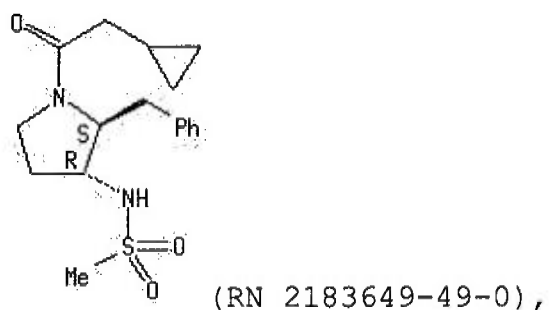


(RN 2185279-48-3),



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(RN 2184868-49-1),



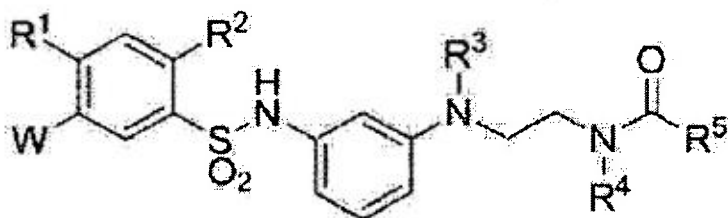
5 [0013]

are reported.

In addition, as compounds having an orexin type 2 receptor agonist activity, the following compounds have been reported.

10 A compound represented by the formula

[0014]

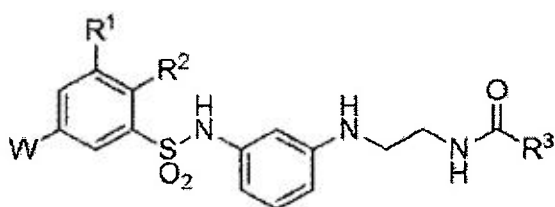


[0015]

wherein each symbol is as described in the document (Patent Document 5).

5 A compound represented by the formula

[0016]



(I)

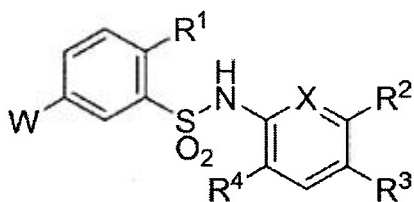
[0017]

wherein each symbol is as described in the document (Patent

10 Document 6).

A compound represented by the formula

[0018]



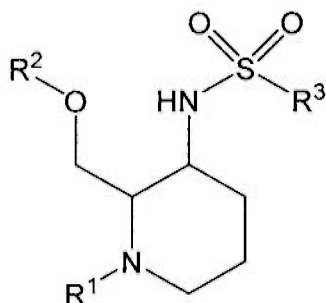
(II)

[0019]

15 wherein each symbol is as described in the document (Patent Document 7).

A compound represented by the formula

[0020]



[0021]

wherein each symbol is as described in the document (Patent Document 8).

5 [0022]

However, it is considered that these compounds are not satisfactory in terms of activity, pharmacokinetics or safety, and the development of a compound having an orexin type 2 receptor agonist activity is still desired.

10 Document List

Patent Document

[0023]

[Patent Document 1] WO 2015/073707 A1

[Patent Document 2] WO 2015/048091 A1

15 [Patent Document 3] WO 2015/147240 A1

[Patent Document 4] WO 2012/137982 A9

[Patent Document 5] WO 2015/088000 A1

[Patent Document 6] WO 2016/133160 A1

[Patent Document 7] WO 2016/199906 A1

20 [Patent Document 8] WO 2017/135306 A1

Non-Patent Document

[0024]

[Non-Patent Document 1] Cell, Vol.92, 573-585, 1998

[Non-Patent Document 2] Cell, Vol.98, 365-376, 1999

25 [Non-Patent Document 3] Proc. Natl. Acad. Sci. USA, Vol.101, 4649-4654, 2004

[Non-Patent Document 4] Cell, Vol.98, 437-451, 1999

[Non-Patent Document 5] Neuron, Vol.38, 715-730, 2003

[Non-Patent Document 6] CNS Drugs, Vol.27, 83-90, 2013

30 [Non-Patent Document 7] Cell Metabolism, Vol.9, 64-76, 2009

5 Cardiology. Vol. 66, 2015, Pages 2522-2533

[Non-Patent Document 12] Brain. Vol. 130, 2007, Pages 1586-1595

Problems to be Solved by the Invention

[0025]

10 The present invention aims to provide a heterocyclic compound having an orexin type 2 receptor agonist activity.

Means of Solving the Problems

[0026]

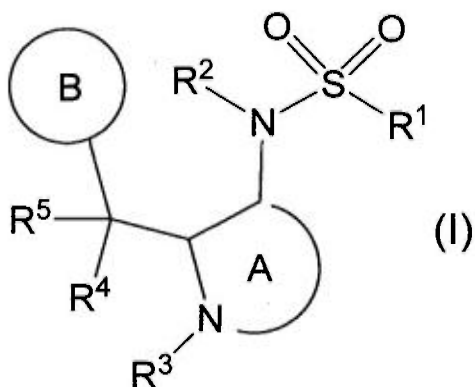
The present inventors have found that a compound
15 represented by the following formula (I) or a salt thereof
(sometimes to be referred to as compound (I) in the present
specification) has an orexin type 2 receptor agonist activity.
As a result of further studies, they have completed the present
invention.

20 [0027]

Accordingly, the present invention provides the following.

[1] A compound represented by the formula:

[0028]



25 [0029]

wherein

R¹ is a substituent;

R^2 , R^3 , R^4 and R^5 are each independently a hydrogen atom, or a

substituent;

Ring A is an optionally further substituted 4- to 7-membered nitrogen-containing monocyclic saturated heterocycle; and

Ring B is an optionally further substituted ring,

5 or a salt thereof,

provided that N-(2-benzylpyrrolidin-3-yl)methanesulfonamide is excluded.

[0030]

[2] The compound or salt of the above-mentioned [1], wherein

10 Ring B is a ring

further substituted by

(a) an optionally substituted C₆₋₁₄ aryl group,

(b) an optionally substituted C₆₋₁₄ aryloxy group,

(c) an optionally substituted C₇₋₁₆ aralkyl group,

15 (d) an optionally substituted C₃₋₁₀ cycloalkyl group,

(e) an optionally substituted C₃₋₁₀ cycloalkenyl group,

(f) an optionally substituted C₃₋₁₀ cycloalkoxy group,

(g) an optionally substituted 5- to 14-membered aromatic heterocyclic group, or

20 (h) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group, and

optionally having additional substituent(s).

[0031]

[3] The compound or salt of the above-mentioned [1], wherein

25 R¹ is

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

(a) a halogen atom,

(b) a cyano group,

30 (c) a hydroxy group, and

(d) a C₁₋₆ alkoxy group,

(2) a C₂₋₆ alkenyl group,

(3) a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 3 halogen atoms,

35 (4) a mono- or di-C₁₋₆ alkylamino group, or

(5) a 3- to 14-membered non-aromatic heterocyclic group;

R² is a hydrogen atom;

R³ is

(1) a hydrogen atom,

5 (2) a C₁₋₆ alkoxy-carbonyl group optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom,

(b) a C₁₋₆ alkoxy group,

10 (c) a C₃₋₁₀ cycloalkyl group optionally substituted by 1 to 3 substituents selected from

(i) a halogen atom, and

(ii) a C₁₋₆ alkyl group, and

(d) a 3- to 14-membered non-aromatic heterocyclic group,

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

(a) a halogen atom,

(b) a C₃₋₁₀ cycloalkyl group,

(c) a hydroxy group, and

(d) a C₁₋₆ alkoxy group,

20 (4) a mono- or di-C₁₋₆ alkyl-carbamoyl group,

(5) a N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group,

(6) a C₃₋₁₀ cycloalkyl-carbonyl group (the C₃₋₁₀ cycloalkyl in the C₃₋₁₀ cycloalkyl-carbonyl group may be a bridged ring group) optionally substituted by 1 to 3 substituents selected from

25 (a) a halogen atom,

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

(i) a halogen atom, and

(ii) a hydroxy group,

30 (c) a hydroxy group,

(d) a C₁₋₆ alkoxy group, and

(e) a cyano group,

(7) a C₃₋₁₀ cycloalkoxy-carbonyl group optionally substituted by 1 to 3 substituents selected from

35 (a) a halogen atom, and

- (b) a C₁₋₆ alkyl group,
- (8) a 3- to 14-membered non-aromatic heterocyclylcarbonyl group (the non-aromatic heterocycle in the non-aromatic heterocyclylcarbonyl group may be a spiro ring) optionally substituted by 1 to 3 substituents selected from
- 5 (a) a halogen atom, and
- (b) a C₁₋₆ alkyl group,
- (9) a 3- to 14-membered non-aromatic heterocyclyloxycarbonyl group,
- 10 (10) a C₆₋₁₄ aryloxy-carbonyl group,
- (11) a C₇₋₁₆ aralkyloxy-carbonyl group,
- (12) a 5- to 14-membered aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from
- (i) a halogen atom, and
- 15 (ii) a C₁₋₆ alkyl group,
- (13) a 5- to 14-membered aromatic heterocyclylcarbonyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups, or
- (14) a tri-C₁₋₆ alkylhydrazino-carbonyl group;
- R⁴ and R⁵ are each independently a hydrogen atom or a halogen
- 20 atom;

Ring A is

- (1) a pyrrolidine ring,
- (2) a piperidine ring, or
- (3) an azetidine ring; and

25 Ring B is

- (1) a C₆₋₁₄ aromatic hydrocarbon ring optionally further substituted by 1 to 3 substituents selected from
- (a) a halogen atom,
- (b) a C₁₋₆ alkyl group optionally substituted by 1 to 3
- 30 halogen atoms,
- (c) a C₂₋₆ alkenyl group,
- (d) a mono- or di-C₁₋₆ alkylamino group,
- (e) a tri-C₁₋₆ alkylsilyloxy group,
- (f) a C₆₋₁₄ aryl group optionally substituted by 1 to 4
- 35 substituents selected from

- (i) a halogen atom,
 - (ii) a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms, and
 - (iii) a C₁₋₆ alkoxy group,
- 5 (g) a C₆₋₁₄ aryloxy group,
- (h) a C₇₋₁₆ aralkyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups,
- (i) a C₃₋₁₀ cycloalkyl group,
- (j) a C₃₋₁₀ cycloalkenyl group,
- 10 (k) a C₃₋₁₀ cycloalkoxy group,
- (l) a 5- to 14-membered aromatic heterocyclic group optionally substituted by 1 to 3 C₁₋₆ alkyl groups, and
- (m) a 3- to 14-membered non-aromatic heterocyclic group,
- (2) a 5- to 14-membered aromatic heterocycle optionally further
- 15 substituted by 1 to 3 substituents selected from
- (a) a C₆₋₁₄ aryl group optionally substituted by 1 to 3 halogen atoms,
 - (b) a C₁₋₆ alkyl group, and
 - (c) a C₂₋₆ alkenyl group, or
- 20 (3) a 3- to 14-membered non-aromatic heterocycle optionally further substituted by 1 to 3 substituents selected from
- (a) a C₆₋₁₄ aryl group, and
 - (b) a 5- to 14-membered aromatic heterocyclic group.

[0032]

- 25 [4] The compound or salt of the above-mentioned [1], wherein R¹ is

- (1) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from
 - (a) a halogen atom, and
 - 30 (b) a C₁₋₆ alkoxy group,
 - (2) a C₃₋₆ cycloalkyl group optionally substituted by 1 to 3 halogen atoms, or
 - (3) a mono- or di-C₁₋₆ alkylamino group;
- R² is a hydrogen atom;

- 35 R³ is

- (1) a C₁₋₆ alkoxy-carbonyl group,
- (2) a C₁₋₆ alkyl-carbonyl group optionally substituted by 1 to 3 hydroxy groups,
- (3) a mono- or di-C₁₋₆ alkyl-carbamoyl group,
- 5 (4) a N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group,
- (5) a C₃₋₆ cycloalkyl-carbonyl group (the C₃₋₆ cycloalkyl in the C₃₋₆ cycloalkyl-carbonyl group may be a bridged ring group) optionally substituted by 1 to 3 substituents selected from
 - (a) a halogen atom,
 - 10 (b) a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms,
 - (c) a hydroxy group,
 - (d) a C₁₋₆ alkoxy group, and
 - (e) a cyano group,
- 15 (6) an oxetanylcabonyl group,
- (7) an azetidinylcabonyl group optionally substituted by 1 to 3 substituents selected from
 - (a) a halogen atom, and
 - (b) a C₁₋₆ alkyl group, or
- 20 (8) a 5-azaspiro[2.3]hexylcarbonyl group;
R⁴ and R⁵ are both hydrogen atoms;
Ring A is
 - (1) a pyrrolidine ring, or
 - (2) a piperidine ring; and
- 25 Ring B is
 - (1) a benzene ring
further substituted by one phenyl group optionally substituted by 1 to 3 substituents selected from
 - (i) a halogen atom, and
 - 30 (ii) a C₁₋₆ alkyl group, andoptionally further substituted by one halogen atom,
 - (2) a pyridine ring further substituted by one phenyl group optionally substituted by 1 to 3 halogen atoms,
 - (3) a thiazole ring further substituted by one phenyl group
 - 35 optionally substituted by 1 to 3 halogen atoms, or

(4) a piperidine ring further substituted by one phenyl group.
[0033]

[5] The compound or salt of the above-mentioned [1], wherein
R¹ is

5 (1) a C₁₋₆ alkyl group,

(2) a C₃₋₆ cycloalkyl group optionally substituted by 1 to 3
halogen atoms, or

(3) a mono- or di-C₁₋₆ alkylamino group;

R² is a hydrogen atom;

10 R³ is

(1) a C₁₋₆ alkyl-carbonyl group optionally substituted by 1 to 3
hydroxy groups,

(2) a mono- or di-C₁₋₆ alkyl-carbamoyl group,

(3) a N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group, or

15 (4) an azetidinyllcarbonyl group;

R⁴ and R⁵ are both hydrogen atoms;

Ring A is a pyrrolidine ring; and

Ring B is a benzene ring

further substituted by one phenyl group optionally substituted
20 by 1 to 3 halogen atoms, and
optionally further substituted by one halogen atom.

[0034]

[6] N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-
hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide or
25 a salt thereof.

[7] N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3',5'-
trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-
yl)methanesulfonamide or a salt thereof.

[8] N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3',5'-
30 trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide
or a salt thereof.

[0035]

[9] A compound selected from

(1) N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3'-
35 difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide,

- (2) N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((3',5'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide,
(3) N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-(biphenyl-3-ylmethyl)pyrrolidin-3-yl)ethanesulfonamide,
5 (4) N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide,
(5) (2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((ethylsulfonyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide,
(6) (2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-
10 ((dimethylsulfamoyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide,
(7) (2S,3S)-3-((ethylsulfonyl)amino)-N,N-dimethyl-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidine-1-carboxamide,
(8) (2S,3S)-2-(biphenyl-3-ylmethyl)-3-((ethylsulfonyl)amino)-N-
15 methoxy-N-methylpyrrolidine-1-carboxamide,
(9) N-[(2S,3S)-2-[(2,3'-difluoro[1,1'-biphenyl]-3-yl)methyl]-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl]-1-fluorocyclopropane-1-sulfonamide,
(10) N-[(2S,3S)-1-(azetidine-1-carbonyl)-2-[(2-fluoro[1,1'-
20 biphenyl]-3-yl)methyl]pyrrolidin-3-yl]ethanesulfonamide,
(11) (2S,3S)-3-[(ethanesulfonyl)amino]-2-[(3'-fluoro[1,1'-biphenyl]-3-yl)methyl]-N-methoxy-N-methylpyrrolidine-1-carboxamide,
(12) (2S,3S)-3-[(dimethylsulfamoyl)amino]-2-[(2-fluoro[1,1'-
25 biphenyl]-3-yl)methyl]-N,N-dimethylpyrrolidine-1-carboxamide,
(13) (2S,3S)-3-[(dimethylsulfamoyl)amino]-N,N-dimethyl-2-[(2,3',5'-trifluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidine-1-carboxamide, and
(14) (2S,3S)-2-[(3',5'-difluoro[1,1'-biphenyl]-3-yl)methyl]-3-
30 [(ethanesulfonyl)amino]-N-methoxy-N-methylpyrrolidine-1-carboxamide
or a salt thereof.

[0036]

[10] A medicament comprising the compound or salt of the above-
35 mentioned [1]-[9].

[11] The medicament of the above-mentioned [10], which is an orexin type 2 receptor agonist.

[12] The medicament of the above-mentioned [10], which is an agent for the prophylaxis or treatment of narcolepsy.

5 [13] The compound or salt of the above-mentioned [1]-[9] for use in the prophylaxis or treatment of narcolepsy.

[0037]

[14] A method of activating an orexin type 2 receptor in a mammal, which comprises administering an effective amount of
10 the compound or salt of the above-mentioned [1]-[9] to the mammal.

[15] A method for the prophylaxis or treatment of narcolepsy in a mammal, which comprises administering an effective amount of the compound or salt of the above-mentioned [1]-[9] to the
15 mammal.

[16] Use of the compound or salt of the above-mentioned [1]-[9] for the manufacture of an agent for the prophylaxis or treatment of narcolepsy.

Effect of the Invention

20 [0038]

The compound of the present invention has an orexin type 2 receptor agonist activity, and is useful as an agent for the prophylaxis or treatment of narcolepsy.

[0039]

25 (Detailed Description of the Invention)

The definition of each substituent used in the present specification is described in detail in the following. Unless otherwise specified, each substituent has the following definition.

30 In the present specification, examples of the "halogen atom" include fluorine, chlorine, bromine and iodine.

In the present specification, examples of the "C₁₋₆ alkyl group" include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl,
35 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-

dimethylbutyl, 3,3-dimethylbutyl and 2-ethylbutyl.

In the present specification, examples of the "optionally halogenated C₁₋₆ alkyl group" include a C₁₋₆ alkyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms.

5 Specific examples thereof include methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, tetrafluoroethyl, pentafluoroethyl, propyl, 2,2-difluoropropyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl,
10 isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl and 6,6,6-trifluorohexyl.

In the present specification, examples of the "C₂₋₆ alkenyl group" include ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-
15 butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl and 5-hexenyl.

In the present specification, examples of the "C₂₋₆ alkynyl group" include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-
20 pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl and 4-methyl-2-pentynyl.

In the present specification, examples of the "C₃₋₁₀ cycloalkyl group" include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl,
25 bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl and adamantyl.

In the present specification, examples of the "optionally halogenated C₃₋₁₀ cycloalkyl group" include a C₃₋₁₀ cycloalkyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include cyclopropyl, 2,2-
30 difluorocyclopropyl, 2,3-difluorocyclopropyl, cyclobutyl, difluorocyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

In the present specification, examples of the "C₃₋₁₀ cycloalkenyl group" include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.
35

In the present specification, examples of the "C₆₋₁₄ aryl group" include phenyl, 1-naphthyl, 2-naphthyl, 1-anthryl, 2-anthryl and 9-anthryl.

In the present specification, examples of the "C₇₋₁₆ aralkyl group" include benzyl, phenethyl, naphthylmethyl and phenylpropyl.

[0040]

In the present specification, examples of the "C₁₋₆ alkoxy group" include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy and hexyloxy.

In the present specification, examples of the "optionally halogenated C₁₋₆ alkoxy group" include a C₁₋₆ alkoxy group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy and hexyloxy.

In the present specification, examples of the "C₃₋₁₀ cycloalkyloxy group" include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and cyclooctyloxy.

In the present specification, examples of the "C₁₋₆ alkylthio group" include methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, pentylthio and hexylthio.

In the present specification, examples of the "optionally halogenated C₁₋₆ alkylthio group" include a C₁₋₆ alkylthio group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include methylthio, difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentylthio and hexylthio.

In the present specification, examples of the "C₁₋₆ alkyl-carbonyl group" include acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 3-methylbutanoyl, 2-methylbutanoyl, 2,2-dimethylpropanoyl, hexanoyl and heptanoyl.

In the present specification, examples of the "optionally halogenated C₁₋₆ alkyl-carbonyl group" include a C₁₋₆ alkyl-carbonyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include acetyl,
5 chloroacetyl, trifluoroacetyl, trichloroacetyl, propanoyl, butanoyl, pentanoyl and hexanoyl.

In the present specification, examples of the "C₁₋₆ alkoxy-carbonyl group" include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl,
10 isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl and hexyloxycarbonyl.

In the present specification, examples of the "C₆₋₁₄ aryl-carbonyl group" include benzoyl, 1-naphthoyl and 2-naphthoyl.

In the present specification, examples of the "C₇₋₁₆ aralkyl-carbonyl group" include phenylacetyl and
15 phenylpropionyl.

In the present specification, examples of the "5- to 14-membered aromatic heterocyclylcarbonyl group" include nicotinoyl, isonicotinoyl, thenoyl and furoyl.

20 In the present specification, examples of the "3- to 14-membered non-aromatic heterocyclylcarbonyl group" include morpholinylcarbonyl, piperidinylcarbonyl and pyrrolidinylcarbonyl.

[0041]

25 In the present specification, examples of the "mono- or di-C₁₋₆ alkyl-carbamoyl group" include methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl and N-ethyl-N-methylcarbamoyl.

In the present specification, examples of the "mono- or
30 di-C₇₋₁₆ aralkyl-carbamoyl group" include benzylcarbamoyl and phenethylcarbamoyl.

In the present specification, examples of the "C₁₋₆ alkylsulfonyl group" include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, sec-
35 butylsulfonyl and tert-butylsulfonyl.

In the present specification, examples of the "optionally halogenated C₁₋₆ alkylsulfonyl group" include a C₁₋₆ alkylsulfonyl group optionally having 1 to 7, preferably 1 to 5, halogen atoms. Specific examples thereof include

5 methylsulfonyl, difluoromethylsulfonyl, trifluoromethylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, 4,4,4-trifluorobutylsulfonyl, pentylsulfonyl and hexylsulfonyl.

In the present specification, examples of the "C₆₋₁₄ arylsulfonyl group" include phenylsulfonyl, 1-naphthylsulfonyl

10 and 2-naphthylsulfonyl.

[0042]

In the present specification, examples of the "substituent" include a halogen atom, a cyano group, a nitro group, an optionally substituted hydrocarbon group, an

15 optionally substituted heterocyclic group, an acyl group, an optionally substituted amino group, an optionally substituted carbamoyl group, an optionally substituted thiocarbamoyl group, an optionally substituted sulfamoyl group, an optionally substituted hydroxy group, an optionally substituted sulfanyl

20 (SH) group and an optionally substituted silyl group.

In the present specification, examples of the "hydrocarbon group" (including "hydrocarbon group" of "optionally substituted hydrocarbon group") include a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₂₋₆ alkynyl group, a C₃₋₁₀

25 cycloalkyl group, a C₃₋₁₀ cycloalkenyl group, a C₆₋₁₄ aryl group and a C₇₋₁₆ aralkyl group.

[0043]

In the present specification, examples of the "optionally substituted hydrocarbon group" include a hydrocarbon group

30 optionally having substituent(s) selected from the following Substituent group A.

[Substituent group A]

- (1) a halogen atom,
- (2) a nitro group,
- 35 (3) a cyano group,

- (4) an oxo group,
- (5) a hydroxy group,
- (6) an optionally halogenated C₁₋₆ alkoxy group,
- (7) a C₆₋₁₄ aryloxy group (e.g., phenoxy, naphthoxy),
- 5 (8) a C₇₋₁₆ aralkyloxy group (e.g., benzyloxy),
- (9) a 5- to 14-membered aromatic heterocyclyloxy group (e.g., pyridyloxy),
- (10) a 3- to 14-membered non-aromatic heterocyclyloxy group (e.g., morpholinylloxy, piperidinylloxy),
- 10 (11) a C₁₋₆ alkyl-carbonyloxy group (e.g., acetoxy, propanoyloxy),
- (12) a C₆₋₁₄ aryl-carbonyloxy group (e.g., benzoyloxy, 1-naphthoyloxy, 2-naphthoyloxy),
- (13) a C₁₋₆ alkoxy-carbonyloxy group (e.g., methoxycarbonyloxy, 15 ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy),
- (14) a mono- or di-C₁₋₆ alkyl-carbamoyloxy group (e.g., methylcarbamoyloxy, ethylcarbamoyloxy, dimethylcarbamoyloxy, diethylcarbamoyloxy),
- (15) a C₆₋₁₄ aryl-carbamoyloxy group (e.g., phenylcarbamoyloxy, 20 naphthylcarbamoyloxy),
- (16) a 5- to 14-membered aromatic heterocyclylcarbonyloxy group (e.g., nicotinoyloxy),
- (17) a 3- to 14-membered non-aromatic heterocyclylcarbonyloxy group (e.g., morpholinylcarbonyloxy, piperidinylcarbonyloxy),
- 25 (18) an optionally halogenated C₁₋₆ alkylsulfonyloxy group (e.g., methylsulfonyloxy, trifluoromethylsulfonyloxy),
- (19) a C₆₋₁₄ arylsulfonyloxy group optionally substituted by a C₁₋₆ alkyl group (e.g., phenylsulfonyloxy, toluenesulfonyloxy),
- (20) an optionally halogenated C₁₋₆ alkylthio group,
- 30 (21) a 5- to 14-membered aromatic heterocyclic group,
- (22) a 3- to 14-membered non-aromatic heterocyclic group,
- (23) a formyl group,
- (24) a carboxy group,
- (25) an optionally halogenated C₁₋₆ alkyl-carbonyl group,
- 35 (26) a C₆₋₁₄ aryl-carbonyl group,

- (27) a 5- to 14-membered aromatic heterocyclylcarbonyl group,
(28) a 3- to 14-membered non-aromatic heterocyclylcarbonyl group,
(29) a C₁₋₆ alkoxy-carbonyl group,
5 (30) a C₆₋₁₄ aryloxy-carbonyl group (e.g., phenyloxycarbonyl, 1-naphthyloxycarbonyl, 2-naphthyloxycarbonyl),
(31) a C₇₋₁₆ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, phenethyloxycarbonyl),
(32) a carbamoyl group,
10 (33) a thiocarbamoyl group,
(34) a mono- or di-C₁₋₆ alkyl-carbamoyl group,
(35) a C₆₋₁₄ aryl-carbamoyl group (e.g., phenylcarbamoyl),
(36) a 5- to 14-membered aromatic heterocyclylcarbamoyl group (e.g., pyridylcarbamoyl, thienylcarbamoyl),
15 (37) a 3- to 14-membered non-aromatic heterocyclylcarbamoyl group (e.g., morpholinylcarbamoyl, piperidinylcarbamoyl),
(38) an optionally halogenated C₁₋₆ alkylsulfonyl group,
(39) a C₆₋₁₄ arylsulfonyl group,
(40) a 5- to 14-membered aromatic heterocyclylsulfonyl group
20 (e.g., pyridylsulfonyl, thienylsulfonyl),
(41) an optionally halogenated C₁₋₆ alkylsulfinyl group,
(42) a C₆₋₁₄ arylsulfinyl group (e.g., phenylsulfinyl, 1-naphthylsulfinyl, 2-naphthylsulfinyl),
(43) a 5- to 14-membered aromatic heterocyclylsulfinyl group
25 (e.g., pyridylsulfinyl, thienylsulfinyl),
(44) an amino group,
(45) a mono- or di-C₁₋₆ alkylamino group (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, N-ethyl-N-methylamino),
30 (46) a mono- or di-C₆₋₁₄ arylamino group (e.g., phenylamino),
(47) a 5- to 14-membered aromatic heterocyclylamino group (e.g., pyridylamino),
(48) a C₇₋₁₆ aralkylamino group (e.g., benzylamino),
35 (49) a formylamino group,

- (50) a C₁₋₆ alkyl-carbonylamino group (e.g., acetylamino, propanoylamino, butanoylamino),
- (51) a (C₁₋₆ alkyl)(C₁₋₆ alkyl-carbonyl) amino group (e.g., N-acetyl-N-methylamino),
- 5 (52) a C₆₋₁₄ aryl-carbonylamino group (e.g., phenylcarbonylamino, naphthylcarbonylamino),
- (53) a C₁₋₆ alkoxy-carbonylamino group (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, butoxycarbonylamino, tert-butoxycarbonylamino),
- 10 (54) a C₇₋₁₆ aralkyloxy-carbonylamino group (e.g., benzyloxycarbonylamino),
- (55) a C₁₋₆ alkylsulfonylamino group (e.g., methylsulfonylamino, ethylsulfonylamino),
- (56) a C₆₋₁₄ arylsulfonylamino group optionally substituted by a
- 15 C₁₋₆ alkyl group (e.g., phenylsulfonylamino, toluenesulfonylamino),
- (57) an optionally halogenated C₁₋₆ alkyl group,
- (58) a C₂₋₆ alkenyl group,
- (59) a C₂₋₆ alkynyl group,
- 20 (60) a C₃₋₁₀ cycloalkyl group,
- (61) a C₃₋₁₀ cycloalkenyl group, and
- (62) a C₆₋₁₄ aryl group.
- [0044]

The number of the above-mentioned substituents in the

25 "optionally substituted hydrocarbon group" is, for example, 1 to 5, preferably 1 to 3. When the number of the substituents is two or more, the respective substituents may be the same or different.

In the present specification, examples of the

30 "heterocyclic group" (including "heterocyclic group" of "optionally substituted heterocyclic group") include (i) an aromatic heterocyclic group, (ii) a non-aromatic heterocyclic group and (iii) a 7- to 10-membered bridged heterocyclic group, each containing, as a ring-constituting atom besides carbon

35 atom, 1 to 4 heteroatoms selected from a nitrogen atom, a

sulfur atom and an oxygen atom.

[0045]

In the present specification, examples of the "aromatic heterocyclic group" (including "5- to 14-membered aromatic heterocyclic group") include a 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atom, 1 to 4 heteroatoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

Preferable examples of the "aromatic heterocyclic group" include 5- or 6-membered monocyclic aromatic heterocyclic groups such as thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, triazolyl, tetrazolyl, triazinyl and the like; and 8- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) aromatic heterocyclic groups such as benzothiophenyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzotriazolyl, imidazopyridinyl, thienopyridinyl, furopyridinyl, pyrrolopyridinyl, pyrazolopyridinyl, oxazolopyridinyl, thiazolopyridinyl, imidazopyrazinyl, imidazopyrimidinyl, thienopyrimidinyl, furopyrimidinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, oxazolopyrimidinyl, thiazolopyrimidinyl, pyrazolotriazinyl, naphtho[2,3-b]thienyl, phenoxathiinyl, indolyl, isoindolyl, 1H-indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl and the like.

[0046]

In the present specification, examples of the "non-aromatic heterocyclic group" (including "3- to 14-membered non-aromatic heterocyclic group") include a 3- to 14-membered (preferably 4- to 10-membered) non-aromatic heterocyclic group

containing, as a ring-constituting atom besides carbon atom, 1 to 4 heteroatoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

Preferable examples of the "non-aromatic heterocyclic group" include 3- to 8-membered monocyclic non-aromatic heterocyclic groups such as aziridinyl, oxiranyl, thiranyl, azetidiny, oxetanyl, thietanyl, tetrahydrothienyl, tetrahydrofuranyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, oxazolinyl, oxazolidinyl, pyrazolinyl, pyrazolidinyl, thiazolinyl, thiazolidinyl, tetrahydroisothiazolyl, tetrahydrooxazolyl, tetrahydroisooxazolyl, piperidinyl, piperazinyl, tetrahydropyridinyl, dihydropyridinyl, dihydrothiopyranyl, tetrahydropyrimidinyl, tetrahydropyridazinyl, dihydropyranly, tetrahydropyranly, tetrahydrothiopyranly, morpholinyl, thiomorpholinyl, azepanyl, diazepanyl, azepinyl, oxepanyl, azocanyl, diazocanyl and the like; and 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocyclic groups such as dihydrobenzofuranyl, dihydrobenzimidazolyl, dihydrobenzoxazolyl, dihydrobenzothiazolyl, dihydrobenzisoctiazolyl, dihydronaphtho[2,3-b]thienyl, tetrahydroisoquinolyl, tetrahydroquinolyl, 4H-quinoliziny, indoliny, isoindoliny, tetrahydrothieno[2,3-c]pyridiny, tetrahydrobenzazepiny, tetrahydroquinoxaliny, tetrahydrophenanthridiny, hexahydrophenothiaziny, hexahydrophenoxaziny, tetrahydrophthalaziny, tetrahydronaphththyridiny, tetrahydroquinazoliny, tetrahydrocinnoliny, tetrahydrocarbazolyl, tetrahydro- β -carboly, tetrahydroacrydiny, tetrahydrophenaziny, tetrahydrothioxantheny, octahydroisoquinolyl and the like.

[0047]

In the present specification, preferable examples of the "7- to 10-membered bridged heterocyclic group" include quinuclidiny and 7-azabicyclo[2.2.1]heptanyl.

In the present specification, examples of the "nitrogen-containing heterocyclic group" include a "heterocyclic group" containing at least one nitrogen atom as a ring-constituting atom.

5 In the present specification, examples of the "optionally substituted heterocyclic group" include a heterocyclic group optionally having substituent(s) selected from the above-mentioned Substituent group A.

The number of the substituents in the "optionally substituted heterocyclic group" is, for example, 1 to 3. When the number of the substituents is two or more, the respective substituents may be the same or different.

[0048]

In the present specification, examples of the "acyl group" include a formyl group, a carboxy group, a carbamoyl group, a thiocarbamoyl group, a sulfinio group, a sulfo group, a sulfamoyl group and a phosphono group, each optionally having "1 or 2 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₃₋₁₀ cycloalkenyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a 5- to 14-membered aromatic heterocyclic group and a 3- to 14-membered non-aromatic heterocyclic group, each of which optionally has 1 to 3 substituents selected from a halogen atom, an optionally halogenated C₁₋₆ alkoxy group, a hydroxy group, a nitro group, a cyano group, an amino group and a carbamoyl group".

Examples of the "acyl group" also include a hydrocarbon-sulfonyl group, a heterocyclylsulfonyl group, a hydrocarbon-sulfinyl group and a heterocyclylsulfinyl group.

Here, the hydrocarbon-sulfonyl group means a hydrocarbon group-bonded sulfonyl group, the heterocyclylsulfonyl group means a heterocyclic group-bonded sulfonyl group, the hydrocarbon-sulfinyl group means a hydrocarbon group-bonded sulfinyl group and the heterocyclylsulfinyl group means a heterocyclic group-bonded sulfinyl group.

35 Preferable examples of the "acyl group" include a formyl

group, a carboxy group, a C₁₋₆ alkyl-carbonyl group, a C₂₋₆ alkenyl-carbonyl group (e.g., crotonoyl), a C₃₋₁₀ cycloalkyl-carbonyl group (e.g., cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl), a C₃₋₁₀ cycloalkenyl-carbonyl group (e.g., 2-cyclohexenecarbonyl), a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a C₆₋₁₄ aryloxy-carbonyl group (e.g., phenyloxycarbonyl, naphthyloxycarbonyl), a C₇₋₁₆ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, phenethyloxycarbonyl), a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a mono- or di-C₂₋₆ alkenyl-carbamoyl group (e.g., diallylcarbamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-carbamoyl group (e.g., cyclopropylcarbamoyl), a mono- or di-C₆₋₁₄ aryl-carbamoyl group (e.g., phenylcarbamoyl), a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, a 5- to 14-membered aromatic heterocyclylcarbamoyl group (e.g., pyridylcarbamoyl), a thiocarbamoyl group, a mono- or di-C₁₋₆ alkyl-thiocarbamoyl group (e.g., methylthiocarbamoyl, N-ethyl-N-methylthiocarbamoyl), a mono- or di-C₂₋₆ alkenyl-thiocarbamoyl group (e.g., diallylthiocarbamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-thiocarbamoyl group (e.g., cyclopropylthiocarbamoyl, cyclohexylthiocarbamoyl), a mono- or di-C₆₋₁₄ aryl-thiocarbamoyl group (e.g., phenylthiocarbamoyl), a mono- or di-C₇₋₁₆ aralkyl-thiocarbamoyl group (e.g., benzylthiocarbamoyl, phenethylthiocarbamoyl), a 5- to 14-membered aromatic heterocyclylthiocarbamoyl group (e.g., pyridylthiocarbamoyl), a sulfinio group, a C₁₋₆ alkylsulfinyl group (e.g., methylsulfinyl, ethylsulfinyl), a sulfo group, a C₁₋₆ alkylsulfonyl group, a C₆₋₁₄ arylsulfonyl group, a phosphono group and a mono- or di-C₁₋₆ alkylphosphono group (e.g., dimethylphosphono, diethylphosphono, diisopropylphosphono, dibutylphosphono).

[0049]

In the present specification, examples of the "optionally

substituted amino group" include an amino group optionally having "1 or 2 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, a C₁₋₆ alkylsulfonyl group and a C₆₋₁₄ arylsulfonyl group, each of which optionally has 1 to 3 substituents selected from Substituent group A".

Preferable examples of the optionally substituted amino group include an amino group, a mono- or di-(optionally halogenated C₁₋₆ alkyl) amino group (e.g., methylamino, trifluoromethylamino, dimethylamino, ethylamino, diethylamino, propylamino, dibutylamino), a mono- or di-C₂₋₆ alkenylamino group (e.g., diallylamino), a mono- or di-C₃₋₁₀ cycloalkylamino group (e.g., cyclopropylamino, cyclohexylamino), a mono- or di-C₆₋₁₄ arylamino group (e.g., phenylamino), a mono- or di-C₇₋₁₆ aralkylamino group (e.g., benzylamino, dibenzylamino), a mono- or di-(optionally halogenated C₁₋₆ alkyl)-carbonylamino group (e.g., acetylamino, propionylamino), a mono- or di-C₆₋₁₄ aryl-carbonylamino group (e.g., benzoylamino), a mono- or di-C₇₋₁₆ aralkyl-carbonylamino group (e.g., benzylcarbonylamino), a mono- or di-5- to 14-membered aromatic heterocyclylcarbonylamino group (e.g., nicotinoylamino, isonicotinoylamino), a mono- or di-3- to 14-membered non-aromatic heterocyclylcarbonylamino group (e.g., piperidinylcarbonylamino), a mono- or di-C₁₋₆ alkoxy-carbonylamino group (e.g., tert-butoxycarbonylamino), a 5- to 14-membered aromatic heterocyclylamino group (e.g., pyridylamino), a carbamoylamino group, a (mono- or di-C₁₋₆ alkyl-carbamoyl) amino group (e.g., methylcarbamoylamino), a (mono- or di-C₇₋₁₆ aralkyl-carbamoyl) amino group (e.g.,

benzylcarbamoylamino), a C₁₋₆ alkylsulfonylamino group (e.g., methylsulfonylamino, ethylsulfonylamino), a C₆₋₁₄ arylsulfonylamino group (e.g., phenylsulfonylamino), a (C₁₋₆ alkyl)(C₁₋₆ alkyl-carbonyl) amino group (e.g., N-acetyl-N-methylamino) and a (C₁₋₆ alkyl)(C₆₋₁₄ aryl-carbonyl) amino group (e.g., N-benzoyl-N-methylamino).

[0050]

In the present specification, examples of the "optionally substituted carbamoyl group" include a carbamoyl group optionally having "1 or 2 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group and a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, each of which optionally has 1 to 3 substituents selected from Substituent group A".

Preferable examples of the optionally substituted carbamoyl group include a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a mono- or di-C₂₋₆ alkenyl-carbamoyl group (e.g., diallylcarbamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-carbamoyl group (e.g., cyclopropylcarbamoyl, cyclohexylcarbamoyl), a mono- or di-C₆₋₁₄ aryl-carbamoyl group (e.g., phenylcarbamoyl), a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbonyl-carbamoyl group (e.g., acetylcarbamoyl, propionylcarbamoyl), a mono- or di-C₆₋₁₄ aryl-carbonyl-carbamoyl group (e.g., benzoylcarbamoyl) and a 5- to 14-membered aromatic heterocyclylcarbamoyl group (e.g., pyridylcarbamoyl).

[0051]

In the present specification, examples of the "optionally substituted thiocarbamoyl group" include a thiocarbamoyl group

optionally having "1 or 2 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5-
5 to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group and a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, each of which
10 optionally has 1 to 3 substituents selected from Substituent group A".

Preferable examples of the optionally substituted thiocarbamoyl group include a thiocarbamoyl group, a mono- or di-C₁₋₆ alkyl-thiocarbamoyl group (e.g., methylthiocarbamoyl,
15 ethylthiocarbamoyl, dimethylthiocarbamoyl, diethylthiocarbamoyl, N-ethyl-N-methylthiocarbamoyl), a mono- or di-C₂₋₆ alkenyl-thiocarbamoyl group (e.g., diallylthiocarbamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-thiocarbamoyl group (e.g., cyclopropylthiocarbamoyl, cyclohexylthiocarbamoyl), a mono- or
20 di-C₆₋₁₄ aryl-thiocarbamoyl group (e.g., phenylthiocarbamoyl), a mono- or di-C₇₋₁₆ aralkyl-thiocarbamoyl group (e.g., benzylthiocarbamoyl, phenethylthiocarbamoyl), a mono- or di-C₁₋₆ alkyl-carbonyl-thiocarbamoyl group (e.g., acetylthiocarbamoyl, propionylthiocarbamoyl), a mono- or di-C₆₋₁₄ aryl-carbonyl-
25 thiocarbamoyl group (e.g., benzoylthiocarbamoyl) and a 5- to 14-membered aromatic heterocyclylthiocarbamoyl group (e.g., pyridylthiocarbamoyl).

[0052]

In the present specification, examples of the "optionally
30 substituted sulfamoyl group" include a sulfamoyl group optionally having "1 or 2 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5-
35 to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-

membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group, a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group and a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, each of which
5 optionally has 1 to 3 substituents selected from Substituent group A".

Preferable examples of the optionally substituted sulfamoyl group include a sulfamoyl group, a mono- or di-C₁₋₆ alkyl-sulfamoyl group (e.g., methylsulfamoyl, ethylsulfamoyl, 10 dimethylsulfamoyl, diethylsulfamoyl, N-ethyl-N-methylsulfamoyl), a mono- or di-C₂₋₆ alkenyl-sulfamoyl group (e.g., diallylsulfamoyl), a mono- or di-C₃₋₁₀ cycloalkyl-sulfamoyl group (e.g., cyclopropylsulfamoyl, cyclohexylsulfamoyl), a mono- or di-C₆₋₁₄ aryl-sulfamoyl group (e.g., phenylsulfamoyl),
15 a mono- or di-C₇₋₁₆ aralkyl-sulfamoyl group (e.g., benzylsulfamoyl, phenethylsulfamoyl), a mono- or di-C₁₋₆ alkyl-carbonyl-sulfamoyl group (e.g., acetylsulfamoyl, propionylsulfamoyl), a mono- or di-C₆₋₁₄ aryl-carbonyl-sulfamoyl group (e.g., benzoylsulfamoyl) and a 5- to 14-membered aromatic
20 heterocyclylsulfamoyl group (e.g., pyridylsulfamoyl).

[0053]

In the present specification, examples of the "optionally substituted hydroxy group" include a hydroxy group optionally having "a substituent selected from a C₁₋₆ alkyl group, a C₂₋₆
25 alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group, a C₇₋₁₆ aralkyl-carbonyl group, a 5- to 14-membered aromatic heterocyclylcarbonyl group, a 3- to 14-membered non-aromatic heterocyclylcarbonyl group, a C₁₋₆ alkoxy-carbonyl group, a 5- to 14-membered aromatic heterocyclic group,
30 a carbamoyl group, a mono- or di-C₁₋₆ alkyl-carbamoyl group, a mono- or di-C₇₋₁₆ aralkyl-carbamoyl group, a C₁₋₆ alkylsulfonyl group and a C₆₋₁₄ arylsulfonyl group, each of which optionally has 1 to 3 substituents selected from Substituent group A".

35 Preferable examples of the optionally substituted hydroxy

group include a hydroxy group, a C₁₋₆ alkoxy group, a C₂₋₆ alkenyloxy group (e.g., allyloxy, 2-butenyloxy, 2-pentenylloxy, 3-hexenyloxy), a C₃₋₁₀ cycloalkyloxy group (e.g., cyclohexyloxy), a C₆₋₁₄ aryloxy group (e.g., phenoxy, naphthyloxy), a C₇₋₁₆ aralkyloxy group (e.g., benzyloxy, phenethyloxy), a C₁₋₆ alkyl-carbonyloxy group (e.g., acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, pivaloyloxy), a C₆₋₁₄ aryl-carbonyloxy group (e.g., benzoyloxy), a C₇₋₁₆ aralkyl-carbonyloxy group (e.g., benzylcarbonyloxy), a 5- to 14-membered aromatic heterocyclylcarbonyloxy group (e.g., nicotinoyloxy), a 3- to 14-membered non-aromatic heterocyclylcarbonyloxy group (e.g., piperidinylcarbonyloxy), a C₁₋₆ alkoxy-carbonyloxy group (e.g., tert-butoxycarbonyloxy), a 5- to 14-membered aromatic heterocyclyloxy group (e.g., pyridyloxy), a carbamoyloxy group, a C₁₋₆ alkyl-carbamoyloxy group (e.g., methylcarbamoyloxy), a C₇₋₁₆ aralkyl-carbamoyloxy group (e.g., benzylcarbamoyloxy), a C₁₋₆ alkylsulfonyloxy group (e.g., methylsulfonyloxy, ethylsulfonyloxy) and a C₆₋₁₄ arylsulfonyloxy group (e.g., phenylsulfonyloxy).

[0054]

In the present specification, examples of the "optionally substituted sulfanyl group" include a sulfanyl group optionally having "a substituent selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group, a C₇₋₁₆ aralkyl group, a C₁₋₆ alkyl-carbonyl group, a C₆₋₁₄ aryl-carbonyl group and a 5- to 14-membered aromatic heterocyclic group, each of which optionally has 1 to 3 substituents selected from Substituent group A" and a halogenated sulfanyl group.

Preferable examples of the optionally substituted sulfanyl group include a sulfanyl (-SH) group, a C₁₋₆ alkylthio group, a C₂₋₆ alkenylthio group (e.g., allylthio, 2-butenylthio, 2-pentenylthio, 3-hexenylthio), a C₃₋₁₀ cycloalkylthio group (e.g., cyclohexylthio), a C₆₋₁₄ arylthio group (e.g., phenylthio, naphthylthio), a C₇₋₁₆ aralkylthio group (e.g., benzylthio,

phenethylthio), a C₁₋₆ alkyl-carbonylthio group (e.g., acetylthio, propionylthio, butyrylthio, isobutyrylthio, pivaloylthio), a C₆₋₁₄ aryl-carbonylthio group (e.g., benzoylthio), a 5- to 14-membered aromatic heterocyclylthio
5 group (e.g., pyridylthio) and a halogenated thio group (e.g., pentafluorothio).

[0055]

In the present specification, examples of the "optionally substituted silyl group" include a silyl group optionally
10 having "1 to 3 substituents selected from a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₆₋₁₄ aryl group and a C₇₋₁₆ aralkyl group, each of which optionally has 1 to 3 substituents selected from Substituent group A".

Preferable examples of the optionally substituted silyl
15 group include a tri-C₁₋₆ alkylsilyl group (e.g., trimethylsilyl, tert-butyl(dimethyl)silyl).

[0056]

In the present specification, examples of the "hydrocarbon ring" include a C₆₋₁₄ aromatic hydrocarbon ring, C₃₋₁₀ cycloalkane and C₃₋₁₀ cycloalkene.
20

In the present specification, examples of the "C₆₋₁₄ aromatic hydrocarbon ring" include benzene and naphthalene.

In the present specification, examples of the "C₃₋₁₀ cycloalkane" include cyclopropane, cyclobutane, cyclopentane,
25 cyclohexane, cycloheptane and cyclooctane.

In the present specification, examples of the "C₃₋₁₀ cycloalkene" include cyclopropene, cyclobutene, cyclopentene, cyclohexene, cycloheptene and cyclooctene.

In the present specification, examples of the
30 "heterocycle" include an aromatic heterocycle and a non-aromatic heterocycle, each containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom.

[0057]

In the present specification, examples of the "aromatic heterocycle" include a 5- to 14-membered (preferably 5- to 10-membered) aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom. Preferable examples of the "aromatic heterocycle" include 5- or 6-membered monocyclic aromatic heterocycles such as thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, triazole, tetrazole, triazine and the like; and 8- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) aromatic heterocycles such as benzothiophene, benzofuran, benzimidazole, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, benzotriazole, imidazopyridine, thienopyridine, furopyridine, pyrrolopyridine, pyrazolopyridine, oxazolopyridine, thiazolopyridine, imidazopyrazine, imidazopyrimidine, thienopyrimidine, furopyrimidine, pyrrolopyrimidine, pyrazolopyrimidine, oxazolopyrimidine, thiazolopyrimidine, pyrazolopyrimidine, pyrazolotriazine, naphtho[2,3-b]thiophene, phenoxathiin, indole, isoindole, 1H-indazole, purine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, carbazole, β -carboline, phenanthridine, acridine, phenazine, phenothiazine, phenoxazine and the like.

[0058]

In the present specification, examples of the "non-aromatic heterocycle" include a 3- to 14-membered (preferably 4- to 10-membered) non-aromatic heterocycle containing, as a ring-constituting atom besides carbon atom, 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom and an oxygen atom. Preferable examples of the "non-aromatic heterocycle" include 3- to 8-membered monocyclic non-aromatic heterocycles such as aziridine, oxirane, thiirane, azetidene,

oxetane, thietane, tetrahydrothiophene, tetrahydrofuran, pyrroline, pyrrolidine, imidazoline, imidazolidine, oxazoline, oxazolidine, pyrazoline, pyrazolidine, thiazoline, thiazolidine, tetrahydroisothiazole, tetrahydrooxazole, 5 tetrahydroisoxazole, piperidine, piperazine, tetrahydropyridine, dihydropyridine, dihydrothiopyran, tetrahydropyrimidine, tetrahydropyridazine, dihydropyran, tetrahydropyran, tetrahydrothiopyran, morpholine, thiomorpholine, azepane, diazepane, azepine, azocane, 10 diazocane, oxepane and the like; and 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocycles such as dihydrobenzofuran, dihydrobenzimidazole, dihydrobenzoxazole, dihydrobenzothiazole, dihydrobenzisothiazole, dihydronaphtho[2,3-b]thiophene, 15 tetrahydroisoquinoline, tetrahydroquinoline, 4H-quinolizine, indoline, isoindoline, tetrahydrothieno[2,3-c]pyridine, tetrahydrobenzazepine, tetrahydroquinoxaline, tetrahydrophenanthridine, hexahydrophenothiazine, hexahydrophenoxazine, tetrahydrophthalazine, 20 tetrahydronaphthyridine, tetrahydroquinazoline, tetrahydrocinnoline, tetrahydrocarbazole, tetrahydro- β -carboline, tetrahydroacridine, tetrahydrophenazine, tetrahydrothioxanthene, octahydroisoquinoline and the like.

In the present specification, examples of the "nitrogen- 25 containing heterocycle" include a heterocycle containing at least one nitrogen atom as a ring-constituting atom, from among the "heterocycle".

[0059]

In the present specification, examples of the "4- to 7- 30 membered nitrogen-containing monocyclic saturated heterocycle" include a 4- to 7-membered saturated heterocycle containing at least one nitrogen atom as a ring-constituting atom, from among the "3- to 8-membered monocyclic non-aromatic heterocycle".

In the present specification, examples of the "ring" 35 include a "hydrocarbon ring" and a "heterocycle".

[0060]

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

R¹ is a substituent.

5 R¹ is preferably

(1) an optionally substituted C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl),

(2) an optionally substituted C₂₋₆ alkenyl group (e.g., vinyl, allyl),

10 (3) an optionally substituted C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),

(4) an optionally substituted mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino), or

(5) an optionally substituted 3- to 14-membered non-aromatic
15 heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., oxetanyl)).

Examples of the substituent of the above-mentioned "optionally substituted C₁₋₆ alkyl group", "optionally substituted C₂₋₆ alkenyl group", "optionally substituted C₃₋₁₀
20 cycloalkyl group", "optionally substituted mono- or di-C₁₋₆ alkylamino group" and "optionally substituted 3- to 14-membered non-aromatic heterocyclic group" include substituents selected from Substituent group A. The number of the substituents is preferably 1 to 3. When the number of the substituents is 2 or
25 more, the respective substituents may be the same or different.

[0061]

R¹ is more preferably

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

30 selected from

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

(b) a cyano group,

(c) a hydroxy group, and

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

35 (2) a C₂₋₆ alkenyl group (e.g., vinyl, allyl),

- (3) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),
(4) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),
or
(5) a 3- to 14-membered non-aromatic heterocyclic group
5 (preferably a 3- to 8-membered monocyclic non-aromatic
heterocyclic group (e.g., oxetanyl)).

[0062]

R¹ is further more preferably

- (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl,
10 butyl, isobutyl) optionally substituted by 1 to 3 substituents
selected from
(a) a halogen atom (e.g., a fluorine atom, a chlorine atom),
(b) a cyano group,
(c) a hydroxy group, and
15 (d) a C₁₋₆ alkoxy group (e.g., methoxy),
(2) a C₂₋₆ alkenyl group (e.g., vinyl, allyl),
(3) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl),
(4) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),
or
20 (5) an oxetanyl group.

[0063]

R¹ is still more preferably

- (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl) optionally
substituted by 1 to 3 substituents selected from
25 (a) a halogen atom (e.g., a fluorine atom, a chlorine atom),
and
(b) a C₁₋₆ alkoxy group (e.g., methoxy),
(2) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl), or
(3) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino).

30 [0064]

R¹ is particularly preferably

- (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally
substituted by 1 to 3 substituents selected from
(a) a halogen atom (e.g., a fluorine atom), and
35 (b) a C₁₋₆ alkoxy group (e.g., methoxy), or

(2) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl).

[0065]

As another embodiment, R¹ is more preferably

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

- (a) a halogen atom (e.g., a fluorine atom, a chlorine atom),
- (b) a cyano group,
- (c) a hydroxy group, and

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

(2) a C₂₋₆ alkenyl group (e.g., vinyl, allyl),

(3) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl) optionally
substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),

(4) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),

15 or

(5) a 3- to 14-membered non-aromatic heterocyclic group
(preferably a 3- to 8-membered monocyclic non-aromatic
heterocyclic group (e.g., oxetanyl)).

[0066]

20 In this embodiment, R¹ is further more preferably

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

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

25 (b) a cyano group,

(c) a hydroxy group, and

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

(2) a C₂₋₆ alkenyl group (e.g., vinyl, allyl),

(3) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl) optionally
30 substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),

(4) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),

or

(5) an oxetanyl group.

[0067]

35 In this embodiment, R¹ is still more preferably

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

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

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

(2) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), or

(3) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino).

[0068]

10 In this embodiment, R¹ is even more preferably

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

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

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

15 (2) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), or

(3) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino).

[0069]

In this embodiment, R¹ is particularly preferably

20 (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl),

(2) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), or

(3) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino).

Or, R¹ is particularly preferably a C₁₋₆ alkyl group (e.g.,
25 methyl, ethyl).

[0070]

R², R³, R⁴ and R⁵ are each independently a hydrogen atom, or a substituent.

[0071]

30 R² is preferably a hydrogen atom .

[0072]

R³ is preferably a hydrogen atom, or an acyl group.

[0073]

R³ is more preferably

35 (1) a hydrogen atom,

- (2) an optionally substituted C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 1,2-dimethylpropoxycarbonyl),
- (3) an optionally substituted C₁₋₆ alkyl-carbonyl group (e.g., acetyl, propanoyl, 2-methylpropanoyl, butanoyl, 2-methylbutanoyl, 3-methylbutanoyl, pivaloyl),
- (4) an optionally substituted mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, ethylcarbamoyl, N-ethyl-N-methylcarbamoyl),
- (5) an optionally substituted C₃₋₁₀ cycloalkyl-carbonyl group (the C₃₋₁₀ cycloalkyl in the C₃₋₁₀ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, bicyclo[1.1.1]pentylcarbonyl),
- (6) an optionally substituted C₃₋₁₀ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl),
- (7) an optionally substituted 3- to 14-membered non-aromatic heterocyclylcarbonyl group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclylcarbonyl group (the non-aromatic heterocycle in the non-aromatic heterocyclylcarbonyl group may be a spiro ring, e.g., oxetanylcarbonyl, azetidiny carbonyl, 5-azaspiro[2.3]hexylcarbonyl)),
- (8) an optionally substituted 3- to 14-membered non-aromatic heterocyclyloxycarbonyl group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclyloxycarbonyl group (e.g., oxetanyloxycarbonyl, tetrahydrofuryloxycarbonyl, tetrahydropyranyloxycarbonyl)),
- (9) an optionally substituted C₆₋₁₄ aryloxy-carbonyl group (e.g., phenoxycarbonyl), or
- (10) an optionally substituted C₇₋₁₆ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl).

Examples of the substituent of the above-mentioned

"optionally substituted C₁₋₆ alkoxy-carbonyl group", "optionally substituted C₁₋₆ alkyl-carbonyl group", "optionally substituted mono- or di-C₁₋₆ alkyl-carbamoyl group", "optionally substituted C₃₋₁₀ cycloalkyl-carbonyl group", "optionally substituted C₃₋₁₀ cycloalkoxy-carbonyl group", "optionally substituted 3- to 14-membered non-aromatic heterocyclylcarbonyl group", "optionally substituted 3- to 14-membered non-aromatic heterocyclyloxy carbonyl group", "optionally substituted C₆₋₁₄ aryloxy-carbonyl group" and "optionally substituted C₇₋₁₆ aralkyloxy-carbonyl group" each include the above-mentioned "substituent". The number of the substituents is preferably 1 to 3. When the number of the substituents is 2 or more, the respective substituents may be the same or different.

[0074]

R³ is further more preferably

- (1) a hydrogen atom,
- (2) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 1,2-dimethylpropoxycarbonyl) optionally substituted by 1 to 3 substituents selected from
 - (a) a halogen atom (e.g., a fluorine atom),
 - (b) a C₁₋₆ alkoxy group (e.g., methoxy),
 - (c) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl) optionally substituted by 1 to 3 substituents selected from
 - (i) a halogen atom (e.g., a fluorine atom), and
 - (ii) a C₁₋₆ alkyl group (e.g., methyl), and
 - (d) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., oxetanyl, tetrahydrofuryl)),
- (3) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, propanoyl, 2-methylpropanoyl, butanoyl, 2-methylbutanoyl, 3-methylbutanoyl, pivaloyl) optionally substituted by 1 to 3 substituents selected from

- (a) a halogen atom (e.g., a fluorine atom), and
(b) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),
(4) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, ethylcarbamoyl, N-ethyl-N-methylcarbamoyl),
5 (5) a C₃₋₁₀ cycloalkyl-carbonyl group (the C₃₋₁₀ cycloalkyl in the C₃₋₁₀ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3 substituents selected from
10 (a) a halogen atom (e.g., a fluorine atom),
(b) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
(c) a hydroxy group,
(d) a C₁₋₆ alkoxy group (e.g., methoxy), and
15 (e) a cyano group,
(6) a C₃₋₁₀ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl) optionally substituted by 1 to 3 substituents selected from
20 (a) a halogen atom (e.g., a fluorine atom), and
(b) a C₁₋₆ alkyl group (e.g., methyl),
(7) a 3- to 14-membered non-aromatic heterocyclylcarbonyl group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclylcarbonyl group (the non-aromatic heterocycle in the
25 non-aromatic heterocyclylcarbonyl group may be a spiro ring, e.g., oxetanylcarbonyl, azetidiny carbonyl, 5-azaspiro[2.3]hexylcarbonyl)) optionally substituted by 1 to 3 substituents selected from
(a) a halogen atom (e.g., a fluorine atom), and
30 (b) a C₁₋₆ alkyl group (e.g., methyl),
(8) a 3- to 14-membered non-aromatic heterocyclyloxycarbonyl group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclyloxycarbonyl group (e.g., oxetanyloxycarbonyl, tetrahydrofuryloxycarbonyl, tetrahydropyranyloxycarbonyl)),
35 (9) a C₆₋₁₄ aryloxy-carbonyl group (e.g., phenoxycarbonyl), or

(10) a C₇₋₁₆ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl).
[0075]

R³ is still more preferably

- (1) a hydrogen atom,
- 5 (2) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 1,2-dimethylpropoxycarbonyl) optionally substituted by 1 to 3 substituents selected from
 - 10 (a) a halogen atom (e.g., a fluorine atom),
 - (b) a C₁₋₆ alkoxy group (e.g., methoxy),
 - (c) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl) optionally substituted by 1 to 3 substituents selected from
 - 15 (i) a halogen atom (e.g., a fluorine atom), and
 - (ii) a C₁₋₆ alkyl group (e.g., methyl),
 - (d) an oxetanyl group, and
 - (e) a tetrahydrofuryl group,
 - (3) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, propanoyl, 2-methylpropanoyl, butanoyl, 2-methylbutanoyl, 3-methylbutanoyl, pivaloyl) optionally substituted by 1 to 3 substituents selected from
 - (a) a halogen atom (e.g., a fluorine atom), and
 - (b) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl),
 - 25 (4) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, ethylcarbamoyl, N-ethyl-N-methylcarbamoyl),
 - (5) a C₃₋₆ cycloalkyl-carbonyl group (the C₃₋₆ cycloalkyl in the C₃₋₆ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3
 - 30 substituents selected from
 - (a) a halogen atom (e.g., a fluorine atom),
 - (b) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
 - 35 (c) a hydroxy group,

- (d) a C₁₋₆ alkoxy group (e.g., methoxy), and
(e) a cyano group,
(6) a C₃₋₆ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl) optionally substituted by 1 to 3 substituents selected from
(a) a halogen atom (e.g., a fluorine atom), and
(b) a C₁₋₆ alkyl group (e.g., methyl),
(7) an oxetanylcarbonyl group,
(8) an azetidinyldcarbonyl group optionally substituted by 1 to 3 substituents selected from
(a) a halogen atom (e.g., a fluorine atom), and
(b) a C₁₋₆ alkyl group (e.g., methyl),
(9) a 5-azaspiro[2.3]hexylcarbonyl group,
(10) an oxetanyloxycarbonyl group,
(11) a tetrahydrofuryloxycarbonyl group,
(12) a tetrahydropyranyloxycarbonyl group,
(13) a phenoxycarbonyl group, or
(14) a benzyloxycarbonyl group.
- [0076]
- R³ is even more preferably
(1) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl),
(2) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, 2-methylpropanoyl, pivaloyl),
(3) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, ethylcarbamoyl),
(4) a C₃₋₆ cycloalkyl-carbonyl group (the C₃₋₆ cycloalkyl in the C₃₋₆ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3 substituents selected from
(a) a halogen atom (e.g., a fluorine atom),
(b) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),

- (c) a hydroxy group,
 - (d) a C₁₋₆ alkoxy group (e.g., methoxy), and
 - (e) a cyano group,
 - (5) a C₃₋₆ cycloalkoxy-carbonyl group (e.g.,
5 cyclopropoxycarbonyl),
 - (6) a phenoxycarbonyl group,
 - (7) an oxetanylcabonyl group,
 - (8) an azetidinylcabonyl group optionally substituted by 1 to
3 substituents selected from
 - 10 (a) a halogen atom (e.g., a fluorine atom), and
 - (b) a C₁₋₆ alkyl group (e.g., methyl), or
 - (9) a 5-azaspiro[2.3]hexylcarbonyl group.
- [0077]

R³ is particularly preferably

- 15 (1) a C₁₋₆ alkoxy-carbonyl group (e.g., ethoxycarbonyl,
isopropoxycarbonyl),
- (2) a C₁₋₆ alkyl-carbonyl group (e.g., 2-methylpropanoyl,
pivaloyl),
- (3) a C₃₋₆ cycloalkyl-carbonyl group (the C₃₋₆ cycloalkyl in the
20 C₃₋₆ cycloalkyl-carbonyl group may be a bridged ring group, e.g.,
cyclopropylcarbonyl, cyclobutylcarbonyl,
bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3
substituents selected from
- (a) a halogen atom (e.g., a fluorine atom),
- 25 (b) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted
by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (c) a hydroxy group,
- (d) a C₁₋₆ alkoxy group (e.g., methoxy), and
- (e) a cyano group,
- 30 (4) an oxetanylcabonyl group,
- (5) an azetidinylcabonyl group optionally substituted by 1 to
3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom), and
- (b) a C₁₋₆ alkyl group (e.g., methyl), or
- 35 (6) a 5-azaspiro[2.3]hexylcarbonyl group.

[0078]

As another embodiment, R³ is more preferably

- (1) a hydrogen atom,
- (2) an optionally substituted C₁₋₆ alkoxy-carbonyl group (e.g.,
5 methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl,
isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-
butoxycarbonyl, tert-butoxycarbonyl, 1,2-
dimethylpropoxycarbonyl),
- (3) an optionally substituted C₁₋₆ alkyl-carbonyl group (e.g.,
10 acetyl, propanoyl, 2-methylpropanoyl, butanoyl, 2-
methylbutanoyl, 3-methylbutanoyl, pivaloyl),
- (4) an optionally substituted mono- or di-C₁₋₆ alkyl-carbamoyl
group (e.g., dimethylcarbamoyl, ethylcarbamoyl, N-ethyl-N-
methylcarbamoyl, N-isopropyl-N-methylcarbamoyl),
- 15 (5) an optionally substituted N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-
carbamoyl group (e.g., N-methoxy-N-methylcarbamoyl),
- (6) an optionally substituted C₃₋₁₀ cycloalkyl-carbonyl group
(the C₃₋₁₀ cycloalkyl in the C₃₋₁₀ cycloalkyl-carbonyl group may
be a bridged ring group, e.g., cyclopropylcarbonyl,
20 cyclobutylcarbonyl, cyclopentylcarbonyl,
bicyclo[1.1.1]pentylcarbonyl),
- (7) an optionally substituted C₃₋₁₀ cycloalkoxy-carbonyl group
(e.g., cyclopropoxycarbonyl, cyclobutyloxycarbonyl,
cyclopentyloxycarbonyl, cyclohexyloxycarbonyl),
- 25 (8) an optionally substituted 3- to 14-membered non-aromatic
heterocyclylcarbonyl group (preferably a 3- to 8-membered
monocyclic non-aromatic heterocyclylcarbonyl group (the non-
aromatic heterocycle in the non-aromatic heterocyclylcarbonyl
group may be a spiro ring, e.g., oxetanylcarbonyl,
30 azetidiny carbonyl, 5-azaspiro[2.3]hexylcarbonyl)),
- (9) an optionally substituted 3- to 14-membered non-aromatic
heterocyclyloxycarbonyl group (preferably a 3- to 8-membered
monocyclic non-aromatic heterocyclyloxycarbonyl group (e.g.,
oxetanyloxycarbonyl, tetrahydrofuryloxycarbonyl,
35 tetrahydropyranyloxycarbonyl)),

- (10) an optionally substituted C₆₋₁₄ aryloxy-carbonyl group (e.g., phenoxycarbonyl), or
(11) an optionally substituted C₇₋₁₆ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl).

5 Examples of the substituent of the above-mentioned "optionally substituted C₁₋₆ alkoxy-carbonyl group", "optionally substituted C₁₋₆ alkyl-carbonyl group", "optionally substituted mono- or di-C₁₋₆ alkyl-carbamoyl group", "optionally substituted N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group", "optionally
10 substituted C₃₋₁₀ cycloalkyl-carbonyl group", "optionally substituted C₃₋₁₀ cycloalkoxy-carbonyl group", "optionally substituted 3- to 14-membered non-aromatic heterocyclylcarbonyl group", "optionally substituted 3- to 14-membered non-aromatic heterocyclyloxycarbonyl group", "optionally substituted C₆₋₁₄
15 aryloxy-carbonyl group" and "optionally substituted C₇₋₁₆ aralkyloxy-carbonyl group" each include the above-mentioned "substituent". The number of the substituents is preferably 1 to 3. When the number of the substituents is 2 or more, the respective substituents may be the same or different.

20 [0079]

In this embodiment, R³ is further more preferably
(1) a hydrogen atom,
(2) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl,
25 butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 1,2-dimethylpropoxycarbonyl) optionally substituted by 1 to 3 substituents selected from

- (a) a halogen atom (e.g., a fluorine atom),
(b) a C₁₋₆ alkoxy group (e.g., methoxy),
30 (c) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl) optionally substituted by 1 to 3 substituents selected from

- (i) a halogen atom (e.g., a fluorine atom), and
(ii) a C₁₋₆ alkyl group (e.g., methyl), and
35 (d) a 3- to 14-membered non-aromatic heterocyclic group

- (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., oxetanyl, tetrahydrofuryl)),
- (3) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, propanoyl, 2-methylpropanoyl, butanoyl, 2-methylbutanoyl, 3-methylbutanoyl, 5 pivaloyl) optionally substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom),
 - (b) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),
 - (c) a hydroxy group, and
 - 10 (d) a C₁₋₆ alkoxy group (e.g., methoxy),
- (4) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, ethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N-isopropyl-N-methylcarbamoyl),
- (5) a N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group (e.g., N- 15 methoxy-N-methylcarbamoyl),
- (6) a C₃₋₁₀ cycloalkyl-carbonyl group (the C₃₋₁₀ cycloalkyl in the C₃₋₁₀ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, bicyclo[1.1.1]pentylcarbonyl) optionally 20 substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom),
 - (b) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
 - (c) a hydroxy group,
 - 25 (d) a C₁₋₆ alkoxy group (e.g., methoxy), and
 - (e) a cyano group,
- (7) a C₃₋₁₀ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl) optionally 30 substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom), and
 - (b) a C₁₋₆ alkyl group (e.g., methyl),
- (8) a 3- to 14-membered non-aromatic heterocyclylcarbonyl group (preferably a 3- to 8-membered monocyclic non-aromatic 35 heterocyclylcarbonyl group (the non-aromatic heterocycle in the

non-aromatic heterocyclylcarbonyl group may be a spiro ring, e.g., oxetanylcarbonyl, azetidiny carbonyl, 5-azaspiro[2.3]hexylcarbonyl)) optionally substituted by 1 to 3 substituents selected from

- 5 (a) a halogen atom (e.g., a fluorine atom), and
(b) a C₁₋₆ alkyl group (e.g., methyl),
(9) a 3- to 14-membered non-aromatic heterocyclyloxycarbonyl group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclyloxycarbonyl group (e.g., oxetanyloxycarbonyl,
10 tetrahydrofuryloxycarbonyl, tetrahydropyranyloxycarbonyl)),
(10) a C₆₋₁₄ aryloxy-carbonyl group (e.g., phenoxy carbonyl), or
(11) a C₇₋₁₆ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl).
[0080]

In this embodiment, R³ is still more preferably

- 15 (1) a hydrogen atom,
(2) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 1,2-dimethylpropoxycarbonyl) optionally
20 substituted by 1 to 3 substituents selected from
(a) a halogen atom (e.g., a fluorine atom),
(b) a C₁₋₆ alkoxy group (e.g., methoxy),
(c) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl) optionally substituted by 1 to 3 substituents
25 selected from
(i) a halogen atom (e.g., a fluorine atom), and
(ii) a C₁₋₆ alkyl group (e.g., methyl),
(d) an oxetanyl group, and
(e) a tetrahydrofuryl group,
30 (3) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, propanoyl, 2-methylpropanoyl, butanoyl, 2-methylbutanoyl, 3-methylbutanoyl, pivaloyl) optionally substituted by 1 to 3 substituents
selected from
(a) a halogen atom (e.g., a fluorine atom),
35 (b) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl),

- (c) a hydroxy group, and
- (d) a C₁₋₆ alkoxy group (e.g., methoxy),
- (4) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, ethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N-isopropyl-N-methylcarbamoyl),
- (5) a N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group (e.g., N-methoxy-N-methylcarbamoyl),
- (6) a C₃₋₆ cycloalkyl-carbonyl group (the C₃₋₆ cycloalkyl in the C₃₋₆ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3 substituents selected from
 - (a) a halogen atom (e.g., a fluorine atom),
 - (b) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
 - (c) a hydroxy group,
 - (d) a C₁₋₆ alkoxy group (e.g., methoxy), and
 - (e) a cyano group,
- (7) a C₃₋₆ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl) optionally substituted by 1 to 3 substituents selected from
 - (a) a halogen atom (e.g., a fluorine atom), and
 - (b) a C₁₋₆ alkyl group (e.g., methyl),
- (8) an oxetanylcabonyl group,
- (9) an azetidinylcabonyl group optionally substituted by 1 to 3 substituents selected from
 - (a) a halogen atom (e.g., a fluorine atom), and
 - (b) a C₁₋₆ alkyl group (e.g., methyl),
- (10) a 5-azaspiro[2.3]hexylcarbonyl group,
- (11) an oxetanyloxycarbonyl group,
- (12) a tetrahydrofuryloxycarbonyl group,
- (13) a tetrahydropyranyloxycarbonyl group,
- (14) a phenoxycarbonyl group, or
- (15) a benzyloxycarbonyl group.

[0081]

In this embodiment, R³ is even more preferably

(1) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl),

5 (2) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, 2-methylpropanoyl, pivaloyl) optionally substituted by 1 to 3 hydroxy groups,

(3) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, ethylcarbamoyl),

(4) a C₃₋₆ cycloalkyl-carbonyl group (the C₃₋₆ cycloalkyl in the
10 C₃₋₆ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3 substituents selected from

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

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

(c) a hydroxy group,

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

(e) a cyano group,

20 (5) a C₃₋₆ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl),

(6) a phenoxycarbonyl group,

(7) an oxetanylcabonyl group,

(8) an azetidinylcabonyl group optionally substituted by 1 to
25 3 substituents selected from

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

(b) a C₁₋₆ alkyl group (e.g., methyl), or

(9) a 5-azaspiro[2.3]hexylcarbonyl group.

[0082]

30 In this embodiment, R³ is particularly preferably

(1) a C₁₋₆ alkoxy-carbonyl group (e.g., ethoxycarbonyl, isopropoxycarbonyl),

(2) a C₁₋₆ alkyl-carbonyl group (e.g., 2-methylpropanoyl, pivaloyl) optionally substituted by 1 to 3 hydroxy groups,

35 (3) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g.,

dimethylcarbamoyl),

(4) a C₃₋₆ cycloalkyl-carbonyl group (the C₃₋₆ cycloalkyl in the C₃₋₆ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl,

5 bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3 substituents selected from

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

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

10 (c) a hydroxy group,

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

(e) a cyano group,

(5) an oxetanylcabonyl group,

(6) an azetidinylcabonyl group optionally substituted by 1 to

15 3 substituents selected from

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

(b) a C₁₋₆ alkyl group (e.g., methyl), or

(7) a 5-azaspiro[2.3]hexylcarbonyl group.

[0083]

20 As another embodiment, R³ is more preferably

(1) a hydrogen atom,

(2) an optionally substituted C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-
25 butoxycarbonyl, tert-butoxycarbonyl, 1,2-dimethylpropoxycarbonyl),

(3) an optionally substituted C₁₋₆ alkyl-carbonyl group (e.g., acetyl, propanoyl, 2-methylpropanoyl, butanoyl, 2-methylbutanoyl, 3-methylbutanoyl, pivaloyl),

30 (4) an optionally substituted mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, ethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N-isopropyl-N-methylcarbamoyl),

(5) an optionally substituted N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group (e.g., N-methoxy-N-methylcarbamoyl),

35 (6) an optionally substituted C₃₋₁₀ cycloalkyl-carbonyl group

(the C₃₋₁₀ cycloalkyl in the C₃₋₁₀ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, bicyclo[1.1.1]pentylcarbonyl),

5 (7) an optionally substituted C₃₋₁₀ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl),

(8) an optionally substituted 3- to 14-membered non-aromatic heterocyclylcarbonyl group (preferably a 3- to 8-membered
10 monocyclic non-aromatic heterocyclylcarbonyl group (the non-aromatic heterocycle in the non-aromatic heterocyclylcarbonyl group may be a spiro ring, e.g., oxetanylcarbonyl, azetidiny carbonyl, 5-azaspiro[2.3]hexylcarbonyl, isoxazolidiny carbonyl)),

15 (9) an optionally substituted 3- to 14-membered non-aromatic heterocyclyloxycarbonyl group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclyloxycarbonyl group (e.g., oxetanyloxycarbonyl, tetrahydrofuryloxycarbonyl, tetrahydropyranyloxycarbonyl)),

20 (10) an optionally substituted C₆₋₁₄ aryloxy-carbonyl group (e.g., phenoxycarbonyl),

(11) an optionally substituted C₇₋₁₆ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl),

(12) an optionally substituted 5- to 14-membered aromatic
25 heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., imidazolyl, pyridazinyl)),

(13) an optionally substituted 5- to 14-membered aromatic heterocyclylcarbonyl group (preferably a 5- to 6-membered monocyclic aromatic heterocyclylcarbonyl group (e.g.,

30 pyrazolylcarbonyl, furylcarbonyl)), or

(14) an optionally substituted tri-C₁₋₆ alkylhydrazino-carbonyl group (e.g., trimethylhydrazinocarbonyl).

Examples of the substituent of the above-mentioned
"optionally substituted C₁₋₆ alkoxy-carbonyl group", "optionally
35 substituted C₁₋₆ alkyl-carbonyl group", "optionally substituted

mono- or di-C₁₋₆ alkyl-carbamoyl group", "optionally substituted N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group", "optionally substituted C₃₋₁₀ cycloalkyl-carbonyl group", "optionally substituted C₃₋₁₀ cycloalkoxy-carbonyl group", "optionally substituted 3- to 14-membered non-aromatic heterocyclylcarbonyl group", "optionally substituted 3- to 14-membered non-aromatic heterocyclyloxy carbonyl group", "optionally substituted C₆₋₁₄ aryloxy-carbonyl group", "optionally substituted C₇₋₁₆ aralkyloxy-carbonyl group", "optionally substituted 5- to 14-membered aromatic heterocyclic group", "optionally substituted 5- to 14-membered aromatic heterocyclylcarbonyl group" and "tri-C₁₋₆ alkylhydrazino-carbonyl group" each include the above-mentioned "substituent". The number of the substituents is preferably 1 to 3. When the number of the substituents is 2 or more, the respective substituents may be the same or different.

[0084]

In this embodiment, R³ is further more preferably

- (1) a hydrogen atom,
- (2) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 1,2-dimethylpropoxycarbonyl) optionally substituted by 1 to 3 substituents selected from
 - (a) a halogen atom (e.g., a fluorine atom),
 - (b) a C₁₋₆ alkoxy group (e.g., methoxy),
 - (c) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl) optionally substituted by 1 to 3 substituents selected from
 - (i) a halogen atom (e.g., a fluorine atom), and
 - (ii) a C₁₋₆ alkyl group (e.g., methyl), and
 - (d) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., oxetanyl, tetrahydrofuryl)),
- (3) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, propanoyl, 2-methylpropanoyl, butanoyl, 2-methylbutanoyl, 3-methylbutanoyl,

pivaloyl) optionally substituted by 1 to 3 substituents selected from

- (a) a halogen atom (e.g., a fluorine atom),
- (b) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),
- 5 (c) a hydroxy group, and
- (d) a C₁₋₆ alkoxy group (e.g., methoxy),
- (4) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, ethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N-isopropyl-N-methylcarbamoyl),
- 10 (5) a N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group (e.g., N-methoxy-N-methylcarbamoyl),
- (6) a C₃₋₁₀ cycloalkyl-carbonyl group (the C₃₋₁₀ cycloalkyl in the C₃₋₁₀ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl,
- 15 cyclopentylcarbonyl, bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3 substituents selected from
 - (a) a halogen atom (e.g., a fluorine atom),
 - (b) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 substituents selected from
 - 20 (i) a halogen atom (e.g., a fluorine atom), and
 - (ii) a hydroxy group,
 - (c) a hydroxy group,
 - (d) a C₁₋₆ alkoxy group (e.g., methoxy), and
 - (e) a cyano group,
- 25 (7) a C₃₋₁₀ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl) optionally substituted by 1 to 3 substituents selected from
 - (a) a halogen atom (e.g., a fluorine atom), and
 - 30 (b) a C₁₋₆ alkyl group (e.g., methyl),
- (8) a 3- to 14-membered non-aromatic heterocyclylcarbonyl group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclylcarbonyl group (the non-aromatic heterocycle in the non-aromatic heterocyclylcarbonyl group may be a spiro ring,
- 35 e.g., oxetanylcarbonyl, azetidiny carbonyl, 5-

azaspiro[2.3]hexylcarbonyl, isoxazolidinylcarbonyl)) optionally substituted by 1 to 3 substituents selected from

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

(b) a C₁₋₆ alkyl group (e.g., methyl),

5 (9) a 3- to 14-membered non-aromatic heterocyclyloxy carbonyl group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclyloxy carbonyl group (e.g., oxetanyloxy carbonyl, tetrahydrofuryloxy carbonyl, tetrahydropyranyloxy carbonyl)),
(10) a C₆₋₁₄ aryloxy-carbonyl group (e.g., phenoxy carbonyl),
10 (11) a C₇₋₁₆ aralkyloxy-carbonyl group (e.g., benzyloxy carbonyl),
(12) a 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., imidazolyl, pyridazinyl)) optionally substituted by 1 to 3 substituents selected from

15 (i) a halogen atom (e.g., a chlorine atom), and

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

(13) a 5- to 14-membered aromatic heterocyclyl carbonyl group (preferably a 5- to 6-membered monocyclic aromatic heterocyclyl carbonyl group (e.g., pyrazolyl carbonyl, furyl carbonyl)) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), or
20 (14) a tri-C₁₋₆ alkylhydrazino-carbonyl group (e.g., trimethylhydrazinocarbonyl).

[0085]

25 In this embodiment, R³ is still more preferably

(1) a hydrogen atom,

(2) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 1,2-dimethylpropoxycarbonyl) optionally substituted by 1 to 3 substituents selected from

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

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

(c) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl) optionally substituted by 1 to 3 substituents

selected from

- (i) a halogen atom (e.g., a fluorine atom), and
 - (ii) a C₁₋₆ alkyl group (e.g., methyl),
 - (d) an oxetanyl group, and
 - 5 (e) a tetrahydrofuryl group,
- (3) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, propanoyl, 2-methylpropanoyl, butanoyl, 2-methylbutanoyl, 3-methylbutanoyl, pivaloyl) optionally substituted by 1 to 3 substituents selected from
- 10 (a) a halogen atom (e.g., a fluorine atom),
 - (b) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl),
 - (c) a hydroxy group, and
 - (d) a C₁₋₆ alkoxy group (e.g., methoxy),
 - (4) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g.,
 - 15 dimethylcarbamoyl, ethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N-isopropyl-N-methylcarbamoyl),
 - (5) a N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group (e.g., N-methoxy-N-methylcarbamoyl),
 - (6) a C₃₋₆ cycloalkyl-carbonyl group (the C₃₋₆ cycloalkyl in the
 - 20 C₃₋₆ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom),
 - 25 (b) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom), and
 - (ii) a hydroxy group,
 - (c) a hydroxy group,
 - 30 (d) a C₁₋₆ alkoxy group (e.g., methoxy), and
 - (e) a cyano group,
 - (7) a C₃₋₆ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl) optionally
 - 35 substituted by 1 to 3 substituents selected from

- (a) a halogen atom (e.g., a fluorine atom), and
(b) a C₁₋₆ alkyl group (e.g., methyl),
(8) an oxetanylcabonyl group,
(9) an azetidinylcabonyl group optionally substituted by 1 to
5 3 substituents selected from
(a) a halogen atom (e.g., a fluorine atom), and
(b) a C₁₋₆ alkyl group (e.g., methyl),
(10) a 5-azaspiro[2.3]hexylcabonyl group,
(11) an oxetanyloxycabonyl group,
10 (12) a tetrahydrofuryloxycabonyl group,
(13) a tetrahydropyranyloxycabonyl group,
(14) a phenoxycabonyl group,
(15) a benzyloxycabonyl group,
(16) an isoxazolidinylcabonyl group,
15 (17) a pyrazolylcabonyl group optionally substituted by 1 to 3
C₁₋₆ alkyl groups (e.g., methyl),
(18) a furylcabonyl group,
(19) an imidazolyl group optionally substituted by 1 to 3 C₁₋₆
alkyl groups (e.g., methyl, ethyl),
20 (20) a pyridazinyl group optionally substituted by 1 to 3
substituents selected from
(i) a halogen atom (e.g., a chlorine atom), and
(ii) a C₁₋₆ alkyl group (e.g., methyl), or
(21) a tri-C₁₋₆ alkylhydrazino-carbonyl group (e.g.,
25 trimethylhydrazinocarbonyl).
[0086]

- In this embodiment, R³ is even more preferably
(1) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycabonyl,
ethoxycabonyl, isopropoxycabonyl),
30 (2) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, 2-methylpropanoyl,
pivaloyl) optionally substituted by 1 to 3 hydroxy groups,
(3) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g.,
dimethylcarbamoyl, ethylcarbamoyl),
(4) a N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group (e.g., N-
35 methoxy-N-methylcarbamoyl),

- (5) a C₃₋₆ cycloalkyl-carbonyl group (the C₃₋₆ cycloalkyl in the C₃₋₆ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3
5 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom),
 - (b) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
 - (c) a hydroxy group,
 - 10 (d) a C₁₋₆ alkoxy group (e.g., methoxy), and
 - (e) a cyano group,
- (6) a C₃₋₆ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl),
- (7) a phenoxycarbonyl group,
- 15 (8) an oxetanylcabonyl group,
- (9) an azetidinylcabonyl group optionally substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom), and
 - (b) a C₁₋₆ alkyl group (e.g., methyl), or
- 20 (10) a 5-azaspiro[2.3]hexylcarbonyl group.
- [0087]

In this embodiment, R³ is even more preferably

- (1) a C₁₋₆ alkoxy-carbonyl group (e.g., ethoxycarbonyl, isopropoxycarbonyl),
- 25 (2) a C₁₋₆ alkyl-carbonyl group (e.g., 2-methylpropanoyl, pivaloyl) optionally substituted by 1 to 3 hydroxy groups,
- (3) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl),
- (4) a N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group (e.g., N-
30 methoxy-N-methylcarbamoyl),
- (5) a C₃₋₆ cycloalkyl-carbonyl group (the C₃₋₆ cycloalkyl in the C₃₋₆ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3
35 substituents selected from

- (a) a halogen atom (e.g., a fluorine atom),
(b) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
(c) a hydroxy group,
5 (d) a C₁₋₆ alkoxy group (e.g., methoxy), and
(e) a cyano group,
(6) an oxetanylcarbonyl group,
(7) an azetidinyldicarbonyl group optionally substituted by 1 to 3 substituents selected from
10 (a) a halogen atom (e.g., a fluorine atom), and
(b) a C₁₋₆ alkyl group (e.g., methyl), or
(8) a 5-azaspiro[2.3]hexyldicarbonyl group.
[0088]

In this embodiment, R³ is particularly preferably
15 (1) a C₁₋₆ alkyl-carbonyl group (e.g., 2-methylpropanoyl) optionally substituted by 1 to 3 hydroxy groups,
(2) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl),
(3) a N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group (e.g., N-
20 methoxy-N-methylcarbamoyl), or
(4) an azetidinyldicarbonyl group.

Or, R³ is particularly preferably a C₁₋₆ alkyl-carbonyl group (e.g., 2-methylpropanoyl) optionally substituted by 1 to 3 hydroxy groups.
25 [0089]

R⁴ and R⁵ are preferably each independently a hydrogen atom or a halogen atom (e.g., a fluorine atom).

R⁴ and R⁵ are particularly preferably both hydrogen atoms.
[0090]

30 Ring A is an optionally further substituted 4- to 7-membered nitrogen-containing monocyclic saturated heterocycle.

Ring A optionally has substituent(s), in addition to R³, -NR²SO₂R¹ and -CR⁴R⁵-Ring B in the formula (I). Examples of the substituent include the above-mentioned "substituent". The
35 number of the substituents is preferably 1 to 3. When the

number of the substituents is 2 or more, the respective substituents may be the same or different.

[0091]

Ring A is preferably

- 5 (1) an optionally further substituted pyrrolidine ring,
(2) an optionally further substituted piperidine ring, or
(3) an optionally further substituted azetidine ring.

[0092]

Ring A is more preferably

- 10 (1) a pyrrolidine ring,
(2) a piperidine ring, or
(3) an azetidine ring.

[0093]

Ring A is still more preferably

- 15 (1) a pyrrolidine ring, or
(2) a piperidine ring.

[0094]

Ring B is an optionally further substituted ring.

Ring B optionally has substituent(s), in addition to -
20 CR⁴R⁵-Ring A in the formula (I). Examples of the substituent include the above-mentioned "substituent". The number of the substituents is preferably 1 to 3. When the number of the substituents is 2 or more, the respective substituents may be the same or different.

25 [0095]

Ring B is preferably

- (1) an optionally further substituted C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene, naphthalene),
(2) an optionally further substituted 5- to 14-membered
30 aromatic heterocycle (preferably a 5- to 6-membered monocyclic aromatic heterocycle (e.g., pyridine, pyrazole, thiazole, oxazole)), or
(3) an optionally further substituted 3- to 14-membered non-aromatic heterocycle (preferably a 3- to 8-membered monocyclic
35 non-aromatic heterocycle (e.g., pyrrolidine, piperidine), a 9-

to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocycle (e.g., dibenzofuran)).

[0096]

Ring B is more preferably

- 5 (1) a C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene, naphthalene) optionally further substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom),
 - 10 (b) a C₁₋₆ alkyl group (e.g., methyl, isopropyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
 - (c) a C₂₋₆ alkenyl group (e.g., vinyl, propen-2-yl),
 - (d) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),
 - (e) a tri-C₁₋₆ alkylsilyloxy group (e.g.,
 - 15 triisopropylsilyloxy),
 - (f) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 4 substituents selected from
 - (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
 - 20 (ii) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
 - (iii) a C₁₋₆ alkoxy group (e.g., methoxy),
 - (g) a C₆₋₁₄ aryloxy group (e.g., phenoxy),
 - 25 (h) a C₇₋₁₆ aralkyl group (e.g., benzyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
 - (i) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),
 - (j) a C₃₋₁₀ cycloalkenyl group (e.g., cyclopenten-1-yl, cyclohexen-1-yl),
 - 30 (k) a C₃₋₁₀ cycloalkoxy group (e.g., cyclohexyloxy),
 - (l) a 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyridyl, thienyl, pyrazolyl, pyrimidinyl), a 8- to 14-membered fused polycyclic
 - 35 (preferably bi- or tri-cyclic) aromatic heterocyclic group

- (e.g., indazolyl)) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), and
- (m) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., pyrrolidinyl), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocyclic group (e.g., dihydroindolyl)),
- (2) a 5- to 14-membered aromatic heterocycle (preferably a 5- to 6-membered monocyclic aromatic heterocycle (e.g., pyridine, pyrazole, thiazole, oxazole)) optionally further substituted by 1 to 3 substituents selected from
- (a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (b) a C₁₋₆ alkyl group (e.g., methyl, isopropyl), and
- (c) a C₂₋₆ alkenyl group (e.g., propen-2-yl), or
- (3) a 3- to 14-membered non-aromatic heterocycle (preferably a 3- to 8-membered monocyclic non-aromatic heterocycle (e.g., pyrrolidine, piperidine), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocycle (e.g., dibenzofuran)) optionally further substituted by 1 to 3 substituents selected from
- (a) a C₆₋₁₄ aryl group (e.g., phenyl), and
- (b) a 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyrimidinyl)).

[0097]

Ring B is further more preferably

- (1) a benzene ring optionally further substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom),
- (b) a C₁₋₆ alkyl group (e.g., methyl, isopropyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (c) a C₂₋₆ alkenyl group (e.g., vinyl, propen-2-yl),
- (d) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),

- (e) a tri-C₁₋₆ alkylsilyloxy group (e.g., triisopropylsilyloxy),
- (f) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 4 substituents selected from
- 5 (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
- (ii) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
- 10 (iii) a C₁₋₆ alkoxy group (e.g., methoxy),
- (g) a C₆₋₁₄ aryloxy group (e.g., phenoxy),
- (h) a C₇₋₁₆ aralkyl group (e.g., benzyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
- (i) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),
- 15 (j) a C₃₋₁₀ cycloalkenyl group (e.g., cyclopenten-1-yl, cyclohexen-1-yl),
- (k) a C₃₋₁₀ cycloalkoxy group (e.g., cyclohexyloxy),
- (l) a 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic
- 20 heterocyclic group (e.g., pyridyl, thienyl, pyrazolyl, pyrimidinyl), a 8- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) aromatic heterocyclic group (e.g., indazolyl)) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), and
- 25 (m) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., pyrrolidinyl), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocyclic group (e.g., dihydroindolyl)),
- 30 (2) a naphthalene ring,
- (3) a pyridine ring optionally further substituted by 1 to 3 substituents selected from
- (a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- 35 (b) a C₁₋₆ alkyl group (e.g., isopropyl), and

- (c) a C₂₋₆ alkenyl group (e.g., propen-2-yl),
(4) a pyrazole ring optionally further substituted by 1 or 2
C₆₋₁₄ aryl groups (e.g., phenyl),
(5) a thiazole ring optionally further substituted by 1 or 2
5 substituents selected from
(a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted
by 1 to 3 halogen atoms (e.g., a fluorine atom), and
(b) a C₁₋₆ alkyl group (e.g., methyl),
(6) an oxazole ring optionally further substituted by 1 or 2
10 C₆₋₁₄ aryl groups (e.g., phenyl),
(7) a pyrrolidine ring optionally further substituted by 1 to 3
C₆₋₁₄ aryl groups (e.g., phenyl),
(8) a piperidine ring optionally further substituted by 1 to 3
substituents selected from
15 (a) a C₆₋₁₄ aryl group (e.g., phenyl), and
(b) a 5- to 14-membered aromatic heterocyclic group
(preferably a 5- to 6-membered monocyclic aromatic
heterocyclic group (e.g., pyrimidinyl)), or
(9) a dibenzofuran ring.

20 [0098]

Ring B is still more preferably

- (1) a benzene ring optionally further substituted by 1 to 3
substituents selected from
(a) a halogen atom (e.g., a fluorine atom, a chlorine atom,
25 a bromine atom, an iodine atom),
(b) a C₁₋₆ alkyl group (e.g., methyl, isopropyl) optionally
substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
(c) a C₂₋₆ alkenyl group (e.g., vinyl, propen-2-yl),
(d) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),
30 (e) a tri-C₁₋₆ alkylsilyloxy group (e.g.,
triisopropylsilyloxy),
(f) a phenyl group optionally substituted by 1 to 4
substituents selected from
(i) a halogen atom (e.g., a fluorine atom, a chlorine
35 atom),

- (ii) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
- (iii) a C₁₋₆ alkoxy group (e.g., methoxy),
- 5 (g) a phenoxy group,
- (h) a benzyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
- (i) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),
- (j) a C₃₋₆ cycloalkenyl group (e.g., cyclopenten-1-yl,
- 10 cyclohexen-1-yl),
- (k) a C₃₋₆ cycloalkoxy group (e.g., cyclohexyloxy),
- (l) a pyridyl group,
- (m) a thienyl group,
- (n) a pyrimidinyl group,
- 15 (o) a pyrazolyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
- (p) an indazolyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
- (q) a pyrrolidinyl group, and
- 20 (r) a dihydroindolyl group,
- (2) a naphthalene ring,
- (3) a pyridine ring optionally further substituted by 1 to 3 substituents selected from
 - (a) a phenyl group optionally substituted by 1 to 3 halogen
 - 25 atoms (e.g., a fluorine atom),
 - (b) a C₁₋₆ alkyl group (e.g., isopropyl), and
 - (c) a C₂₋₆ alkenyl group (e.g., propen-2-yl),
- (4) a pyrazole ring optionally further substituted by 1 or 2 phenyl groups,
- 30 (5) a thiazole ring optionally further substituted by 1 or 2 substituents selected from
 - (a) a phenyl group optionally substituted by 1 to 3 halogen
 - atoms (e.g., a fluorine atom), and
 - (b) a C₁₋₆ alkyl group (e.g., methyl),
- 35 (6) an oxazole ring optionally further substituted by 1 or 2

phenyl groups,

(7) a pyrrolidine ring optionally further substituted by 1 to 3 phenyl groups,

(8) a piperidine ring optionally further substituted by 1 to 3 substituents selected from

(a) a phenyl group, and

(b) a pyrimidinyl group, or

(9) a dibenzofuran ring.

[0099]

10 Ring B is even more preferably

(1) a benzene ring further substituted by 1 or 2 substituents selected from

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

(b) a C₂₋₆ alkenyl group (e.g., propen-2-yl),

15 (c) a tri-C₁₋₆ alkylsilyloxy group (e.g., triisopropylsilyloxy),

(d) a phenyl group optionally substituted by 1 to 3 substituents selected from

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

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

(e) a phenoxy group,

25 (f) a benzyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),

(g) a C₃₋₆ cycloalkyl group (e.g., cyclobutyl),

(h) a C₃₋₆ cycloalkoxy group (e.g., cyclohexyloxy),

(i) a thienyl group,

30 (j) an indazolyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), and

(k) a pyrrolidinyl group,

(2) a pyridine ring further substituted by one substituent selected from

35 (a) a phenyl group optionally substituted by 1 to 3 halogen

- atoms (e.g., a fluorine atom), and
- (b) a C₂₋₆ alkenyl group (e.g., propen-2-yl),
- (3) a pyrazole ring further substituted by one phenyl group,
- (4) a thiazole ring further substituted by one phenyl group
- 5 optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (5) a piperidine ring further substituted by one phenyl group,
- or
- (6) a dibenzofuran ring.

10 [0100]

Ring B is particularly preferably

- (1) a benzene ring further substituted by 1 or 2 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom), and
- 15 (b) a phenyl group optionally substituted by 1 to 3 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom, a chlorine atom), and
- (ii) a C₁₋₆ alkyl group (e.g., methyl),
- 20 (2) a pyridine ring further substituted by one phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (3) a thiazole ring further substituted by one phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a
- 25 fluorine atom), or
- (4) a piperidine ring further substituted by one phenyl group.

[0101]

As another embodiment, Ring B is preferably

- (1) an optionally further substituted C₆₋₁₄ aromatic hydrocarbon
- 30 ring (e.g., benzene, naphthalene),
- (2) an optionally further substituted 5- to 14-membered aromatic heterocycle (preferably a 5- to 6-membered monocyclic aromatic heterocycle (e.g., pyridine, pyrazole, thiazole, oxazole), a 8- to 14-membered fused polycyclic (preferably bi-
- 35 or tri-cyclic) aromatic heterocycle (e.g., benzofuran)), or

(3) an optionally further substituted 3- to 14-membered non-aromatic heterocycle (preferably a 3- to 8-membered monocyclic non-aromatic heterocycle (e.g., pyrrolidine, piperidine), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocycle (e.g., dibenzofuran)).

[0102]

In this embodiment, Ring B is more preferably

(1) a C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene, naphthalene) optionally further substituted by 1 to 3

substituents selected from

(a) a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom),

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

(c) a C₂₋₆ alkenyl group (e.g., vinyl, propen-2-yl),

(d) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),

(e) a tri-C₁₋₆ alkylsilyloxy group (e.g., triisopropylsilyloxy),

(f) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted

by 1 to 4 substituents selected from

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

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

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

(g) a C₆₋₁₄ aryloxy group (e.g., phenoxy),

(h) a C₇₋₁₆ aralkyl group (e.g., benzyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),

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

(j) a C₃₋₁₀ cycloalkenyl group (e.g., cyclopenten-1-yl, cyclohexen-1-yl),

(k) a C₃₋₁₀ cycloalkoxy group (e.g., cyclohexyloxy),

(l) a 5- to 14-membered aromatic heterocyclic group

(preferably a 5- to 6-membered monocyclic aromatic

- heterocyclic group (e.g., pyridyl, thienyl, pyrazolyl, pyrimidinyl), a 8- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) aromatic heterocyclic group (e.g., indazolyl)) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), and
- (m) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., pyrrolidinyl), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocyclic group (e.g., dihydroindolyl)),
- (2) a 5- to 14-membered aromatic heterocycle (preferably a 5- to 6-membered monocyclic aromatic heterocycle (e.g., pyridine, pyrazole, thiazole, oxazole), a 8- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) aromatic heterocycle (e.g., benzofuran)) optionally further substituted by 1 to 3 substituents selected from
- (a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (b) a C₁₋₆ alkyl group (e.g., methyl, isopropyl), and
- (c) a C₂₋₆ alkenyl group (e.g., propen-2-yl), or
- (3) a 3- to 14-membered non-aromatic heterocycle (preferably a 3- to 8-membered monocyclic non-aromatic heterocycle (e.g., pyrrolidine, piperidine), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocycle (e.g., dibenzofuran)) optionally further substituted by 1 to 3 substituents selected from
- (a) a C₆₋₁₄ aryl group (e.g., phenyl), and
- (b) a 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyrimidinyl)).

[0103]

In this embodiment, Ring B is further more preferably

(1) a benzene ring optionally further substituted by 1 to 3 substituents selected from

- (a) a halogen atom (e.g., a fluorine atom, a chlorine atom,

- a bromine atom, an iodine atom),
- (b) a C₁₋₆ alkyl group (e.g., methyl, isopropyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (c) a C₂₋₆ alkenyl group (e.g., vinyl, propen-2-yl),
- 5 (d) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),
- (e) a tri-C₁₋₆ alkylsilyloxy group (e.g., triisopropylsilyloxy),
- (f) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 4 substituents selected from
- 10 (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
- (ii) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
- 15 (iii) a C₁₋₆ alkoxy group (e.g., methoxy),
- (g) a C₆₋₁₄ aryloxy group (e.g., phenoxy),
- (h) a C₇₋₁₆ aralkyl group (e.g., benzyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
- (i) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),
- 20 (j) a C₃₋₁₀ cycloalkenyl group (e.g., cyclopenten-1-yl, cyclohexen-1-yl),
- (k) a C₃₋₁₀ cycloalkoxy group (e.g., cyclohexyloxy),
- (l) a 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic
- 25 heterocyclic group (e.g., pyridyl, thienyl, pyrazolyl, pyrimidinyl), a 8- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) aromatic heterocyclic group (e.g., indazolyl)) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), and
- 30 (m) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., pyrrolidinyl), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocyclic group (e.g., dihydroindolyl)),
- 35 (2) a naphthalene ring,

(3) a pyridine ring optionally further substituted by 1 to 3 substituents selected from

(a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),

5 (b) a C₁₋₆ alkyl group (e.g., isopropyl), and

(c) a C₂₋₆ alkenyl group (e.g., propen-2-yl),

(4) a pyrazole ring optionally further substituted by 1 or 2 C₆₋₁₄ aryl groups (e.g., phenyl),

(5) a thiazole ring optionally further substituted by 1 or 2
10 substituents selected from

(a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and

(b) a C₁₋₆ alkyl group (e.g., methyl),

(6) an oxazole ring optionally further substituted by 1 or 2
15 C₆₋₁₄ aryl groups (e.g., phenyl),

(7) a pyrrolidine ring optionally further substituted by 1 to 3 C₆₋₁₄ aryl groups (e.g., phenyl),

(8) a piperidine ring optionally further substituted by 1 to 3 substituents selected from

20 (a) a C₆₋₁₄ aryl group (e.g., phenyl), and

(b) a 5- to 14-membered aromatic heterocyclic group
(preferably a 5- to 6-membered monocyclic aromatic
heterocyclic group (e.g., pyrimidinyl)),

(9) a dibenzofuran ring, or

25 (10) a benzofuran ring optionally further substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., isopropyl).

[0104]

In this embodiment, Ring B is still more preferably

(1) a benzene ring optionally further substituted by 1 to 3
30 substituents selected from

(a) a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom),

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

35 (c) a C₂₋₆ alkenyl group (e.g., vinyl, propen-2-yl),

- (d) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),
(e) a tri-C₁₋₆ alkylsilyloxy group (e.g., triisopropylsilyloxy),
(f) a phenyl group optionally substituted by 1 to 4
5 substituents selected from
(i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
(ii) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine
10 atom), and
(iii) a C₁₋₆ alkoxy group (e.g., methoxy),
(g) a phenoxy group,
(h) a benzyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
15 (i) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),
(j) a C₃₋₆ cycloalkenyl group (e.g., cyclopenten-1-yl, cyclohexen-1-yl),
(k) a C₃₋₆ cycloalkoxy group (e.g., cyclohexyloxy),
(l) a pyridyl group,
20 (m) a thienyl group,
(n) a pyrimidinyl group,
(o) a pyrazolyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
(p) an indazolyl group optionally substituted by 1 to 3 C₁₋₆
25 alkyl groups (e.g., methyl),
(q) a pyrrolidinyl group, and
(r) a dihydroindolyl group,
(2) a naphthalene ring,
(3) a pyridine ring optionally further substituted by 1 to 3
30 substituents selected from
(a) a phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
(b) a C₁₋₆ alkyl group (e.g., isopropyl), and
(c) a C₂₋₆ alkenyl group (e.g., propen-2-yl),
35 (4) a pyrazole ring optionally further substituted by 1 or 2

phenyl groups,

(5) a thiazole ring optionally further substituted by 1 or 2 substituents selected from

(a) a phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and

(b) a C₁₋₆ alkyl group (e.g., methyl),

(6) an oxazole ring optionally further substituted by 1 or 2 phenyl groups,

(7) a pyrrolidine ring optionally further substituted by 1 to 3 phenyl groups,

(8) a piperidine ring optionally further substituted by 1 to 3 substituents selected from

(a) a phenyl group, and

(b) a pyrimidinyl group,

(9) a dibenzofuran ring, or

(10) a benzofuran ring optionally further substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., isopropyl).

[0105]

In this embodiment, Ring B is even more preferably

(1) a benzene ring further substituted by 1 or 2 substituents selected from

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

(b) a C₂₋₆ alkenyl group (e.g., propen-2-yl),

(c) a tri-C₁₋₆ alkylsilyloxy group (e.g., triisopropylsilyloxy),

(d) a phenyl group optionally substituted by 1 to 3 substituents selected from

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

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

(e) a phenoxy group,

(f) a benzyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),

- (g) a C₃₋₆ cycloalkyl group (e.g., cyclobutyl),
 - (h) a C₃₋₆ cycloalkoxy group (e.g., cyclohexyloxy),
 - (i) a thienyl group,
 - (j) an indazolyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), and
 - (k) a pyrrolidinyl group,
- (2) a pyridine ring further substituted by one substituent selected from
- (a) a phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
 - (b) a C₂₋₆ alkenyl group (e.g., propen-2-yl),
- (3) a pyrazole ring further substituted by one phenyl group,
- (4) a thiazole ring further substituted by one phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (5) a piperidine ring further substituted by one phenyl group,
- or
- (6) a dibenzofuran ring.

[0106]

As another embodiment, Ring B is preferably a ring further substituted by

- (a) an optionally substituted C₆₋₁₄ aryl group,
 - (b) an optionally substituted C₆₋₁₄ aryloxy group,
 - (c) an optionally substituted C₇₋₁₆ aralkyl group,
 - (d) an optionally substituted C₃₋₁₀ cycloalkyl group,
 - (e) an optionally substituted C₃₋₁₀ cycloalkenyl group,
 - (f) an optionally substituted C₃₋₁₀ cycloalkoxy group,
 - (g) an optionally substituted 5- to 14-membered aromatic heterocyclic group, or
 - (h) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group, and
- optionally having additional substituent(s).

[0107]

In this embodiment, Ring B is more preferably

(1) a C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene)

further substituted by

- (a) an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl),
- (b) an optionally substituted C₆₋₁₄ aryloxy group (e.g., phenoxy),
- 5 (c) an optionally substituted C₇₋₁₆ aralkyl group (e.g., benzyl),
- (d) an optionally substituted C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),
- (e) an optionally substituted C₃₋₁₀ cycloalkenyl group (e.g., cyclopenten-1-yl, cyclohexen-1-yl),
- 10 (f) an optionally substituted C₃₋₁₀ cycloalkoxy group (e.g., cyclohexyloxy),
- (g) an optionally substituted 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyridyl, thienyl, pyrazolyl, pyrimidinyl), a 8- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) aromatic heterocyclic group (e.g., indazolyl)), or
- 15 (h) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., pyrrolidinyl), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocyclic group (e.g., dihydroindolyl)), and
- 20 optionally having additional substituent(s),
- (2) a 5- to 14-membered aromatic heterocycle (preferably a 5- to 6-membered monocyclic aromatic heterocycle (e.g., pyridine, pyrazole, thiazole, oxazole)) further substituted by an optionally substituted C₆₋₁₄ aryl
- 30 group (e.g., phenyl), and optionally having additional substituent(s), or
- (3) a 3- to 14-membered non-aromatic heterocycle (preferably a 3- to 8-membered monocyclic non-aromatic heterocycle (e.g., pyrrolidine, piperidine)) further substituted by
- 35 (a) an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl),

or

(b) an optionally substituted 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyrimidinyl)).

5 [0108]

In this embodiment, Ring B is further more preferably (1) a C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene) further substituted by

- (a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted
10 by 1 to 4 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
 - (ii) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine
15 atom), and
 - (iii) a C₁₋₆ alkoxy group (e.g., methoxy),
- (b) a C₆₋₁₄ aryloxy group (e.g., phenoxy),
- (c) a C₇₋₁₆ aralkyl group (e.g., benzyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
- 20 (d) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),
- (e) a C₃₋₁₀ cycloalkenyl group (e.g., cyclopenten-1-yl, cyclohexen-1-yl),
- (f) a C₃₋₁₀ cycloalkoxy group (e.g., cyclohexyloxy),
- (g) a 5- to 14-membered aromatic heterocyclic group
- 25 (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyridyl, thienyl, pyrazolyl, pyrimidinyl), a 8- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) aromatic heterocyclic group (e.g., indazolyl)) optionally substituted by 1 to 3 C₁₋₆
- 30 alkyl groups (e.g., methyl), or
- (h) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., pyrrolidinyl), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic)
- 35 non-aromatic heterocyclic group (e.g., dihydroindolyl)),

and

optionally further substituted by 1 or 2 substituents selected from

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

5 (j) a C₁₋₆ alkyl group (e.g., methyl),

(2) a 5- to 14-membered aromatic heterocycle (preferably a 5- to 6-membered monocyclic aromatic heterocycle (e.g., pyridine, pyrazole, thiazole, oxazole))

further substituted by a C₆₋₁₄ aryl group (e.g., phenyl)

10 optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and

optionally further substituted by 1 or 2 C₁₋₆ alkyl groups (e.g., methyl), or

(3) a 3- to 14-membered non-aromatic heterocycle (preferably a
15 3- to 8-membered monocyclic non-aromatic heterocycle (e.g., pyrrolidine, piperidine)) further substituted by

(a) a C₆₋₁₄ aryl group (e.g., phenyl), or

(b) a 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic

20 heterocyclic group (e.g., pyrimidinyl)).

[0109]

In this embodiment, Ring B is still more preferably

(1) a benzene ring

further substituted by

25 (a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 4 substituents selected from

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

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

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

(b) a C₆₋₁₄ aryloxy group (e.g., phenoxy),

35 (c) a C₇₋₁₆ aralkyl group (e.g., benzyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),

- (d) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),
(e) a C₃₋₁₀ cycloalkenyl group (e.g., cyclopenten-1-yl, cyclohexen-1-yl),
(f) a C₃₋₁₀ cycloalkoxy group (e.g., cyclohexyloxy),
5 (g) a 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyridyl, thienyl, pyrazolyl, pyrimidinyl), a 8- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) aromatic heterocyclic group
10 (e.g., indazolyl)) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), or
(h) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., pyrrolidinyl), a 9- to 14-
15 membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocyclic group (e.g., dihydroindolyl)),
and
optionally further substituted by 1 or 2 substituents selected from
20 (i) a halogen atom (e.g., a fluorine atom), and
(j) a C₁₋₆ alkyl group (e.g., methyl),
(2) a pyridine ring further substituted by a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
25 (3) a pyrazole ring further substituted by a C₆₋₁₄ aryl group (e.g., phenyl),
(4) a thiazole ring
further substituted by a C₆₋₁₄ aryl group (e.g., phenyl)
optionally substituted by 1 to 3 halogen atoms (e.g., a
30 fluorine atom), and
optionally further substituted by one C₁₋₆ alkyl group (e.g., methyl),
(5) an oxazole ring further substituted by a C₆₋₁₄ aryl group (e.g., phenyl),
35 (6) a pyrrolidine ring further substituted by a C₆₋₁₄ aryl group

(e.g., phenyl), or

(7) a piperidine ring further substituted by

(a) a C₆₋₁₄ aryl group (e.g., phenyl), and

(b) a 5- to 14-membered aromatic heterocyclic group

5 (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyrimidinyl)).

[0110]

In this embodiment, Ring B is still more preferably

(1) a benzene ring

10 further substituted by

(a) a phenyl group optionally substituted by 1 to 4 substituents selected from

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

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

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

(b) a phenoxy group,

20 (c) a benzyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),

(d) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),

(e) a C₃₋₆ cycloalkenyl group (e.g., cyclopenten-1-yl, cyclohexen-1-yl),

25 (f) a C₃₋₆ cycloalkoxy group (e.g., cyclohexyloxy),

(g) a pyridyl group,

(h) a thienyl group,

(i) a pyrimidinyl group,

30 (j) a pyrazolyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),

(k) an indazolyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),

(l) a pyrrolidinyl group, or

(m) a dihydroindolyl group, and

35 optionally further substituted by 1 or 2 substituents selected

from

- (o) a halogen atom (e.g., a fluorine atom), and
- (p) a C₁₋₆ alkyl group (e.g., methyl),
- (2) a pyridine ring further substituted by a phenyl group
- 5 optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (3) a pyrazole ring further substituted by a phenyl group,
- (4) a thiazole ring
- further substituted by a phenyl group optionally substituted by
- 10 1 to 3 halogen atoms (e.g., a fluorine atom), and
- optionally further substituted by one C₁₋₆ alkyl group (e.g., methyl),
- (5) an oxazole ring further substituted by a phenyl group,
- (6) a pyrrolidine ring further substituted by a phenyl group,
- 15 or
- (7) a piperidine ring further substituted by
- (a) a phenyl group, or
- (b) a pyrimidinyl group.

[0111]

20 In this embodiment, Ring B is even more preferably

(1) a benzene ring

further substituted by

- (a) a phenyl group optionally substituted by 1 to 3 substituents selected from
- 25 (i) a halogen atom (e.g., a fluorine atom, a chlorine atom), and
- (ii) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- 30 (b) a phenoxy group,
- (c) a benzyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
- (d) a C₃₋₆ cycloalkyl group (e.g., cyclobutyl),
- (e) a C₃₋₆ cycloalkoxy group (e.g., cyclohexyloxy),
- 35 (f) a thienyl group,

- (g) an indazolyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), or
- (h) a pyrrolidinyl group, and optionally further substituted by one halogen atom (e.g., a fluorine atom),
- (2) a pyridine ring further substituted by one phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (3) a pyrazole ring further substituted by one phenyl group,
- 10 (4) a thiazole ring further substituted by one phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), or
- (5) a piperidine ring further substituted by one phenyl group.
- [0112]

- 15 In this embodiment, Ring B is particularly preferably
- (1) a benzene ring further substituted by one phenyl group optionally substituted by 1 to 3 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
- 20 and
- (ii) a C₁₋₆ alkyl group (e.g., methyl), and optionally further substituted by one halogen atom (e.g., a fluorine atom),
- (2) a pyridine ring further substituted by one phenyl group
- 25 optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (3) a thiazole ring further substituted by one phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), or
- 30 (4) a piperidine ring further substituted by one phenyl group.
- [0113]

In this embodiment, Ring B is most preferably a benzene ring further substituted by one phenyl group optionally substituted

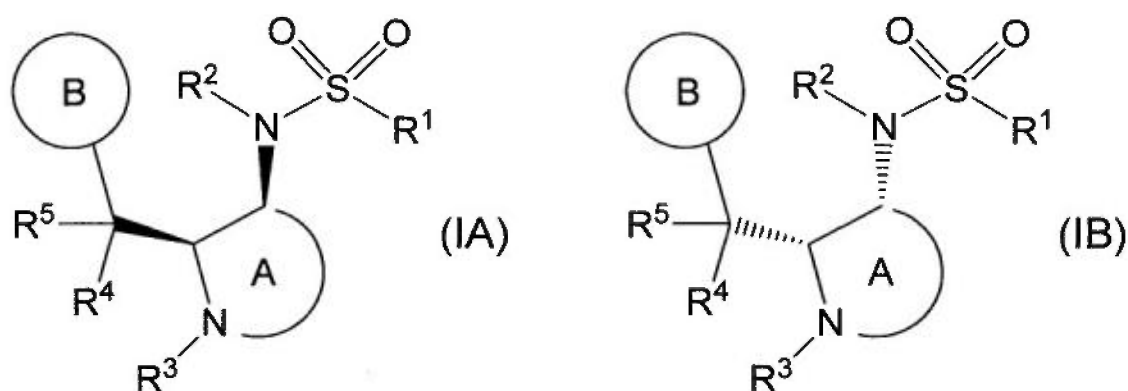
35 by 1 to 3 halogen atoms (e.g., a fluorine atoms), and

optionally further substituted by one halogen atom (e.g., a fluorine atoms).

[0114]

Regarding Ring A of compound (I), the configuration based
 5 on the carbon atom that $-NR^2SO_2R^1$ is bonded to and the carbon
 atom that $-CR^4R^5$ -Ring B is bonded to (for example, when Ring A
 is a pyrrolidine ring or a piperidine ring, the configuration
 based on 2- and 3-positions) is preferably cis-form. That is,
 compound (I) is preferably represented by the formula (IA) or
 10 (IB):

[0115]

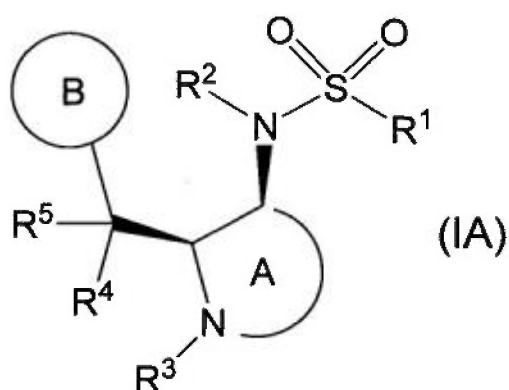


[0116]

wherein each symbol is as defined above,

15 more preferably represented by the formula (IA):

[0117]



[0118]

wherein each symbol is as defined above.

20 [0119]

Preferable examples of compound (I) include the following

compounds. These compounds are preferably represented by the above formula (IA) or (IB), more preferably represented by the formula (IA).

[Compound A-1]

5 Compound (I) wherein

R¹ is

(1) an optionally substituted C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl),

(2) an optionally substituted C₂₋₆ alkenyl group (e.g., vinyl,
10 allyl),

(3) an optionally substituted C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),

(4) an optionally substituted mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino), or

15 (5) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., oxetanyl));

R² is a hydrogen atom;

R³ is

20 (1) a hydrogen atom,

(2) an optionally substituted C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 1,2-

25 dimethylpropoxycarbonyl),

(3) an optionally substituted C₁₋₆ alkyl-carbonyl group (e.g., acetyl, propanoyl, 2-methylpropanoyl, butanoyl, 2-methylbutanoyl, 3-methylbutanoyl, pivaloyl),

(4) an optionally substituted mono- or di-C₁₋₆ alkyl-carbamoyl
30 group (e.g., dimethylcarbamoyl, ethylcarbamoyl, N-ethyl-N-methylcarbamoyl),

(5) an optionally substituted C₃₋₁₀ cycloalkyl-carbonyl group (the C₃₋₁₀ cycloalkyl in the C₃₋₁₀ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl,
35 cyclobutylcarbonyl, cyclopentylcarbonyl,

- bicyclo[1.1.1]pentylcarbonyl),
- (6) an optionally substituted C₃₋₁₀ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl),
- 5 (7) an optionally substituted 3- to 14-membered non-aromatic heterocyclylcarbonyl group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclylcarbonyl group (the non-aromatic heterocycle in the non-aromatic heterocyclylcarbonyl group may be a spiro ring, e.g., oxetanylcarbonyl,
- 10 azetidiny carbonyl, 5-azaspiro[2.3]hexylcarbonyl)),
- (8) an optionally substituted 3- to 14-membered non-aromatic heterocyclyloxycarbonyl group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclyloxycarbonyl group (e.g., oxetanyloxycarbonyl, tetrahydrofuryloxycarbonyl,
- 15 tetrahydropyranyloxycarbonyl)),
- (9) an optionally substituted C₆₋₁₄ aryloxy-carbonyl group (e.g., phenoxycarbonyl), or
- (10) an optionally substituted C₇₋₁₆ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl);
- 20 R⁴ and R⁵ are each independently a hydrogen atom or a halogen atom (e.g., a fluorine atom);
- Ring A is
- (1) an optionally further substituted pyrrolidine ring,
- (2) an optionally further substituted piperidine ring, or
- 25 (3) an optionally further substituted azetidine ring; and
- Ring B is
- (1) an optionally further substituted C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene, naphthalene),
- (2) an optionally further substituted 5- to 14-membered
- 30 aromatic heterocycle (preferably a 5- to 6-membered monocyclic aromatic heterocycle (e.g., pyridine, pyrazole, thiazole, oxazole)), or
- (3) an optionally further substituted 3- to 14-membered non-aromatic heterocycle (preferably a 3- to 8-membered monocyclic
- 35 non-aromatic heterocycle (e.g., pyrrolidine, piperidine), a 9-

to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocycle (e.g., dibenzofuran)).

[0120]

[Compound B-1]

5 Compound (I) wherein

R¹ is

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

- 10 (a) a halogen atom (e.g., a fluorine atom, a chlorine atom),
 (b) a cyano group,
 (c) a hydroxy group, and

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

(2) a C₂₋₆ alkenyl group (e.g., vinyl, allyl),

- 15 (3) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),

 (4) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),

or

(5) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic

- 20 heterocyclic group (e.g., oxetanyl));

R² is a hydrogen atom;

R³ is

(1) a hydrogen atom,

(2) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl,

- 25 ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 1,2-dimethylpropoxycarbonyl) optionally substituted by 1 to 3 substituents selected from

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

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

 (c) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl) optionally substituted by 1 to 3 substituents selected from

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

- 35 (ii) a C₁₋₆ alkyl group (e.g., methyl), and

- (d) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., oxetanyl, tetrahydrofuryl)),
- (3) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, propanoyl, 2-methylpropanoyl, butanoyl, 2-methylbutanoyl, 3-methylbutanoyl, pivaloyl) optionally substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom), and
- (b) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),
- 10 (4) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, ethylcarbamoyl, N-ethyl-N-methylcarbamoyl),
- (5) a C₃₋₁₀ cycloalkyl-carbonyl group (the C₃₋₁₀ cycloalkyl in the C₃₋₁₀ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl,
- 15 cyclopentylcarbonyl, bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom),
- (b) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- 20 (c) a hydroxy group,
- (d) a C₁₋₆ alkoxy group (e.g., methoxy), and
- (e) a cyano group,
- (6) a C₃₋₁₀ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl) optionally substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom), and
- (b) a C₁₋₆ alkyl group (e.g., methyl),
- (7) a 3- to 14-membered non-aromatic heterocyclylcarbonyl group
- 30 (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclylcarbonyl group (the non-aromatic heterocycle in the non-aromatic heterocyclylcarbonyl group may be a spiro ring, e.g., oxetanylcarbonyl, azetidiny carbonyl, 5-azaspiro[2.3]hexylcarbonyl)) optionally substituted by 1 to 3
- 35 substituents selected from

- (a) a halogen atom (e.g., a fluorine atom), and
(b) a C₁₋₆ alkyl group (e.g., methyl),
(8) a 3- to 14-membered non-aromatic heterocyclyloxycarbonyl group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclyloxycarbonyl group (e.g., oxetanyloxycarbonyl, tetrahydrofuryloxycarbonyl, tetrahydropyranyloxycarbonyl)),
5 heterocyclyloxycarbonyl group (e.g., oxetanyloxycarbonyl, tetrahydrofuryloxycarbonyl, tetrahydropyranyloxycarbonyl)),
(9) a C₆₋₁₄ aryloxy-carbonyl group (e.g., phenoxycarbonyl), or
(10) a C₇₋₁₆ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl);
- 10 R⁴ and R⁵ are each independently a hydrogen atom or a halogen atom (e.g., a fluorine atom);
Ring A is
(1) a pyrrolidine ring,
(2) a piperidine ring, or
15 (3) an azetidine ring; and
Ring B is
(1) a C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene, naphthalene) optionally further substituted by 1 to 3 substituents selected from
20 (a) a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom),
(b) a C₁₋₆ alkyl group (e.g., methyl, isopropyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
(c) a C₂₋₆ alkenyl group (e.g., vinyl, propen-2-yl),
25 (d) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),
(e) a tri-C₁₋₆ alkylsilyloxy group (e.g., triisopropylsilyloxy),
(f) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 4 substituents selected from
30 (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
(ii) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
35 (iii) a C₁₋₆ alkoxy group (e.g., methoxy),

- (g) a C₆₋₁₄ aryloxy group (e.g., phenoxy),
(h) a C₇₋₁₆ aralkyl group (e.g., benzyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
(i) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),
5 (j) a C₃₋₁₀ cycloalkenyl group (e.g., cyclopenten-1-yl, cyclohexen-1-yl),
(k) a C₃₋₁₀ cycloalkoxy group (e.g., cyclohexyloxy),
(l) a 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic
10 heterocyclic group (e.g., pyridyl, thienyl, pyrazolyl, pyrimidinyl), a 8- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) aromatic heterocyclic group (e.g., indazolyl)) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), and
15 (m) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., pyrrolidinyl), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocyclic group (e.g., dihydroindolyl)),
20 (2) a 5- to 14-membered aromatic heterocycle (preferably a 5- to 6-membered monocyclic aromatic heterocycle (e.g., pyridine, pyrazole, thiazole, oxazole)) optionally further substituted by 1 to 3 substituents selected from
(a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted
25 by 1 to 3 halogen atoms (e.g., a fluorine atom),
(b) a C₁₋₆ alkyl group (e.g., methyl, isopropyl), and
(c) a C₂₋₆ alkenyl group (e.g., propen-2-yl), or
(3) a 3- to 14-membered non-aromatic heterocycle (preferably a 3- to 8-membered monocyclic non-aromatic heterocycle (e.g.,
30 pyrrolidine, piperidine), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocycle (e.g., dibenzofuran)) optionally further substituted by 1 to 3 substituents selected from
(a) a C₆₋₁₄ aryl group (e.g., phenyl), and
35 (b) a 5- to 14-membered aromatic heterocyclic group

(preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyrimidinyl)).

[0121]

[Compound C-1]

5 The above-mentioned Compound B-1 wherein
Ring B is

(1) a benzene ring optionally further substituted by 1 to 3
substituents selected from

- (a) a halogen atom (e.g., a fluorine atom, a chlorine atom,
10 a bromine atom, an iodine atom),
- (b) a C₁₋₆ alkyl group (e.g., methyl, isopropyl) optionally
substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (c) a C₂₋₆ alkenyl group (e.g., vinyl, propen-2-yl),
- (d) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),
- 15 (e) a tri-C₁₋₆ alkylsilyloxy group (e.g.,
triisopropylsilyloxy),
- (f) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted
by 1 to 4 substituents selected from
 - (i) a halogen atom (e.g., a fluorine atom, a chlorine
20 atom),
 - (ii) a C₁₋₆ alkyl group (e.g., methyl) optionally
substituted by 1 to 3 halogen atoms (e.g., a fluorine
atom), and
 - (iii) a C₁₋₆ alkoxy group (e.g., methoxy),
- 25 (g) a C₆₋₁₄ aryloxy group (e.g., phenoxy),
- (h) a C₇₋₁₆ aralkyl group (e.g., benzyl) optionally
substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
- (i) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),
- (j) a C₃₋₁₀ cycloalkenyl group (e.g., cyclopenten-1-yl,
30 cyclohexen-1-yl),
- (k) a C₃₋₁₀ cycloalkoxy group (e.g., cyclohexyloxy),
- (l) a 5- to 14-membered aromatic heterocyclic group
(preferably a 5- to 6-membered monocyclic aromatic
heterocyclic group (e.g., pyridyl, thienyl, pyrazolyl,
35 pyrimidinyl), a 8- to 14-membered fused polycyclic

- (preferably bi- or tri-cyclic) aromatic heterocyclic group (e.g., indazolyl)) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), and
- (m) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., pyrrolidinyl), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocyclic group (e.g., dihydroindolyl)),
- (2) a naphthalene ring,
- 10 (3) a pyridine ring optionally further substituted by 1 to 3 substituents selected from
- (a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (b) a C₁₋₆ alkyl group (e.g., isopropyl), and
- 15 (c) a C₂₋₆ alkenyl group (e.g., propen-2-yl),
- (4) a pyrazole ring optionally further substituted by 1 or 2 C₆₋₁₄ aryl groups (e.g., phenyl),
- (5) a thiazole ring optionally further substituted by 1 or 2 substituents selected from
- 20 (a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
- (b) a C₁₋₆ alkyl group (e.g., methyl),
- (6) an oxazole ring optionally further substituted by 1 or 2 C₆₋₁₄ aryl groups (e.g., phenyl),
- 25 (7) a pyrrolidine ring optionally further substituted by 1 to 3 C₆₋₁₄ aryl groups (e.g., phenyl),
- (8) a piperidine ring optionally further substituted by 1 to 3 substituents selected from
- (a) a C₆₋₁₄ aryl group (e.g., phenyl), and
- 30 (b) a 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyrimidinyl)), or
- (9) a dibenzofuran ring.

[0122]

35 [Compound D-1]

Compound (I) wherein

R¹ is

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

5 selected from

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

(b) a cyano group,

(c) a hydroxy group, and

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

10 (2) a C₂₋₆ alkenyl group (e.g., vinyl, allyl),

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

(4) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),

or

(5) an oxetanyl group;

15 R² is a hydrogen atom;

R³ is

(1) a hydrogen atom,

(2) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl,

20 butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 1,2-dimethylpropoxycarbonyl) optionally substituted by 1 to 3 substituents selected from

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

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

25 (c) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl) optionally substituted by 1 to 3 substituents selected from

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

(ii) a C₁₋₆ alkyl group (e.g., methyl),

30 (d) an oxetanyl group, and

(e) a tetrahydrofuryl group,

(3) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, propanoyl, 2-methylpropanoyl, butanoyl, 2-methylbutanoyl, 3-methylbutanoyl, pivaloyl) optionally substituted by 1 to 3 substituents

35 selected from

- (a) a halogen atom (e.g., a fluorine atom), and
(b) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl),
(4) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, ethylcarbamoyl, N-ethyl-N-methylcarbamoyl),
5 (5) a C₃₋₆ cycloalkyl-carbonyl group (the C₃₋₆ cycloalkyl in the C₃₋₆ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3 substituents selected from
- 10 (a) a halogen atom (e.g., a fluorine atom),
(b) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
(c) a hydroxy group,
(d) a C₁₋₆ alkoxy group (e.g., methoxy), and
15 (e) a cyano group,
(6) a C₃₋₆ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl) optionally substituted by 1 to 3 substituents selected from
- 20 (a) a halogen atom (e.g., a fluorine atom), and
(b) a C₁₋₆ alkyl group (e.g., methyl),
(7) an oxetanylcabonyl group,
(8) an azetidinylcabonyl group optionally substituted by 1 to 3 substituents selected from
- 25 (a) a halogen atom (e.g., a fluorine atom), and
(b) a C₁₋₆ alkyl group (e.g., methyl),
(9) a 5-azaspiro[2.3]hexylcarbonyl group,
(10) an oxetanyloxycarbonyl group,
(11) a tetrahydrofuryloxycarbonyl group,
30 (12) a tetrahydropyranyloxycarbonyl group,
(13) a phenoxy carbonyl group, or
(14) a benzyloxycarbonyl group;
R⁴ and R⁵ are each independently a hydrogen atom or a halogen atom (e.g., a fluorine atom);

35 Ring A is

- (1) a pyrrolidine ring,
- (2) a piperidine ring, or
- (3) an azetidine ring; and

Ring B is

- 5 (1) a benzene ring optionally further substituted by 1 to 3 substituents selected from

- (a) a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom),
- (b) a C₁₋₆ alkyl group (e.g., methyl, isopropyl) optionally
10 substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (c) a C₂₋₆ alkenyl group (e.g., vinyl, propen-2-yl),
- (d) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),
- (e) a tri-C₁₋₆ alkylsilyloxy group (e.g., triisopropylsilyloxy),
- 15 (f) a phenyl group optionally substituted by 1 to 4 substituents selected from
 - (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
 - (ii) a C₁₋₆ alkyl group (e.g., methyl) optionally
20 substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
 - (iii) a C₁₋₆ alkoxy group (e.g., methoxy),
- (g) a phenoxy group,
- (h) a benzyl group optionally substituted by 1 to 3 C₁₋₆
25 alkyl groups (e.g., methyl),
- (i) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),
- (j) a C₃₋₆ cycloalkenyl group (e.g., cyclopenten-1-yl, cyclohexen-1-yl),
- (k) a C₃₋₆ cycloalkoxy group (e.g., cyclohexyloxy),
- 30 (l) a pyridyl group,
- (m) a thienyl group,
- (n) a pyrimidinyl group,
- (o) a pyrazolyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
- 35 (p) an indazolyl group optionally substituted by 1 to 3 C₁₋₆

- alkyl groups (e.g., methyl),
(q) a pyrrolidinyl group, and
(r) a dihydroindolyl group,
(2) a naphthalene ring,
5 (3) a pyridine ring optionally further substituted by 1 to 3
substituents selected from
(a) a phenyl group optionally substituted by 1 to 3 halogen
atoms (e.g., a fluorine atom),
(b) a C₁₋₆ alkyl group (e.g., isopropyl), and
10 (c) a C₂₋₆ alkenyl group (e.g., propen-2-yl),
(4) a pyrazole ring optionally further substituted by 1 or 2
phenyl groups,
(5) a thiazole ring optionally further substituted by 1 or 2
substituents selected from
15 (a) a phenyl group optionally substituted by 1 to 3 halogen
atoms (e.g., a fluorine atom), and
(b) a C₁₋₆ alkyl group (e.g., methyl),
(6) an oxazole ring optionally further substituted by 1 or 2
phenyl groups,
20 (7) a pyrrolidine ring optionally further substituted by 1 to 3
phenyl groups,
(8) a piperidine ring optionally further substituted by 1 to 3
substituents selected from
(a) a phenyl group, and
25 (b) a pyrimidinyl group, or
(9) a dibenzofuran ring.

[0123]

[Compound E-1]

Compound (I) wherein

30 R¹ is

- (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl) optionally
substituted by 1 to 3 substituents selected from
(a) a halogen atom (e.g., a fluorine atom, a chlorine atom),
and
35 (b) a C₁₋₆ alkoxy group (e.g., methoxy),

- (2) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl), or
 - (3) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino);
- R² is a hydrogen atom;
- R³ is

- 5 (1) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl),
- (2) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, 2-methylpropanoyl, pivaloyl),
- (3) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g.,
- 10 dimethylcarbamoyl, ethylcarbamoyl),
- (4) a C₃₋₆ cycloalkyl-carbonyl group (the C₃₋₆ cycloalkyl in the C₃₋₆ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3
- 15 substituents selected from
 - (a) a halogen atom (e.g., a fluorine atom),
 - (b) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
 - (c) a hydroxy group,
 - 20 (d) a C₁₋₆ alkoxy group (e.g., methoxy), and
 - (e) a cyano group,
- (5) a C₃₋₆ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl),
- (6) a phenoxycarbonyl group,
- 25 (7) an oxetanylcabonyl group,
- (8) an azetidinylcabonyl group optionally substituted by 1 to 3 substituents selected from
 - (a) a halogen atom (e.g., a fluorine atom), and
 - (b) a C₁₋₆ alkyl group (e.g., methyl), or
- 30 (9) a 5-azaspiro[2.3]hexylcarbonyl group;

R⁴ and R⁵ are both hydrogen atoms;

Ring A is

- (1) a pyrrolidine ring, or
- (2) a piperidine ring; and

35 Ring B is

(1) a benzene ring further substituted by 1 or 2 substituents selected from

- (a) a halogen atom (e.g., a fluorine atom),
- (b) a C₂₋₆ alkenyl group (e.g., propen-2-yl),
- 5 (c) a tri-C₁₋₆ alkylsilyloxy group (e.g., triisopropylsilyloxy),
- (d) a phenyl group optionally substituted by 1 to 3 substituents selected from
 - (i) a halogen atom (e.g., a fluorine atom), and
 - 10 (ii) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (e) a phenoxy group,
- (f) a benzyl group optionally substituted by 1 to 3 C₁₋₆
- 15 alkyl groups (e.g., methyl),
- (g) a C₃₋₆ cycloalkyl group (e.g., cyclobutyl),
- (h) a C₃₋₆ cycloalkoxy group (e.g., cyclohexyloxy),
- (i) a thienyl group,
- (j) an indazolyl group optionally substituted by 1 to 3 C₁₋₆
- 20 alkyl groups (e.g., methyl), and
- (k) a pyrrolidinyl group,

(2) a pyridine ring further substituted by one substituent selected from

- (a) a phenyl group optionally substituted by 1 to 3 halogen
- 25 atoms (e.g., a fluorine atom), and
- (b) a C₂₋₆ alkenyl group (e.g., propen-2-yl),

(3) a pyrazole ring further substituted by one phenyl group,

(4) a thiazole ring further substituted by one phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a

30 fluorine atom),

(5) a piperidine ring further substituted by one phenyl group, or

(6) a dibenzofuran ring.

[0124]

35 [Compound F-1]

Compound (I) wherein

R¹ is

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

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

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

(2) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl);

R² is a hydrogen atom;

R³ is

10 (1) a C₁₋₆ alkoxy-carbonyl group (e.g., ethoxycarbonyl, isopropoxycarbonyl),

(2) a C₁₋₆ alkyl-carbonyl group (e.g., 2-methylpropanoyl, pivaloyl),

(3) a C₃₋₆ cycloalkyl-carbonyl group (the C₃₋₆ cycloalkyl in the
15 C₃₋₆ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3 substituents selected from

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

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

(c) a hydroxy group,

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

(e) a cyano group,

25 (4) an oxetanylcabonyl group,

(5) an azetidinylcabonyl group optionally substituted by 1 to 3 substituents selected from

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

(b) a C₁₋₆ alkyl group (e.g., methyl), or

30 (6) a 5-azaspiro[2.3]hexylcarbonyl group;

R⁴ and R⁵ are both hydrogen atoms;

Ring A is

(1) a pyrrolidine ring, or

(2) a piperidine ring; and

35 Ring B is

(1) a benzene ring further substituted by 1 or 2 substituents selected from

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

(b) a phenyl group optionally substituted by 1 to 3

5 substituents selected from

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

(ii) a C₁₋₆ alkyl group (e.g., methyl),

(2) a pyridine ring further substituted by one phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a
10 fluorine atom),

(3) a thiazole ring further substituted by one phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), or

(4) a piperidine ring further substituted by one phenyl group.

15 [0125]

[Compound A-2]

Compound (I) wherein

R¹ is

(1) an optionally substituted C₁₋₆ alkyl group (e.g., methyl,
20 ethyl, propyl, isopropyl, butyl, isobutyl),

(2) an optionally substituted C₂₋₆ alkenyl group (e.g., vinyl, allyl),

(3) an optionally substituted C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),

25 (4) an optionally substituted mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino), or

(5) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., oxetanyl));

30 R² is a hydrogen atom;

R³ is

(1) a hydrogen atom,

(2) an optionally substituted C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl,

35 isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-

butoxycarbonyl, tert-butoxycarbonyl, 1,2-dimethylpropoxycarbonyl),

(3) an optionally substituted C₁₋₆ alkyl-carbonyl group (e.g., acetyl, propanoyl, 2-methylpropanoyl, butanoyl, 2-

5 methylbutanoyl, 3-methylbutanoyl, pivaloyl),

(4) an optionally substituted mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, ethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N-isopropyl-N-methylcarbamoyl),

(5) an optionally substituted N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group (e.g., N-methoxy-N-methylcarbamoyl),

(6) an optionally substituted C₃₋₁₀ cycloalkyl-carbonyl group (the C₃₋₁₀ cycloalkyl in the C₃₋₁₀ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl,

15 bicyclo[1.1.1]pentylcarbonyl),

(7) an optionally substituted C₃₋₁₀ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl),

(8) an optionally substituted 3- to 14-membered non-aromatic heterocyclylcarbonyl group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclylcarbonyl group (the non-aromatic heterocycle in the non-aromatic heterocyclylcarbonyl group may be a spiro ring, e.g., oxetanylcarbonyl, azetidiny carbonyl, 5-azaspiro[2.3]hexylcarbonyl)),

25 (9) an optionally substituted 3- to 14-membered non-aromatic heterocyclyloxycarbonyl group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclyloxycarbonyl group (e.g., oxetanyloxycarbonyl, tetrahydrofuryloxycarbonyl, tetrahydropyranyloxycarbonyl)),

30 (10) an optionally substituted C₆₋₁₄ aryloxy-carbonyl group (e.g., phenoxycarbonyl), or

(11) an optionally substituted C₇₋₁₆ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl);

R⁴ and R⁵ are each independently a hydrogen atom or a halogen atom (e.g., a fluorine atom);

Ring A is

- (1) an optionally further substituted pyrrolidine ring,
- (2) an optionally further substituted piperidine ring, or
- (3) an optionally further substituted azetidine ring; and

5 Ring B is

- (1) an optionally further substituted C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene, naphthalene),
- (2) an optionally further substituted 5- to 14-membered aromatic heterocycle (preferably a 5- to 6-membered monocyclic aromatic heterocycle (e.g., pyridine, pyrazole, thiazole, oxazole)), or
- (3) an optionally further substituted 3- to 14-membered non-aromatic heterocycle (preferably a 3- to 8-membered monocyclic non-aromatic heterocycle (e.g., pyrrolidine, piperidine), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocycle (e.g., dibenzofuran)).

[0126]

[Compound B-2]

Compound (I) wherein

20 R¹ is

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

- (a) a halogen atom (e.g., a fluorine atom, a chlorine atom),
- 25 (b) a cyano group,
- (c) a hydroxy group, and

- (d) a C₁₋₆ alkoxy group (e.g., methoxy),
- (2) a C₂₋₆ alkenyl group (e.g., vinyl, allyl),
- (3) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),
- 30 (4) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),
- or

- (5) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., oxetanyl));

35 R² is a hydrogen atom;

R³ is

- (1) a hydrogen atom,
- (2) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 1,2-dimethylpropoxycarbonyl) optionally substituted by 1 to 3 substituents selected from
 - (a) a halogen atom (e.g., a fluorine atom),
 - (b) a C₁₋₆ alkoxy group (e.g., methoxy),
 - 10 (c) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl) optionally substituted by 1 to 3 substituents selected from
 - (i) a halogen atom (e.g., a fluorine atom), and
 - (ii) a C₁₋₆ alkyl group (e.g., methyl), and
 - 15 (d) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., oxetanyl, tetrahydrofuryl)),
- (3) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, propanoyl, 2-methylpropanoyl, butanoyl, 2-methylbutanoyl, 3-methylbutanoyl, pivaloyl) optionally substituted by 1 to 3 substituents selected from
 - (a) a halogen atom (e.g., a fluorine atom),
 - (b) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),
 - (c) a hydroxy group, and
 - 25 (d) a C₁₋₆ alkoxy group (e.g., methoxy),
- (4) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, ethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N-isopropyl-N-methylcarbamoyl),
- (5) a N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group (e.g., N-methoxy-N-methylcarbamoyl),
- 30 (6) a C₃₋₁₀ cycloalkyl-carbonyl group (the C₃₋₁₀ cycloalkyl in the C₃₋₁₀ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3 substituents selected from

- (a) a halogen atom (e.g., a fluorine atom),
(b) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted
by 1 to 3 halogen atoms (e.g., a fluorine atom),
(c) a hydroxy group,
5 (d) a C₁₋₆ alkoxy group (e.g., methoxy), and
(e) a cyano group,
(7) a C₃₋₁₀ cycloalkoxy-carbonyl group (e.g.,
cyclopropoxycarbonyl, cyclobutyloxycarbonyl,
cyclopentyloxycarbonyl, cyclohexyloxycarbonyl) optionally
10 substituted by 1 to 3 substituents selected from
(a) a halogen atom (e.g., a fluorine atom), and
(b) a C₁₋₆ alkyl group (e.g., methyl),
(8) a 3- to 14-membered non-aromatic heterocyclylcarbonyl group
(preferably a 3- to 8-membered monocyclic non-aromatic
15 heterocyclylcarbonyl group (the non-aromatic heterocycle in the
non-aromatic heterocyclylcarbonyl group may be a spiro ring,
e.g., oxetanylcarbonyl, azetidiny carbonyl, 5-
azaspiro[2.3]hexylcarbonyl)) optionally substituted by 1 to 3
substituents selected from
20 (a) a halogen atom (e.g., a fluorine atom), and
(b) a C₁₋₆ alkyl group (e.g., methyl),
(9) a 3- to 14-membered non-aromatic heterocyclyloxycarbonyl
group (preferably a 3- to 8-membered monocyclic non-aromatic
heterocyclyloxycarbonyl group (e.g., oxetanyloxycarbonyl,
25 tetrahydrofuryloxycarbonyl, tetrahydropyranyloxycarbonyl)),
(10) a C₆₋₁₄ aryloxy-carbonyl group (e.g., phenoxycarbonyl), or
(11) a C₇₋₁₆ aralkyloxy-carbonyl group (e.g.,
benzyloxycarbonyl);

R⁴ and R⁵ are each independently a hydrogen atom or a halogen
30 atom (e.g., a fluorine atom);

Ring A is

- (1) a pyrrolidine ring,
(2) a piperidine ring, or
(3) an azetidine ring; and

35 Ring B is

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

- (a) a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom),
- (b) a C₁₋₆ alkyl group (e.g., methyl, isopropyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (c) a C₂₋₆ alkenyl group (e.g., vinyl, propen-2-yl),
- (d) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),
- (e) a tri-C₁₋₆ alkylsilyloxy group (e.g., triisopropylsilyloxy),
- (f) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 4 substituents selected from
 - (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
 - (ii) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
 - (iii) a C₁₋₆ alkoxy group (e.g., methoxy),
- (g) a C₆₋₁₄ aryloxy group (e.g., phenoxy),
- (h) a C₇₋₁₆ aralkyl group (e.g., benzyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
- (i) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),
- (j) a C₃₋₁₀ cycloalkenyl group (e.g., cyclopenten-1-yl, cyclohexen-1-yl),
- (k) a C₃₋₁₀ cycloalkoxy group (e.g., cyclohexyloxy),
- (l) a 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyridyl, thienyl, pyrazolyl, pyrimidinyl), a 8- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) aromatic heterocyclic group (e.g., indazolyl)) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), and
- (m) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic

- heterocyclic group (e.g., pyrrolidinyl), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocyclic group (e.g., dihydroindolyl)),
- (2) a 5- to 14-membered aromatic heterocycle (preferably a 5- to 6-membered monocyclic aromatic heterocycle (e.g., pyridine, pyrazole, thiazole, oxazole)) optionally further substituted by 1 to 3 substituents selected from
- (a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
 - (b) a C₁₋₆ alkyl group (e.g., methyl, isopropyl), and
 - (c) a C₂₋₆ alkenyl group (e.g., propen-2-yl), or
- (3) a 3- to 14-membered non-aromatic heterocycle (preferably a 3- to 8-membered monocyclic non-aromatic heterocycle (e.g., pyrrolidine, piperidine), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocycle (e.g., dibenzofuran)) optionally further substituted by 1 to 3 substituents selected from
- (a) a C₆₋₁₄ aryl group (e.g., phenyl), and
 - (b) a 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyrimidinyl)).

[0127]

[Compound C-2]

The above-mentioned Compound B-2 wherein
Ring B is

- (1) a benzene ring optionally further substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom),
 - (b) a C₁₋₆ alkyl group (e.g., methyl, isopropyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
 - (c) a C₂₋₆ alkenyl group (e.g., vinyl, propen-2-yl),
 - (d) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),
 - (e) a tri-C₁₋₆ alkylsilyloxy group (e.g., triisopropylsilyloxy),

- (f) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 4 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
 - 5 (ii) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
 - (iii) a C₁₋₆ alkoxy group (e.g., methoxy),
- (g) a C₆₋₁₄ aryloxy group (e.g., phenoxy),
- 10 (h) a C₇₋₁₆ aralkyl group (e.g., benzyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
- (i) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),
 - (j) a C₃₋₁₀ cycloalkenyl group (e.g., cyclopenten-1-yl, cyclohexen-1-yl),
- 15 (k) a C₃₋₁₀ cycloalkoxy group (e.g., cyclohexyloxy),
- (l) a 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyridyl, thienyl, pyrazolyl, pyrimidinyl), a 8- to 14-membered fused polycyclic
- 20 (preferably bi- or tri-cyclic) aromatic heterocyclic group (e.g., indazolyl)) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), and
- (m) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic
- 25 heterocyclic group (e.g., pyrrolidinyl), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocyclic group (e.g., dihydroindolyl)),
- (2) a naphthalene ring,
- (3) a pyridine ring optionally further substituted by 1 to 3
- 30 substituents selected from
- (a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
 - (b) a C₁₋₆ alkyl group (e.g., isopropyl), and
 - (c) a C₂₋₆ alkenyl group (e.g., propen-2-yl),
- 35 (4) a pyrazole ring optionally further substituted by 1 or 2

C₆₋₁₄ aryl groups (e.g., phenyl),

(5) a thiazole ring optionally further substituted by 1 or 2 substituents selected from

(a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted
5 by 1 to 3 halogen atoms (e.g., a fluorine atom), and

(b) a C₁₋₆ alkyl group (e.g., methyl),

(6) an oxazole ring optionally further substituted by 1 or 2 C₆₋₁₄ aryl groups (e.g., phenyl),

(7) a pyrrolidine ring optionally further substituted by 1 to 3
10 C₆₋₁₄ aryl groups (e.g., phenyl),

(8) a piperidine ring optionally further substituted by 1 to 3 substituents selected from

(a) a C₆₋₁₄ aryl group (e.g., phenyl), and

(b) a 5- to 14-membered aromatic heterocyclic group
15 (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyrimidinyl)), or

(9) a dibenzofuran ring.

[0128]

[Compound D-2]

20 Compound (I) wherein

R¹ is

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

25 (a) a halogen atom (e.g., a fluorine atom, a chlorine atom),

(b) a cyano group,

(c) a hydroxy group, and

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

(2) a C₂₋₆ alkenyl group (e.g., vinyl, allyl),

30 (3) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl),

(4) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),

or

(5) an oxetanyl group;

R² is a hydrogen atom;

35 R³ is

- (1) a hydrogen atom,
- (2) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 1,2-dimethylpropoxycarbonyl) optionally substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom),
- (b) a C₁₋₆ alkoxy group (e.g., methoxy),
- (c) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl) optionally substituted by 1 to 3 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom), and
- (ii) a C₁₋₆ alkyl group (e.g., methyl),
- (d) an oxetanyl group, and
- (e) a tetrahydrofuryl group,
- (3) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, propanoyl, 2-methylpropanoyl, butanoyl, 2-methylbutanoyl, 3-methylbutanoyl, pivaloyl) optionally substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom),
- (b) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl),
- (c) a hydroxy group, and
- (d) a C₁₋₆ alkoxy group (e.g., methoxy),
- (4) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, ethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N-isopropyl-N-methylcarbamoyl),
- (5) a N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group (e.g., N-methoxy-N-methylcarbamoyl),
- (6) a C₃₋₆ cycloalkyl-carbonyl group (the C₃₋₆ cycloalkyl in the C₃₋₆ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom),
- (b) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted

- by 1 to 3 halogen atoms (e.g., a fluorine atom),
(c) a hydroxy group,
(d) a C₁₋₆ alkoxy group (e.g., methoxy), and
(e) a cyano group,
- 5 (7) a C₃₋₆ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl) optionally substituted by 1 to 3 substituents selected from
(a) a halogen atom (e.g., a fluorine atom), and
10 (b) a C₁₋₆ alkyl group (e.g., methyl),
(8) an oxetanylcabonyl group,
(9) an azetidinylcabonyl group optionally substituted by 1 to 3 substituents selected from
(a) a halogen atom (e.g., a fluorine atom), and
15 (b) a C₁₋₆ alkyl group (e.g., methyl),
(10) a 5-azaspiro[2.3]hexylcarbonyl group,
(11) an oxetanyloxycarbonyl group,
(12) a tetrahydrofuryloxycarbonyl group,
(13) a tetrahydropyranyloxycarbonyl group,
20 (14) a phenoxycarbonyl group, or
(15) a benzyloxycarbonyl group;
R⁴ and R⁵ are each independently a hydrogen atom or a halogen atom (e.g., a fluorine atom);
Ring A is
25 (1) a pyrrolidine ring,
(2) a piperidine ring, or
(3) an azetidine ring; and
Ring B is
(1) a benzene ring optionally further substituted by 1 to 3
30 substituents selected from
(a) a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom),
(b) a C₁₋₆ alkyl group (e.g., methyl, isopropyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
35 (c) a C₂₋₆ alkenyl group (e.g., vinyl, propen-2-yl),

- (d) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),
(e) a tri-C₁₋₆ alkylsilyloxy group (e.g., triisopropylsilyloxy),
(f) a phenyl group optionally substituted by 1 to 4
5 substituents selected from
(i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
(ii) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine
10 atom), and
(iii) a C₁₋₆ alkoxy group (e.g., methoxy),
(g) a phenoxy group,
(h) a benzyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
15 (i) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),
(j) a C₃₋₆ cycloalkenyl group (e.g., cyclopenten-1-yl, cyclohexen-1-yl),
(k) a C₃₋₆ cycloalkoxy group (e.g., cyclohexyloxy),
(l) a pyridyl group,
20 (m) a thienyl group,
(n) a pyrimidinyl group,
(o) a pyrazolyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
(p) an indazolyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
25 (q) a pyrrolidinyl group, and
(r) a dihydroindolyl group,
(2) a naphthalene ring,
(3) a pyridine ring optionally further substituted by 1 to 3
30 substituents selected from
(a) a phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
(b) a C₁₋₆ alkyl group (e.g., isopropyl), and
(c) a C₂₋₆ alkenyl group (e.g., propen-2-yl),
35 (4) a pyrazole ring optionally further substituted by 1 or 2

phenyl groups,

(5) a thiazole ring optionally further substituted by 1 or 2 substituents selected from

(a) a phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and

(b) a C₁₋₆ alkyl group (e.g., methyl),

(6) an oxazole ring optionally further substituted by 1 or 2 phenyl groups,

(7) a pyrrolidine ring optionally further substituted by 1 to 3 phenyl groups,

(8) a piperidine ring optionally further substituted by 1 to 3 substituents selected from

(a) a phenyl group, and

(b) a pyrimidinyl group, or

(9) a dibenzofuran ring.

[0129]

[Compound E-2]

Compound (I) wherein

R¹ is

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

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

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

(2) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl), or

(3) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino);

R² is a hydrogen atom;

R³ is

(1) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl),

(2) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, 2-methylpropanoyl, pivaloyl) optionally substituted by 1 to 3 hydroxy groups,

(3) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, ethylcarbamoyl),

(4) a C₃₋₆ cycloalkyl-carbonyl group (the C₃₋₆ cycloalkyl in the

C₃₋₆ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3 substituents selected from

- 5 (a) a halogen atom (e.g., a fluorine atom),
 - (b) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
 - (c) a hydroxy group,
 - (d) a C₁₋₆ alkoxy group (e.g., methoxy), and
 - 10 (e) a cyano group,
 - (5) a C₃₋₆ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl),
 - (6) a phenoxycarbonyl group,
 - (7) an oxetanylcabonyl group,
 - 15 (8) an azetidinylcabonyl group optionally substituted by 1 to 3 substituents selected from
 - (a) a halogen atom (e.g., a fluorine atom), and
 - (b) a C₁₋₆ alkyl group (e.g., methyl), or
 - (9) a 5-azaspiro[2.3]hexylcarbonyl group;
 - 20 R⁴ and R⁵ are both hydrogen atoms;
- Ring A is
- (1) a pyrrolidine ring, or
 - (2) a piperidine ring; and
- Ring B is
- 25 (1) a benzene ring further substituted by 1 or 2 substituents selected from
 - (a) a halogen atom (e.g., a fluorine atom),
 - (b) a C₂₋₆ alkenyl group (e.g., propen-2-yl),
 - (c) a tri-C₁₋₆ alkylsilyloxy group (e.g.,
 - 30 triisopropylsilyloxy),
 - (d) a phenyl group optionally substituted by 1 to 3 substituents selected from
 - (i) a halogen atom (e.g., a fluorine atom, a chlorine atom), and
 - 35 (ii) a C₁₋₆ alkyl group (e.g., methyl) optionally

- substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (e) a phenoxy group,
- (f) a benzyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
- (g) a C₃₋₆ cycloalkyl group (e.g., cyclobutyl),
- (h) a C₃₋₆ cycloalkoxy group (e.g., cyclohexyloxy),
- (i) a thienyl group,
- (j) an indazolyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), and
- (k) a pyrrolidinyl group,
- (2) a pyridine ring further substituted by one substituent selected from
- (a) a phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
- (b) a C₂₋₆ alkenyl group (e.g., propen-2-yl),
- (3) a pyrazole ring further substituted by one phenyl group,
- (4) a thiazole ring further substituted by one phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (5) a piperidine ring further substituted by one phenyl group, or
- (6) a dibenzofuran ring.

[0130]

[Compound F-2]

Compound (I) wherein

R¹ is

- (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom), and
- (b) a C₁₋₆ alkoxy group (e.g., methoxy), or
- (2) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl);

R² is a hydrogen atom;

R³ is

- (1) a C₁₋₆ alkoxy-carbonyl group (e.g., ethoxycarbonyl,

isopropoxycarbonyl),

(2) a C₁₋₆ alkyl-carbonyl group (e.g., 2-methylpropanoyl, pivaloyl) optionally substituted by 1 to 3 hydroxy groups,

(3) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g.,
5 dimethylcarbamoyl),

(4) a C₃₋₆ cycloalkyl-carbonyl group (the C₃₋₆ cycloalkyl in the C₃₋₆ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl,

bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3
10 substituents selected from

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

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

(c) a hydroxy group,

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

(e) a cyano group,

(5) an oxetanylcabonyl group,

(6) an azetidinylcabonyl group optionally substituted by 1 to 3 substituents selected from

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

(b) a C₁₋₆ alkyl group (e.g., methyl), or

(7) a 5-azaspiro[2.3]hexylcarbonyl group;

R⁴ and R⁵ are both hydrogen atoms;

Ring A is

25 (1) a pyrrolidine ring, or

(2) a piperidine ring; and

Ring B is

(1) a benzene ring further substituted by 1 or 2 substituents selected from

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

(b) a phenyl group optionally substituted by 1 to 3 substituents selected from

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

35 (ii) a C₁₋₆ alkyl group (e.g., methyl),

(2) a pyridine ring further substituted by one phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),

(3) a thiazole ring further substituted by one phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), or

(4) a piperidine ring further substituted by one phenyl group.
[0131]

[Compound A-3]

10 Compound (I) wherein

R¹ is

(1) an optionally substituted C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl),

(2) an optionally substituted C₂₋₆ alkenyl group (e.g., vinyl, allyl),

(3) an optionally substituted C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),

(4) an optionally substituted mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino), or

20 (5) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., oxetanyl));

R² is a hydrogen atom;

R³ is

25 (1) a hydrogen atom,

(2) an optionally substituted C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 1,2-

30 dimethylpropoxycarbonyl),

(3) an optionally substituted C₁₋₆ alkyl-carbonyl group (e.g., acetyl, propanoyl, 2-methylpropanoyl, butanoyl, 2-methylbutanoyl, 3-methylbutanoyl, pivaloyl),

(4) an optionally substituted mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, ethylcarbamoyl, N-ethyl-N-

- methylcarbamoyl, N-isopropyl-N-methylcarbamoyl),
- (5) an optionally substituted N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group (e.g., N-methoxy-N-methylcarbamoyl),
- (6) an optionally substituted C₃₋₁₀ cycloalkyl-carbonyl group
- 5 (the C₃₋₁₀ cycloalkyl in the C₃₋₁₀ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, bicyclo[1.1.1]pentylcarbonyl),
- (7) an optionally substituted C₃₋₁₀ cycloalkoxy-carbonyl group
- 10 (e.g., cyclopropoxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl),
- (8) an optionally substituted 3- to 14-membered non-aromatic heterocyclylcarbonyl group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclylcarbonyl group (the non-
- 15 aromatic heterocycle in the non-aromatic heterocyclylcarbonyl group may be a spiro ring, e.g., oxetanylcarbonyl, azetidiny carbonyl, 5-azaspiro[2.3]hexylcarbonyl, isoxazolidiny carbonyl)),
- (9) an optionally substituted 3- to 14-membered non-aromatic
- 20 heterocyclyloxycarbonyl group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclyloxycarbonyl group (e.g., oxetanyloxycarbonyl, tetrahydrofuryloxycarbonyl, tetrahydropyranyloxycarbonyl)),
- (10) an optionally substituted C₆₋₁₄ aryloxy-carbonyl group
- 25 (e.g., phenoxycarbonyl),
- (11) an optionally substituted C₇₋₁₆ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl),
- (12) an optionally substituted 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic
- 30 aromatic heterocyclic group (e.g., imidazolyl, pyridazinyl)),
- (13) an optionally substituted 5- to 14-membered aromatic heterocyclylcarbonyl group (preferably a 5- to 6-membered monocyclic aromatic heterocyclylcarbonyl group (e.g., pyrazoly carbonyl, furylcarbonyl)), or
- 35 (14) an optionally substituted tri-C₁₋₆ alkylhydrazino-carbonyl

group (e.g., trimethylhydrazinocarbonyl);

R⁴ and R⁵ are each independently a hydrogen atom or a halogen atom (e.g., a fluorine atom);

Ring A is

- 5 (1) an optionally further substituted pyrrolidine ring,
(2) an optionally further substituted piperidine ring, or
(3) an optionally further substituted azetidine ring; and

Ring B is

- (1) an optionally further substituted C₆₋₁₄ aromatic hydrocarbon
10 ring (e.g., benzene, naphthalene),
(2) an optionally further substituted 5- to 14-membered
aromatic heterocycle (preferably a 5- to 6-membered monocyclic
aromatic heterocycle (e.g., pyridine, pyrazole, thiazole,
oxazole), a 8- to 14-membered fused polycyclic (preferably bi-
15 or tri-cyclic) aromatic heterocycle (e.g., benzofuran)), or
(3) an optionally further substituted 3- to 14-membered non-
aromatic heterocycle (preferably a 3- to 8-membered monocyclic
non-aromatic heterocycle (e.g., pyrrolidine, piperidine), a 9-
to 14-membered fused polycyclic (preferably bi- or tri-cyclic)
20 non-aromatic heterocycle (e.g., dibenzofuran)).

[0132]

[Compound Aa-3]

The above-mentioned Compound A-3 wherein

Ring B is

- 25 (1) a C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene)
further substituted by
(a) an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl),
(b) an optionally substituted C₆₋₁₄ aryloxy group (e.g.,
phenoxy),
30 (c) an optionally substituted C₇₋₁₆ aralkyl group (e.g.,
benzyl),
(d) an optionally substituted C₃₋₁₀ cycloalkyl group (e.g.,
cyclopropyl, cyclobutyl),
(e) an optionally substituted C₃₋₁₀ cycloalkenyl group (e.g.,
35 cyclopenten-1-yl, cyclohexen-1-yl),

- (f) an optionally substituted C₃₋₁₀ cycloalkoxy group (e.g., cyclohexyloxy),
- (g) an optionally substituted 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyridyl, thienyl, pyrazolyl, pyrimidinyl), a 8- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) aromatic heterocyclic group (e.g., indazolyl)), or
- (h) an optionally substituted 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., pyrrolidinyl), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocyclic group (e.g., dihydroindolyl)), and
- optionally having additional substituent(s),
- (2) a 5- to 14-membered aromatic heterocycle (preferably a 5- to 6-membered monocyclic aromatic heterocycle (e.g., pyridine, pyrazole, thiazole, oxazole)) further substituted by an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), and optionally having additional substituent(s), or
- (3) a 3- to 14-membered non-aromatic heterocycle (preferably a 3- to 8-membered monocyclic non-aromatic heterocycle (e.g., pyrrolidine, piperidine)) further substituted by
- (a) an optionally substituted C₆₋₁₄ aryl group (e.g., phenyl), or
- (b) an optionally substituted 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyrimidinyl)).

[0133]

[Compound B-3]

Compound (I) wherein

R¹ is

- (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl) optionally substituted by 1 to 3 substituents

selected from

- (a) a halogen atom (e.g., a fluorine atom, a chlorine atom),
- (b) a cyano group,
- (c) a hydroxy group, and

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

(2) a C₂₋₆ alkenyl group (e.g., vinyl, allyl),

(3) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),

(4) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),

10 or

(5) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., oxetanyl));

R² is a hydrogen atom;

15 R³ is

(1) a hydrogen atom,

(2) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-
20 butoxycarbonyl, 1,2-dimethylpropoxycarbonyl) optionally substituted by 1 to 3 substituents selected from

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

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

(c) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl) optionally substituted by 1 to 3 substituents
25 selected from

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

(ii) a C₁₋₆ alkyl group (e.g., methyl), and

(d) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic
30 heterocyclic group (e.g., oxetanyl, tetrahydrofuryl)),

(3) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, propanoyl, 2-methylpropanoyl, butanoyl, 2-methylbutanoyl, 3-methylbutanoyl, pivaloyl) optionally substituted by 1 to 3 substituents

35 selected from

- (a) a halogen atom (e.g., a fluorine atom),
 - (b) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl),
 - (c) a hydroxy group, and
 - (d) a C₁₋₆ alkoxy group (e.g., methoxy),
- 5 (4) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, ethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N-isopropyl-N-methylcarbamoyl),
- (5) a N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group (e.g., N-methoxy-N-methylcarbamoyl),
- 10 (6) a C₃₋₁₀ cycloalkyl-carbonyl group (the C₃₋₁₀ cycloalkyl in the C₃₋₁₀ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3 substituents selected from
- 15 (a) a halogen atom (e.g., a fluorine atom),
- (b) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom), and
 - (ii) a hydroxy group,
- 20 (c) a hydroxy group,
- (d) a C₁₋₆ alkoxy group (e.g., methoxy), and
- (e) a cyano group,
- (7) a C₃₋₁₀ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl) optionally
- 25 substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom), and
 - (b) a C₁₋₆ alkyl group (e.g., methyl),
- (8) a 3- to 14-membered non-aromatic heterocyclylcarbonyl group
- 30 (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclylcarbonyl group (the non-aromatic heterocycle in the non-aromatic heterocyclylcarbonyl group may be a spiro ring, e.g., oxetanylcabonyl, azetidinylcabonyl, 5-azaspiro[2.3]hexylcarbonyl, isoxazolidinylcabonyl)) optionally
- 35 substituted by 1 to 3 substituents selected from

- (a) a halogen atom (e.g., a fluorine atom), and
(b) a C₁₋₆ alkyl group (e.g., methyl),
(9) a 3- to 14-membered non-aromatic heterocyclyloxycarbonyl group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclyloxycarbonyl group (e.g., oxetanyloxycarbonyl, tetrahydrofuryloxycarbonyl, tetrahydropyranyloxycarbonyl)),
(10) a C₆₋₁₄ aryloxy-carbonyl group (e.g., phenoxycarbonyl),
(11) a C₇₋₁₆ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl),
(12) a 5- to 14-membered aromatic heterocyclic group
(preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., imidazolyl, pyridazinyl)) optionally substituted by 1 to 3 substituents selected from
(i) a halogen atom (e.g., a chlorine atom), and
(ii) a C₁₋₆ alkyl group (e.g., methyl, ethyl),
(13) a 5- to 14-membered aromatic heterocyclylcarbonyl group (preferably a 5- to 6-membered monocyclic aromatic heterocyclylcarbonyl group (e.g., pyrazolylcarbonyl, furylcarbonyl)) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), or
(14) a tri-C₁₋₆ alkylhydrazino-carbonyl group (e.g., trimethylhydrazinocarbonyl);

R⁴ and R⁵ are each independently a hydrogen atom or a halogen atom (e.g., a fluorine atom);

Ring A is

- (1) a pyrrolidine ring,
(2) a piperidine ring, or
(3) an azetidine ring; and

Ring B is

- (1) a C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene, naphthalene) optionally further substituted by 1 to 3 substituents selected from

- (a) a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom),
(b) a C₁₋₆ alkyl group (e.g., methyl, isopropyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),

- (c) a C₂₋₆ alkenyl group (e.g., vinyl, propen-2-yl),
(d) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),
(e) a tri-C₁₋₆ alkylsilyloxy group (e.g., triisopropylsilyloxy),
5 (f) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 4 substituents selected from
(i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
(ii) a C₁₋₆ alkyl group (e.g., methyl) optionally
10 substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
(iii) a C₁₋₆ alkoxy group (e.g., methoxy),
(g) a C₆₋₁₄ aryloxy group (e.g., phenoxy),
(h) a C₇₋₁₆ aralkyl group (e.g., benzyl) optionally
15 substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
(i) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),
(j) a C₃₋₁₀ cycloalkenyl group (e.g., cyclopenten-1-yl, cyclohexen-1-yl),
(k) a C₃₋₁₀ cycloalkoxy group (e.g., cyclohexyloxy),
20 (l) a 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyridyl, thienyl, pyrazolyl, pyrimidinyl), a 8- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) aromatic heterocyclic group
25 (e.g., indazolyl)) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), and
(m) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., pyrrolidinyl), a 9- to 14-
30 membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocyclic group (e.g., dihydroindolyl)),
(2) a 5- to 14-membered aromatic heterocycle (preferably a 5- to 6-membered monocyclic aromatic heterocycle (e.g., pyridine, pyrazole, thiazole, oxazole), a 8- to 14-membered fused
35 polycyclic (preferably bi- or tri-cyclic) aromatic heterocycle

(e.g., benzofuran)) optionally further substituted by 1 to 3 substituents selected from

- (a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- 5 (b) a C₁₋₆ alkyl group (e.g., methyl, isopropyl), and
- (c) a C₂₋₆ alkenyl group (e.g., propen-2-yl), or
- (3) a 3- to 14-membered non-aromatic heterocycle (preferably a 3- to 8-membered monocyclic non-aromatic heterocycle (e.g., pyrrolidine, piperidine), a 9- to 14-membered fused polycyclic
- 10 (preferably bi- or tri-cyclic) non-aromatic heterocycle (e.g., dibenzofuran)) optionally further substituted by 1 to 3 substituents selected from

- (a) a C₆₋₁₄ aryl group (e.g., phenyl), and
- (b) a 5- to 14-membered aromatic heterocyclic group
- 15 (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyrimidinyl)).

[0134]

[Compound Ba-3]

The above-mentioned Compound B-3 wherein
20 Ring B is

(1) a C₆₋₁₄ aromatic hydrocarbon ring (e.g., benzene) further substituted by

- (a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 4 substituents selected from
- 25 (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
- (ii) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
- 30 (iii) a C₁₋₆ alkoxy group (e.g., methoxy),
- (b) a C₆₋₁₄ aryloxy group (e.g., phenoxy),
- (c) a C₇₋₁₆ aralkyl group (e.g., benzyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
- (d) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),
- 35 (e) a C₃₋₁₀ cycloalkenyl group (e.g., cyclopenten-1-yl,

- cyclohexen-1-yl),
- (f) a C₃₋₁₀ cycloalkoxy group (e.g., cyclohexyloxy),
- (g) a 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyridyl, thienyl, pyrazolyl, pyrimidinyl), a 8- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) aromatic heterocyclic group (e.g., indazolyl)) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), or
- (h) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., pyrrolidinyl), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocyclic group (e.g., dihydroindolyl)), and
- optionally further substituted by 1 or 2 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom), and
- (j) a C₁₋₆ alkyl group (e.g., methyl),
- (2) a 5- to 14-membered aromatic heterocycle (preferably a 5- to 6-membered monocyclic aromatic heterocycle (e.g., pyridine, pyrazole, thiazole, oxazole)) further substituted by a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
- optionally further substituted by 1 or 2 C₁₋₆ alkyl groups (e.g., methyl), or
- (3) a 3- to 14-membered non-aromatic heterocycle (preferably a 3- to 8-membered monocyclic non-aromatic heterocycle (e.g., pyrrolidine, piperidine)) further substituted by
- (a) a C₆₋₁₄ aryl group (e.g., phenyl), or
- (b) a 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyrimidinyl)).

[Compound C-3]

The above-mentioned Compound B-3 wherein
Ring B is

- (1) a benzene ring optionally further substituted by 1 to 3
5 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom, a chlorine atom,
a bromine atom, an iodine atom),
 - (b) a C₁₋₆ alkyl group (e.g., methyl, isopropyl) optionally
substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
 - 10 (c) a C₂₋₆ alkenyl group (e.g., vinyl, propen-2-yl),
 - (d) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),
 - (e) a tri-C₁₋₆ alkylsilyloxy group (e.g.,
triisopropylsilyloxy),
 - (f) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted
15 by 1 to 4 substituents selected from
 - (i) a halogen atom (e.g., a fluorine atom, a chlorine
atom),
 - (ii) a C₁₋₆ alkyl group (e.g., methyl) optionally
substituted by 1 to 3 halogen atoms (e.g., a fluorine
20 atom), and
 - (iii) a C₁₋₆ alkoxy group (e.g., methoxy),
 - (g) a C₆₋₁₄ aryloxy group (e.g., phenoxy),
 - (h) a C₇₋₁₆ aralkyl group (e.g., benzyl) optionally
substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
 - 25 (i) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),
 - (j) a C₃₋₁₀ cycloalkenyl group (e.g., cyclopenten-1-yl,
cyclohexen-1-yl),
 - (k) a C₃₋₁₀ cycloalkoxy group (e.g., cyclohexyloxy),
 - (l) a 5- to 14-membered aromatic heterocyclic group
30 (preferably a 5- to 6-membered monocyclic aromatic
heterocyclic group (e.g., pyridyl, thienyl, pyrazolyl,
pyrimidinyl), a 8- to 14-membered fused polycyclic
(preferably bi- or tri-cyclic) aromatic heterocyclic group
(e.g., indazolyl)) optionally substituted by 1 to 3 C₁₋₆
35 alkyl groups (e.g., methyl), and

- (m) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., pyrrolidinyl), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) non-aromatic heterocyclic group (e.g., dihydroindolyl)),
- (2) a naphthalene ring,
- (3) a pyridine ring optionally further substituted by 1 to 3 substituents selected from
- (a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (b) a C₁₋₆ alkyl group (e.g., isopropyl), and
- (c) a C₂₋₆ alkenyl group (e.g., propen-2-yl),
- (4) a pyrazole ring optionally further substituted by 1 or 2 C₆₋₁₄ aryl groups (e.g., phenyl),
- (5) a thiazole ring optionally further substituted by 1 or 2 substituents selected from
- (a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
- (b) a C₁₋₆ alkyl group (e.g., methyl),
- (6) an oxazole ring optionally further substituted by 1 or 2 C₆₋₁₄ aryl groups (e.g., phenyl),
- (7) a pyrrolidine ring optionally further substituted by 1 to 3 C₆₋₁₄ aryl groups (e.g., phenyl),
- (8) a piperidine ring optionally further substituted by 1 to 3 substituents selected from
- (a) a C₆₋₁₄ aryl group (e.g., phenyl), and
- (b) a 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyrimidinyl)),
- (9) a dibenzofuran ring, or
- (10) a benzofuran ring optionally further substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., isopropyl).

[0136]

[Compound Ca-3]

The above-mentioned Compound B-3 wherein

Ring B is

(1) a benzene ring

further substituted by

- (a) a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted
5 by 1 to 4 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
- (ii) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine
10 atom), and
- (iii) a C₁₋₆ alkoxy group (e.g., methoxy),
- (b) a C₆₋₁₄ aryloxy group (e.g., phenoxy),
- (c) a C₇₋₁₆ aralkyl group (e.g., benzyl) optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
- 15 (d) a C₃₋₁₀ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),
- (e) a C₃₋₁₀ cycloalkenyl group (e.g., cyclopenten-1-yl, cyclohexen-1-yl),
- (f) a C₃₋₁₀ cycloalkoxy group (e.g., cyclohexyloxy),
- (g) a 5- to 14-membered aromatic heterocyclic group
- 20 (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyridyl, thienyl, pyrazolyl, pyrimidinyl), a 8- to 14-membered fused polycyclic (preferably bi- or tri-cyclic) aromatic heterocyclic group (e.g., indazolyl)) optionally substituted by 1 to 3 C₁₋₆
- 25 alkyl groups (e.g., methyl), or
- (h) a 3- to 14-membered non-aromatic heterocyclic group (preferably a 3- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., pyrrolidinyl), a 9- to 14-membered fused polycyclic (preferably bi- or tri-cyclic)
- 30 non-aromatic heterocyclic group (e.g., dihydroindolyl)), and
- optionally further substituted by 1 or 2 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom), and
- 35 (j) a C₁₋₆ alkyl group (e.g., methyl),

- (2) a pyridine ring further substituted by a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (3) a pyrazole ring further substituted by a C₆₋₁₄ aryl group (e.g., phenyl),
- (4) a thiazole ring further substituted by a C₆₋₁₄ aryl group (e.g., phenyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
- optionally further substituted by one C₁₋₆ alkyl group (e.g., methyl),
- (5) an oxazole ring further substituted by a C₆₋₁₄ aryl group (e.g., phenyl),
- (6) a pyrrolidine ring further substituted by a C₆₋₁₄ aryl group (e.g., phenyl), or
- (7) a piperidine ring further substituted by
- (a) a C₆₋₁₄ aryl group (e.g., phenyl), and
- (b) a 5- to 14-membered aromatic heterocyclic group (preferably a 5- to 6-membered monocyclic aromatic heterocyclic group (e.g., pyrimidinyl)).

[0137]

[Compound D-3]

Compound (I) wherein

R¹ is

- (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl) optionally substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom, a chlorine atom),
- (b) a cyano group,
- (c) a hydroxy group, and
- (d) a C₁₋₆ alkoxy group (e.g., methoxy),
- (2) a C₂₋₆ alkenyl group (e.g., vinyl, allyl),
- (3) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (4) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),

or

(5) an oxetanyl group;

R² is a hydrogen atom;

R³ is

5 (1) a hydrogen atom,

(2) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 1,2-dimethylpropoxycarbonyl) optionally

10 substituted by 1 to 3 substituents selected from

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

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

(c) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl) optionally substituted by 1 to 3 substituents

15 selected from

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

(ii) a C₁₋₆ alkyl group (e.g., methyl),

(d) an oxetanyl group, and

(e) a tetrahydrofuryl group,

20 (3) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, propanoyl, 2-methylpropanoyl, butanoyl, 2-methylbutanoyl, 3-methylbutanoyl, pivaloyl) optionally substituted by 1 to 3 substituents selected from

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

25 (b) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl),

(c) a hydroxy group, and

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

(4) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, ethylcarbamoyl, N-ethyl-N-methylcarbamoyl,

30 N-isopropyl-N-methylcarbamoyl),

(5) a N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group (e.g., N-methoxy-N-methylcarbamoyl),

(6) a C₃₋₆ cycloalkyl-carbonyl group (the C₃₋₆ cycloalkyl in the C₃₋₆ cycloalkyl-carbonyl group may be a bridged ring group, e.g.,

35 cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl,

bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3 substituents selected from

- (a) a halogen atom (e.g., a fluorine atom),
- (b) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted
5 by 1 to 3 substituents selected from
 - (i) a halogen atom (e.g., a fluorine atom), and
 - (ii) a hydroxy group,
- (c) a hydroxy group,
- (d) a C₁₋₆ alkoxy group (e.g., methoxy), and
- 10 (e) a cyano group,
- (7) a C₃₋₆ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl) optionally substituted by 1 to 3 substituents selected from
- 15 (a) a halogen atom (e.g., a fluorine atom), and
- (b) a C₁₋₆ alkyl group (e.g., methyl),
- (8) an oxetanylcabonyl group,
- (9) an azetidinylcabonyl group optionally substituted by 1 to 3 substituents selected from
- 20 (a) a halogen atom (e.g., a fluorine atom), and
- (b) a C₁₋₆ alkyl group (e.g., methyl),
- (10) a 5-azaspiro[2.3]hexylcarbonyl group,
- (11) an oxetanyloxycabonyl group,
- (12) a tetrahydrofuryloxycabonyl group,
- 25 (13) a tetrahydropyranyloxycabonyl group,
- (14) a phenoxycarbonyl group,
- (15) a benzyloxycabonyl group,
- (16) an isoxazolidinylcabonyl group,
- (17) a pyrazolylcabonyl group optionally substituted by 1 to 3
- 30 C₁₋₆ alkyl groups (e.g., methyl),
- (18) a furylcabonyl group,
- (19) an imidazolyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl, ethyl),
- (20) a pyridazinyl group optionally substituted by 1 to 3
- 35 substituents selected from

- (i) a halogen atom (e.g., a chlorine atom), and
 - (ii) a C₁₋₆ alkyl group (e.g., methyl), or
- (21) a tri-C₁₋₆ alkylhydrazino-carbonyl group (e.g., trimethylhydrazinocarbonyl);

5 R⁴ and R⁵ are each independently a hydrogen atom or a halogen atom (e.g., a fluorine atom);

Ring A is

- (1) a pyrrolidine ring,
- (2) a piperidine ring, or
- 10 (3) an azetidine ring; and

Ring B is

(1) a benzene ring optionally further substituted by 1 to 3 substituents selected from

- 15 (a) a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom),
- (b) a C₁₋₆ alkyl group (e.g., methyl, isopropyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (c) a C₂₋₆ alkenyl group (e.g., vinyl, propen-2-yl),
- (d) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino),
- 20 (e) a tri-C₁₋₆ alkylsilyloxy group (e.g., triisopropylsilyloxy),
- (f) a phenyl group optionally substituted by 1 to 4 substituents selected from
 - (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
 - 25 (ii) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
 - (iii) a C₁₋₆ alkoxy group (e.g., methoxy),
- 30 (g) a phenoxy group,
- (h) a benzyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
- (i) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),
- (j) a C₃₋₆ cycloalkenyl group (e.g., cyclopenten-1-yl,
- 35 cyclohexen-1-yl),

- (k) a C₃₋₆ cycloalkoxy group (e.g., cyclohexyloxy),
- (l) a pyridyl group,
- (m) a thienyl group,
- (n) a pyrimidinyl group,
- 5 (o) a pyrazolyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
- (p) an indazolyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
- (q) a pyrrolidinyl group, and
- 10 (r) a dihydroindolyl group,
- (2) a naphthalene ring,
- (3) a pyridine ring optionally further substituted by 1 to 3 substituents selected from
 - (a) a phenyl group optionally substituted by 1 to 3 halogen
 - 15 atoms (e.g., a fluorine atom),
 - (b) a C₁₋₆ alkyl group (e.g., isopropyl), and
 - (c) a C₂₋₆ alkenyl group (e.g., propen-2-yl),
- (4) a pyrazole ring optionally further substituted by 1 or 2 phenyl groups,
- 20 (5) a thiazole ring optionally further substituted by 1 or 2 substituents selected from
 - (a) a phenyl group optionally substituted by 1 to 3 halogen
 - atoms (e.g., a fluorine atom), and
 - (b) a C₁₋₆ alkyl group (e.g., methyl),
- 25 (6) an oxazole ring optionally further substituted by 1 or 2 phenyl groups,
- (7) a pyrrolidine ring optionally further substituted by 1 to 3 phenyl groups,
- (8) a piperidine ring optionally further substituted by 1 to 3
- 30 substituents selected from
 - (a) a phenyl group, and
 - (b) a pyrimidinyl group,
 - (9) a dibenzofuran ring, or
 - (10) a benzofuran ring optionally further substituted by 1 to 3
 - 35 C₁₋₆ alkyl groups (e.g., isopropyl).

[0138]

[Compound Da-3]

The above-mentioned Compound D-3 wherein
Ring B is

5 (1) a benzene ring

further substituted by

(a) a phenyl group optionally substituted by 1 to 4
substituents selected from

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

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

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

15 (b) a phenoxy group,

(c) a benzyl group optionally substituted by 1 to 3 C₁₋₆
alkyl groups (e.g., methyl),

(d) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl, cyclobutyl),

20 (e) a C₃₋₆ cycloalkenyl group (e.g., cyclopenten-1-yl,
cyclohexen-1-yl),

(f) a C₃₋₆ cycloalkoxy group (e.g., cyclohexyloxy),

(g) a pyridyl group,

(h) a thienyl group,

(i) a pyrimidinyl group,

25 (j) a pyrazolyl group optionally substituted by 1 to 3 C₁₋₆
alkyl groups (e.g., methyl),

(k) an indazolyl group optionally substituted by 1 to 3 C₁₋₆
alkyl groups (e.g., methyl),

(l) a pyrrolidinyl group, or

30 (m) a dihydroindolyl group, and

optionally further substituted by 1 or 2 substituents selected
from

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

(p) a C₁₋₆ alkyl group (e.g., methyl),

35 (2) a pyridine ring further substituted by a phenyl group

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

(3) a pyrazole ring further substituted by a phenyl group,

(4) a thiazole ring

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

(5) an oxazole ring further substituted by a phenyl group,

10 (6) a pyrrolidine ring further substituted by a phenyl group, or

(7) a piperidine ring further substituted by

(a) a phenyl group, or

(b) a pyrimidinyl group.

15 [0139]

[Compound E-3]

Compound (I) wherein

R¹ is

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

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

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

(2) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl) optionally
25 substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), or

(3) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino);

R² is a hydrogen atom;

R³ is

(1) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl,
30 ethoxycarbonyl, isopropoxycarbonyl),

(2) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, 2-methylpropanoyl, pivaloyl) optionally substituted by 1 to 3 hydroxy groups,

(3) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl, ethylcarbamoyl),

35 (4) a N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group (e.g., N-

methoxy-N-methylcarbamoyl),

(5) a C₃₋₆ cycloalkyl-carbonyl group (the C₃₋₆ cycloalkyl in the C₃₋₆ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl,

5 bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3 substituents selected from

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

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

10 (c) a hydroxy group,

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

(e) a cyano group,

(6) a C₃₋₆ cycloalkoxy-carbonyl group (e.g., cyclopropoxycarbonyl),

15 (7) a phenoxycarbonyl group,

(8) an oxetanylcabonyl group,

(9) an azetidinylcabonyl group optionally substituted by 1 to 3 substituents selected from

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

20 (b) a C₁₋₆ alkyl group (e.g., methyl), or

(10) a 5-azaspiro[2.3]hexylcarbonyl group;

R⁴ and R⁵ are both hydrogen atoms;

Ring A is

(1) a pyrrolidine ring, or

25 (2) a piperidine ring; and

Ring B is

(1) a benzene ring further substituted by 1 or 2 substituents selected from

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

30 (b) a C₂₋₆ alkenyl group (e.g., propen-2-yl),

(c) a tri-C₁₋₆ alkylsilyloxy group (e.g., triisopropylsilyloxy),

(d) a phenyl group optionally substituted by 1 to 3 substituents selected from

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

- atom), and
- (ii) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- 5 (e) a phenoxy group,
- (f) a benzyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
- (g) a C₃₋₆ cycloalkyl group (e.g., cyclobutyl),
- (h) a C₃₋₆ cycloalkoxy group (e.g., cyclohexyloxy),
- 10 (i) a thienyl group,
- (j) an indazolyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), and
- (k) a pyrrolidinyl group,
- (2) a pyridine ring further substituted by one substituent
- 15 selected from
- (a) a phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), and
- (b) a C₂₋₆ alkenyl group (e.g., propen-2-yl),
- (3) a pyrazole ring further substituted by one phenyl group,
- 20 (4) a thiazole ring further substituted by one phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (5) a piperidine ring further substituted by one phenyl group,
- or
- 25 (6) a dibenzofuran ring.

[0140]

[Compound Ea-3]

The above-mentioned Compound E-3 wherein
Ring B is

- 30 (1) a benzene ring
- further substituted by
- (a) a phenyl group optionally substituted by 1 to 3 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom, a chlorine
- 35 atom), and

- (ii) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (b) a phenoxy group,
- 5 (c) a benzyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl),
- (d) a C₃₋₆ cycloalkyl group (e.g., cyclobutyl),
- (e) a C₃₋₆ cycloalkoxy group (e.g., cyclohexyloxy),
- (f) a thienyl group,
- 10 (g) an indazolyl group optionally substituted by 1 to 3 C₁₋₆ alkyl groups (e.g., methyl), or
- (h) a pyrrolidinyl group, and
- optionally further substituted by one halogen atom (e.g., a fluorine atom),
- 15 (2) a pyridine ring further substituted by one phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (3) a pyrazole ring further substituted by one phenyl group,
- (4) a thiazole ring further substituted by one phenyl group
- 20 optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), or
- (5) a piperidine ring further substituted by one phenyl group.

[0141]

[Compound F-3]

25 Compound (I) wherein

R¹ is

- (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom), and
- 30 (b) a C₁₋₆ alkoxy group (e.g., methoxy),
- (2) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), or
- (3) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino);

R² is a hydrogen atom;

35 R³ is

- (1) a C₁₋₆ alkoxy-carbonyl group (e.g., ethoxycarbonyl, isopropoxycarbonyl),
- (2) a C₁₋₆ alkyl-carbonyl group (e.g., 2-methylpropanoyl, pivaloyl) optionally substituted by 1 to 3 hydroxy groups,
- 5 (3) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl),
- (4) a N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group (e.g., N-methoxy-N-methylcarbamoyl),
- (5) a C₃₋₆ cycloalkyl-carbonyl group (the C₃₋₆ cycloalkyl in the
- 10 C₃₋₆ cycloalkyl-carbonyl group may be a bridged ring group, e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, bicyclo[1.1.1]pentylcarbonyl) optionally substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom),
- 15 (b) a C₁₋₆ alkyl group (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),
- (c) a hydroxy group,
- (d) a C₁₋₆ alkoxy group (e.g., methoxy), and
- (e) a cyano group,
- 20 (6) an oxetanylcabonyl group,
- (7) an azetidinylcabonyl group optionally substituted by 1 to 3 substituents selected from
- (a) a halogen atom (e.g., a fluorine atom), and
- (b) a C₁₋₆ alkyl group (e.g., methyl), or
- 25 (8) a 5-azaspiro[2.3]hexylcarbonyl group;
- R⁴ and R⁵ are both hydrogen atoms;
- Ring A is
- (1) a pyrrolidine ring, or
- (2) a piperidine ring; and
- 30 Ring B is
- (1) a benzene ring
- further substituted by one phenyl group optionally substituted by 1 to 3 substituents selected from
- (i) a halogen atom (e.g., a fluorine atom, a chlorine atom),
- 35 and

(ii) a C₁₋₆ alkyl group (e.g., methyl), and optionally further substituted by one halogen atom (e.g., a fluorine atom),

(2) a pyridine ring further substituted by one phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom),

(3) a thiazole ring further substituted by one phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), or

(4) a piperidine ring further substituted by one phenyl group.
[0142]

[Compound G-1]

Compound (I) wherein

R¹ is

- (1) a C₁₋₆ alkyl group (e.g., methyl, ethyl),
(2) a C₃₋₆ cycloalkyl group (e.g., cyclopropyl) optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom), or
(3) a mono- or di-C₁₋₆ alkylamino group (e.g., dimethylamino);
R² is a hydrogen atom;

R³ is

- (1) a C₁₋₆ alkyl-carbonyl group (e.g., 2-methylpropanoyl) optionally substituted by 1 to 3 hydroxy groups,
(2) a mono- or di-C₁₋₆ alkyl-carbamoyl group (e.g., dimethylcarbamoyl),
(3) a N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group (e.g., N-methoxy-N-methylcarbamoyl), or
(4) an azetidinyllcarbonyl group;

R⁴ and R⁵ are both hydrogen atoms;

Ring A is a pyrrolidine ring; and

Ring B is a benzene ring

further substituted by one phenyl group optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atoms), and optionally further substituted by one halogen atom (e.g., a fluorine atoms).

[0143]

[Compound G-2]

Compound (I) wherein

R¹ is a C₁₋₆ alkyl group (e.g., methyl, ethyl);

R² is a hydrogen atom;

5 R³ is a C₁₋₆ alkyl-carbonyl group (e.g., 2-methylpropanoyl)
optionally substituted by 1 to 3 hydroxy groups;

R⁴ and R⁵ are both hydrogen atoms;

Ring A is a pyrrolidine ring; and

Ring B is a benzene ring

10 further substituted by one phenyl group optionally substituted
by 1 to 3 halogen atoms (e.g., a fluorine atoms), and
optionally further substituted by one halogen atom (e.g., a
fluorine atoms).

[0144]

15 [Compound H]

N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-
2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide or a salt
thereof.

[0145]

20 [Compound I]

N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3',5'-
trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-
yl)methanesulfonamide or a salt thereof.

[0146]

25 [Compound J]

N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3',5'-
trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide
or a salt thereof.

[0147]

30 [Compound K]

A compound selected from

(1) N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3'-
difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide,

(2) N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((3',5'-
35 difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide,

- (3) N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-(biphenyl-3-ylmethyl)pyrrolidin-3-yl)ethanesulfonamide,
(4) N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide,
5 (5) (2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((ethylsulfonyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide,
(6) (2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((dimethylsulfamoyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide,
10 (7) (2S,3S)-3-((ethylsulfonyl)amino)-N,N-dimethyl-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidine-1-carboxamide,
(8) (2S,3S)-2-(biphenyl-3-ylmethyl)-3-((ethylsulfonyl)amino)-N-methoxy-N-methylpyrrolidine-1-carboxamide,
(9) N-[(2S,3S)-2-[(2,3'-difluoro[1,1'-biphenyl]-3-yl)methyl]-1-
15 (2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl]-1-fluorocyclopropane-1-sulfonamide,
(10) N-[(2S,3S)-1-(azetidine-1-carbonyl)-2-[(2-fluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl]ethanesulfonamide,
(11) (2S,3S)-3-[(ethanesulfonyl)amino]-2-[(3'-fluoro[1,1'-
20 biphenyl]-3-yl)methyl]-N-methoxy-N-methylpyrrolidine-1-carboxamide,
(12) (2S,3S)-3-[(dimethylsulfamoyl)amino]-2-[(2-fluoro[1,1'-biphenyl]-3-yl)methyl]-N,N-dimethylpyrrolidine-1-carboxamide,
(13) (2S,3S)-3-[(dimethylsulfamoyl)amino]-N,N-dimethyl-2-
25 [(2,3',5'-trifluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidine-1-carboxamide, and
(14) (2S,3S)-2-[(3',5'-difluoro[1,1'-biphenyl]-3-yl)methyl]-3-[(ethanesulfonyl)amino]-N-methoxy-N-methylpyrrolidine-1-carboxamide
30 or a salt thereof.

[0148]

[Compound L]

A compound selected from

- (1) (2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-
35 ((ethylsulfonyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide,

- (2) (2S,3S)-3-((ethylsulfonyl)amino)-N,N-dimethyl-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidine-1-carboxamide,
(3) N-[(2S,3S)-2-[(2,3'-difluoro[1,1'-biphenyl]-3-yl)methyl]-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl]-1-fluorocyclopropane-1-sulfonamide,
5 (4) N-{(2S,3S)-1-(azetidine-1-carbonyl)-2-[(2-fluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl}ethanesulfonamide,
(5) (2S,3S)-3-[(ethanesulfonyl)amino]-2-[(3'-fluoro[1,1'-biphenyl]-3-yl)methyl]-N-methoxy-N-methylpyrrolidine-1-
10 carboxamide, and
(6) (2S,3S)-3-[(dimethylsulfamoyl)amino]-2-[(2-fluoro[1,1'-biphenyl]-3-yl)methyl]-N,N-dimethylpyrrolidine-1-carboxamide
or a salt thereof.

[0149]

- 15 Specific examples of compound (I) include the compounds of the below-mentioned Examples 1 to 488.

[0150]

As a salt of a compound represented by the formula (I), a pharmacologically acceptable salt is preferable, and examples
20 of such salt include a salt with inorganic base, a salt with organic base, a salt with inorganic acid, a salt with organic acid, a salt with basic or acidic amino acid and the like.

Preferable examples of the salt with inorganic base include alkali metal salts such as sodium salt, potassium salt
25 and the like, alkaline earth metal salts such as calcium salt, magnesium salt and the like, aluminum salt, ammonium salt and the like.

Preferable examples of the salt with organic base include salts with trimethylamine, triethylamine, pyridine, picoline,
30 ethanolamine, diethanolamine, triethanolamine, tromethamine[tris(hydroxymethyl)methylamine], tert-butylamine, cyclohexylamine, benzylamine, dicyclohexylamine, N,N-dibenzylethylenediamine and the like.

Preferable examples of the salt with inorganic acid
35 include salts with hydrochloric acid, hydrobromic acid, nitric

acid, sulfuric acid, phosphoric acid and the like.

Preferable examples of the salt with organic acid include salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic
5 acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

Preferable examples of the salt with basic amino acid include salts with arginine, lysine, ornithine and the like.

Preferable examples of the salt with acidic amino acid
10 include salts with aspartic acid, glutamic acid and the like.
[0151]

The production method of the compound of the present invention is explained below.

[0152]

15 The raw material compound and reagent used and the compound obtained in each step in the following production method may be each in a form of a salt, and examples of such salt include those similar to the salts of the compound represented by the formula (I), and the like.

20 [0153]

When the compound obtained in each step is a free form, it can be converted to the objective salt according to a method known per se. When the compound obtained in each step is a salt, it can be converted to the objective free form or
25 the other salt according to a method known per se.

[0154]

The compound obtained in each step can be used directly as the reaction mixture or as a crude product for the next reaction. Alternatively, the compound obtained in each step
30 can be isolated and purified from a reaction mixture according to a method known per se, for example, a separation means such as concentration, crystallization, recrystallization, distillation, solvent extraction, fractional distillation, column chromatography and the like.

35 [0155]

When the raw material compound and reagent used in each step are commercially available, the commercially available product can also be used directly.

[0156]

- 5 In the reaction in each step, while the reaction time varies depending on the kind of the reagent and solvent to be used, it is generally 1 min - 48 hr, preferably 10 min - 8 hr, unless otherwise specified.

[0157]

- 10 In the reaction in each step, while the reaction temperature varies depending on the kind of the reagent and solvent to be used, it is generally -78°C - 300°C, preferably -78°C - 150°C, unless otherwise specified.

[0158]

- 15 In the reaction in each step, while the pressure varies depending on the kind of the reagent and solvent to be used, it is generally 1 atm - 20 atm, preferably 1 atm - 3 atm, unless otherwise specified.

[0159]

- 20 Microwave synthesizer such as Initiator manufactured by Biotage and the like may be used for the reaction in each step. While the reaction temperature varies depending on the kind of the reagent and solvent to be used, it is generally room temperature - 300°C, preferably 50°C - 250°C, unless otherwise
25 specified. While the reaction time varies depending on the kind of the reagent and solvent to be used, it is generally 1 min - 48 hr, preferably 1 min - 8 hr, unless otherwise specified.

[0160]

- 30 In the reaction in each step, the reagent is used in an amount of 0.5 equivalents - 20 equivalents, preferably 0.8 equivalents - 5 equivalents, relative to the substrate, unless otherwise specified. When the reagent is used as a catalyst, the reagent is used in an amount of 0.001 equivalent - 1
35 equivalent, preferably 0.01 equivalent - 0.2 equivalent,

relative to the substrate. When the reagent is used as a reaction solvent, the reagent is used in a solvent amount.

[0161]

Unless otherwise specified, the reaction in each step is
5 carried out without solvent, or by dissolving or suspending the raw material compound in a suitable solvent. Examples of the solvent include those described in Examples and the following solvents.

- alcohols: methanol, ethanol, tert-butyl alcohol, 2-
10 methoxyethanol and the like;
ethers: diethyl ether, diphenyl ether, tetrahydrofuran, 1,2-dimethoxyethane and the like;
aromatic hydrocarbons: chlorobenzene, toluene, xylene and the like;
15 saturated hydrocarbons: cyclohexane, hexane and the like;
amides: N,N-dimethylformamide, N-methylpyrrolidone and the like;
halogenated hydrocarbons: dichloromethane, carbon tetrachloride and the like;
20 nitriles: acetonitrile and the like;
sulfoxides: dimethyl sulfoxide and the like;
aromatic organic bases: pyridine and the like;
anhydrides: acetic anhydride and the like;
organic acids: formic acid, acetic acid, trifluoroacetic acid
25 and the like;
inorganic acids: hydrochloric acid, sulfuric acid and the like;
esters: ethyl acetate and the like;
ketones: acetone, methyl ethyl ketone and the like;
30 water.

The above-mentioned solvent can be used in a mixture of two or more kinds thereof in an appropriate ratio.

[0162]

When a base is used for the reaction in each step, examples thereof include those described in Examples and the following bases.

inorganic bases: sodium hydroxide, magnesium hydroxide, sodium carbonate, calcium carbonate, sodium hydrogen carbonate and the like;

organic bases: triethylamine, diethylamine, pyridine, 4-dimethylaminopyridine, N,N-dimethylaniline, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]-7-undecene, imidazole, piperidine and the like;

metal alkoxides: sodium ethoxide, potassium tert-butoxide and the like;

alkali metal hydrides: sodium hydride and the like;

metal amides: sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide and the like;

organic lithiums: n-butyllithium and the like.

[0163]

When an acid or an acid catalyst is used for the reaction in each step, examples thereof include those described in Examples and the following acids and acid catalysts.

inorganic acids: hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid, phosphoric acid and the like;

organic acids: acetic acid, trifluoroacetic acid, citric acid, p-toluenesulfonic acid, 10-camphorsulfonic acid and the like;

Lewis acid: boron trifluoride diethyl ether complex, zinc iodide, anhydrous aluminum chloride, anhydrous zinc chloride, anhydrous iron chloride and the like.

[0164]

Unless otherwise specified, the reaction in each step is carried out according to a method known per se, for example, the method described in Jikken Kagaku Kouza, 5th Edition, vol.13-19 (the Chemical Society of Japan ed.); Shin Jikken Kagaku Kouza, vol.14-15 (the Chemical Society of Japan ed.); Fine Organic Chemistry, Revised 2nd Edition (L. F. Tietze, Th. Eicher, Nankodo); Organic Name Reactions, the Reaction

Mechanism and Essence, Revised Edition (Hideo Togo, Kodansha); ORGANIC SYNTHESSES Collective Volume I-VII (John Wiley & Sons Inc.); Modern Organic Synthesis in the Laboratory A Collection of Standard Experimental Procedures (Jie Jack Li, OXFORD UNIVERSITY); Comprehensive Heterocyclic Chemistry III, Vol.1 - Vol.14 (Elsevier Japan); Strategic Applications of Named Reactions in Organic Synthesis (translated by Kiyoshi Tomioka, Kagakudojin); Comprehensive Organic Transformations (VCH Publishers Inc.), 1989, or the like, or the method described in Examples.

[0165]

In each step, the protection or deprotection reaction of an functional group is carried out according to a method known per se, for example, the method described in "Protective Groups in Organic Synthesis, 4th Ed", Wiley-Interscience, Inc., 2007 (Theodora W. Greene, Peter G. M. Wuts); "Protecting Groups 3rd Ed." Thieme, 2004 (P.J. Kocienski), or the like, or the method described in Examples.

Examples of the protecting group for a hydroxy group of an alcohol and the like and a phenolic hydroxy group include ether-type protecting groups such as methoxymethyl ether, benzyl ether, tert-butyldimethylsilyl ether, tetrahydropyranyl ether and the like; carboxylate ester-type protecting groups such as acetate ester and the like; sulfonate ester-type protecting groups such as methanesulfonate ester and the like; carbonate ester-type protecting groups such as tert-butylcarbonate and the like, and the like.

Examples of the protecting group for a carbonyl group of an aldehyde include acetal-type protecting groups such as dimethylacetal and the like; cyclic acetal-type protecting groups such as 1,3-dioxane and the like, and the like.

Examples of the protecting group for a carbonyl group of a ketone include ketal-type protecting groups such as dimethylketal and the like; cyclic ketal-type protecting groups such as 1,3-dioxane and the like; oxime-type protecting

groups such as O-methyloxime and the like; hydrazone-type protecting groups such as N,N-dimethylhydrazone and the like, and the like.

Examples of the protecting group for a carboxyl group
5 include ester-type protecting groups such as methyl ester and the like; amide-type protecting groups such as N,N-dimethylamide and the like, and the like.

Examples of the protecting group for a thiol include
10 ether-type protecting groups such as benzyl thioether and the like; ester-type protecting groups such as thioacetate ester, thiocarbonate, thiocarbamate and the like, and the like.

Examples of the protecting group for an amino group and an aromatic heterocycle such as imidazole, pyrrole, indole and the like include carbamate-type protecting groups such as
15 benzyl carbamate and the like; amide-type protecting groups such as acetamide and the like; alkyl amine-type protecting groups such as N-triphenylmethylamine and the like; sulfonamide-type protecting groups such as methanesulfonamide and the like, and the like.

20 The protecting groups can be removed according to a method known per se, for example, by employing a method using acid, base, ultraviolet rays, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, trialkylsilyl halide (e.g., trimethylsilyl
25 iodide, trimethylsilyl bromide) and the like, a reduction method, and the like.

[0166]

When reduction reaction is carried out in each step, examples of the reducing agent to be used include metal
30 hydrides such as lithium aluminum hydride, sodium triacetoxymethylborohydride, sodium cyanoborohydride, diisobutylaluminum hydride (DIBAL-H), sodium borohydride, tetramethylammonium triacetoxymethylborohydride and the like; boranes such as borane tetrahydrofuran complex and the like;
35 Raney nickel; Raney cobalt; hydrogen; formic acid;

triethylsilane and the like. When carbon-carbon double bond or triple bond is reduced, a method using a catalyst such as palladium-carbon, Lindlar's catalyst and the like may be employed.

5 [0167]

When oxidation reaction is carried out in each step, examples of the oxidizing agent to be used include peroxides such as m-chloroperbenzoic acid (mCPBA), hydrogen peroxide, tert-butylhydroperoxide and the like; perchlorates such as
10 tetrabutylammonium perchlorate and the like; chlorates such as sodium chlorate and the like; chlorites such as sodium chlorite and the like; periodates such as sodium periodate and the like; hypervalent iodine reagents such as iodosylbenzene and the like; reagents containing manganese such as manganese
15 dioxide, potassium permanganate and the like; leads such as lead tetraacetate and the like; reagents containing chromium such as pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), Jones reagent and the like; halogen compounds such as N-bromosuccinimide (NBS) and the like; oxygen; ozone; sulfur
20 trioxide-pyridine complex; osmium tetroxide; selenium dioxide; 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and the like.
[0168]

When radical cyclization reaction is carried out in each step, examples of the radical initiator to be used include azo
25 compounds such as azobisisobutyronitrile (AIBN) and the like; water-soluble radical initiators such as 4-4'-azobis-4-cyanopentanoic acid (ACPA) and the like; triethylboron in the presence of air or oxygen; benzoyl peroxide and the like. Examples of the radical reagent to be used include
30 tributylstannane, tris(trimethylsilyl)silane, 1,1,2,2-tetraphenyldisilane, diphenylsilane, samarium iodide and the like.
[0169]

When Wittig reaction is carried out in each step,
35 examples of the Wittig reagent to be used include alkylidene

phosphoranes and the like. The alkylidene phosphoranes can be prepared according to a method known per se, for example, by reacting a phosphonium salt with a strong base.

[0170]

5 When Horner-Emmons reaction is carried out in each step, examples of the reagent to be used include phosphonoacetates such as methyl dimethylphosphonoacetate, ethyl diethylphosphonoacetate and the like; and bases such as alkali metal hydrides, organic lithiums and the like.

10 [0171]

 When Friedel-Crafts reaction is carried out in each step, a combination of a Lewis acid and an acid chloride or a combination of a Lewis acid and an alkylating agent (e.g., an alkyl halide, an alcohol, an olefin etc.) is used as a reagent.
15 Alternatively, an organic acid or an inorganic acid can also be used instead of a Lewis acid, and an anhydride such as acetic anhydride and the like can also be used instead of an acid chloride.

[0172]

20 When aromatic nucleophilic substitution reaction is carried out in each step, a nucleophile (e.g., an amine, imidazole etc.) and a base (e.g., an organic base etc.) are used as a reagent.

[0173]

25 When nucleophilic addition reaction by a carbo anion, nucleophilic 1,4-addition reaction (Michael addition reaction) by a carbo anion or nucleophilic substitution reaction by a carbo anion is carried out in each step, and examples of the base to be used for generation of the carbo anion include
30 organic lithiums, metal alkoxides, inorganic bases, organic bases and the like.

[0174]

 When Grignard reaction is carried out in each step, examples of the Grignard reagent to be used include
35 arylmagnesium halides such as phenylmagnesium bromide and the

like; and alkylmagnesium halides such as methylmagnesium bromide and the like. The Grignard reagent can be prepared according to a method known per se, for example, by reacting an alkyl halide or an aryl halide with a metal magnesium in an ether or tetrahydrofuran as a solvent.

[0175]

When Knoevenagel condensation reaction is carried out in each step, a compound having an activated methylene group with two electron withdrawing groups (e.g., malonic acid, diethyl malonate, malononitrile etc.) and a base (e.g., an organic base, a metal alkoxide, an inorganic base) are used as a reagent.

[0176]

When Vilsmeier-Haack reaction is carried out in each step, phosphoryl chloride and an amide derivative (e.g., N,N-dimethylformamide etc.) are used as a reagent.

[0177]

When azidation reaction of an alcohol, an alkyl halide or a sulfonate is carried out in each step, examples of the azidating agent to be used include diphenylphosphorylazide (DPPA), trimethylsilylazide, sodium azide and the like. For example, for the azidation reaction of an alcohol, a method using diphenylphosphorylazide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a method using trimethylsilylazide and a Lewis acid, and the like are employed.

[0178]

When reductive amination reaction is carried out in each step, examples of the reducing agent to be used include sodium triacetoxyborohydride, sodium cyanoborohydride, hydrogen, formic acid and the like. When the substrate is an amine compound, examples of the carbonyl compound to be used include paraformaldehyde, aldehydes such as acetaldehyde and the like, and ketones such as cyclohexanone and the like. When the substrate is a carbonyl compound, examples of the amine to be

used include ammonia, primary amines such as methylamine and the like; secondary amines such as dimethylamine and the like, and the like.

[0179]

- 5 When Mitsunobu reaction is carried out in each step, an azodicarboxylate (e.g., diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD) etc.) and triphenylphosphine are used as a reagent.

[0180]

- 10 When esterification reaction, amidation reaction or urea formation reaction is carried out in each step, examples of the reagent to be used include acyl halides such as acid chlorides, acid bromides and the like; activated carboxylic acids such as acid anhydrides, activated esters, sulfates and
15 the like. Examples of the activating agent of the carboxylic acid include carbodiimide condensing agents such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD) and the like; triazine condensing agents such as 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride n-hydrate
20 (DMT-MM) and the like; carbonate condensing agents such as 1,1-carbonyldiimidazole (CDI) and the like; diphenylphosphoryl azide (DPPA); benzotriazol-1-yloxy-trisdimethylaminophosphonium salt (BOP reagent); 2-chloro-1-methyl-pyridinium iodide (Mukaiyama reagent); thionyl
25 chloride; lower alkyl haloformates such as ethyl chloroformate and the like; O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU); sulfuric acid; combinations thereof and the like. When carbodiimide condensing agent is used, an additive such as 1-
30 hydroxybenzotriazole (HOBt), N-hydroxysuccinimide (HOSu), dimethylaminopyridine (DMAP) and the like may be added to the reaction system.

[0181]

- When coupling reaction is carried out in each step,
35 examples of the metal catalyst to be used include palladium

compounds such as palladium(II) acetate,
tetrakis(triphenylphosphine)palladium(0),
dichlorobis(triphenylphosphine)palladium(II),
dichlorobis(triethylphosphine)palladium(II),
5 tris(dibenzylideneacetone)dipalladium(0), 1,1'-
bis(diphenylphosphino)ferrocene palladium(II) chloride and the
like; nickel compounds such as
tetrakis(triphenylphosphine)nickel(0) and the like; rhodium
compounds such as tris(triphenylphosphine)rhodium(III)
10 chloride and the like; cobalt compounds; copper compounds such
as copper oxide, copper(I) iodide and the like; platinum
compounds and the like. In addition, a base can be added to
the reaction system, and examples thereof include inorganic
bases and the like.

15 [0182]

When thiocarbonylation reaction is carried out in each
step, phosphorus pentasulfide is typically used as the
thiocarbonylating agent. Alternatively, a reagent having a
1,3,2,4-dithiadiphosphetane-2,4-disulfide structure (e.g.,
20 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-
disulfide (Lawesson reagent) etc.) can also be used instead of
phosphorus pentasulfide.

[0183]

When Wohl-Ziegler reaction is carried out in each step,
25 examples of the halogenating agent to be used include N-
iodosuccinimide, N-bromosuccinimide (NBS), N-chlorosuccinimide
(NCS), bromine, sulfuryl chloride and the like. In addition,
the reaction can be accelerated by subjecting a radical
initiator such as heat, light, benzoyl peroxide,
30 azobisisobutyronitrile and the like to the reaction system
reaction.

[0184]

When halogenation reaction of a hydroxy group is carried
out in each step, examples of the halogenating agent to be
35 used include hydrohalic acids and acid halides of inorganic

acids, specifically, hydrochloric acid, thionyl chloride, phosphorus oxychloride and the like for chlorination, 48% hydrobromic acid and the like for bromination. In addition, a method of producing an alkyl halide by reacting an alcohol
5 with triphenylphosphine and carbon tetrachloride or carbon tetrabromide or the like can be employed. Alternatively, a method of producing an alkyl halide via two step comprising converting an alcohol to the corresponding sulfonate, and then reacting the sulfonate with lithium bromide, lithium chloride
10 or sodium iodide can also be employed.

[0185]

When Arbuzov reaction is carried out in each step, examples of the reagent to be used include alkyl halides such as ethyl bromoacetate and the like; and phosphites such as
15 triethyl phosphite, tri(isopropyl) phosphite and the like.

[0186]

When sulfonate esterification reaction is carried out in each step, examples of the sulfonating agent to be used include methanesulfonyl chloride, p-toluenesulfonyl chloride, methanesulfonic anhydride, p-toluenesulfonic anhydride and the
20 like.

[0187]

When hydrolysis reaction is carried out in each step, an acid or a base is used as a reagent. For acid hydrolysis reaction of tert-butyl ester, formic acid, triethylsilane and
25 the like may be added to reductively-trap tert-butyl cation which is by-produced.

[0188]

When dehydration reaction is carried out in each step, examples of the dehydrating agent to be used include sulfuric
30 acid, diphosphorus pentaoxide, phosphorus oxychloride, N,N'-dicyclohexylcarbodiimide, alumina, polyphosphoric acid and the like.

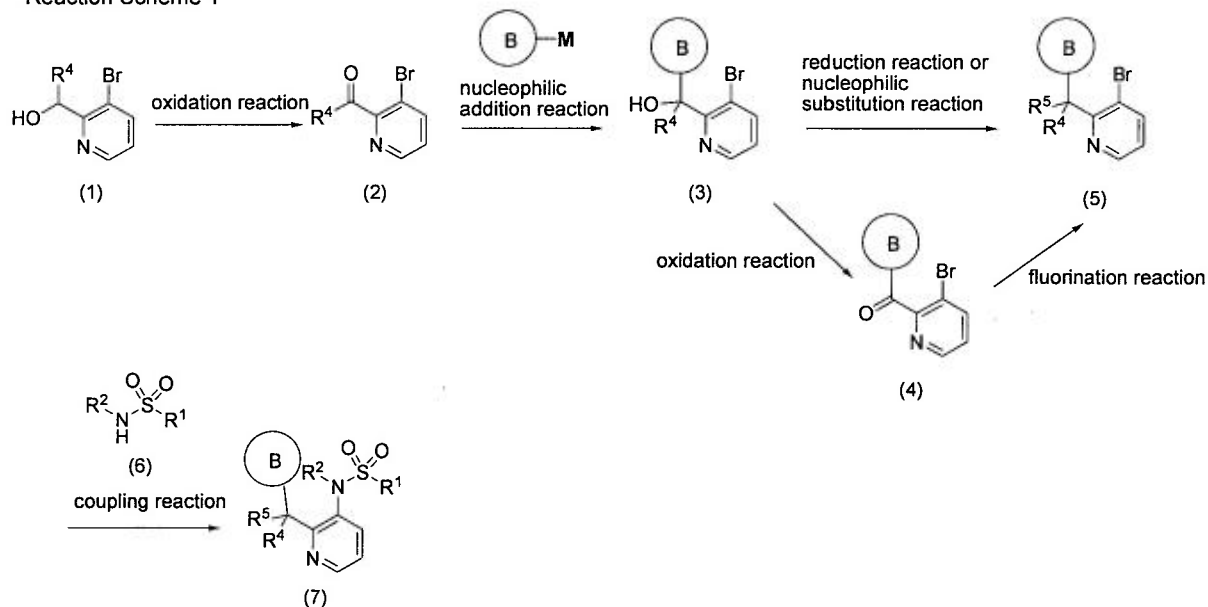
[0189]

35 Compound (7) used in the below-mentioned Reaction Scheme

3 can be produced from compound (1) according to the method shown in the following Reaction Scheme 1. As used herein, M is a magnesium halide, or an alkali metal such as lithium and the like, and the other symbols are as defined above.

5 [0190]

Reaction Scheme 1



[0191]

Compound (1) may be commercially available, or can be produced according to a method known per se or a method analogous thereto.

[0192]

Compound (3) can be produced by subjecting compound (2) to a nucleophilic addition reaction with an organometallic reagent. Examples of the organometallic reagent to be used include organic magnesium halides, organic lithiums and the like. The organometallic reagent can be prepared according to a method known per se.

[0193]

Compound (4) can be produced, for example, by subjecting compound (3) wherein R⁴ is a hydrogen atom to an oxidation reaction.

[0194]

Compound (5) wherein R⁵ is a hydrogen atom can be produced, for example, by subjecting compound (3) to a

reduction reaction.

[0195]

Compound (5) wherein R⁵ is a C₁₋₆ alkoxy group can be produced, for example, by subjecting compound (3) to a nucleophilic substitution reaction with an electrophile in the presence of a base. Examples of the electrophile to be used include alkyl halides and the like. Examples of the base to be used include alkali metal hydrides and the like.

[0196]

Compound (5) wherein R⁴ and R⁵ are both fluorine atoms can be produced, for example, by subjecting compound (4) to a fluorination reaction. Examples of the reagent to be used include fluorinating agents such as diethylaminosulfur trifluoride (DAST), bis(2-methoxyethyl)aminosulfur trifluoride (BAST), 1,1,2,2-tetrafluoroethyl-N,N-dimethylamine (TFEDMA) and the like.

[0197]

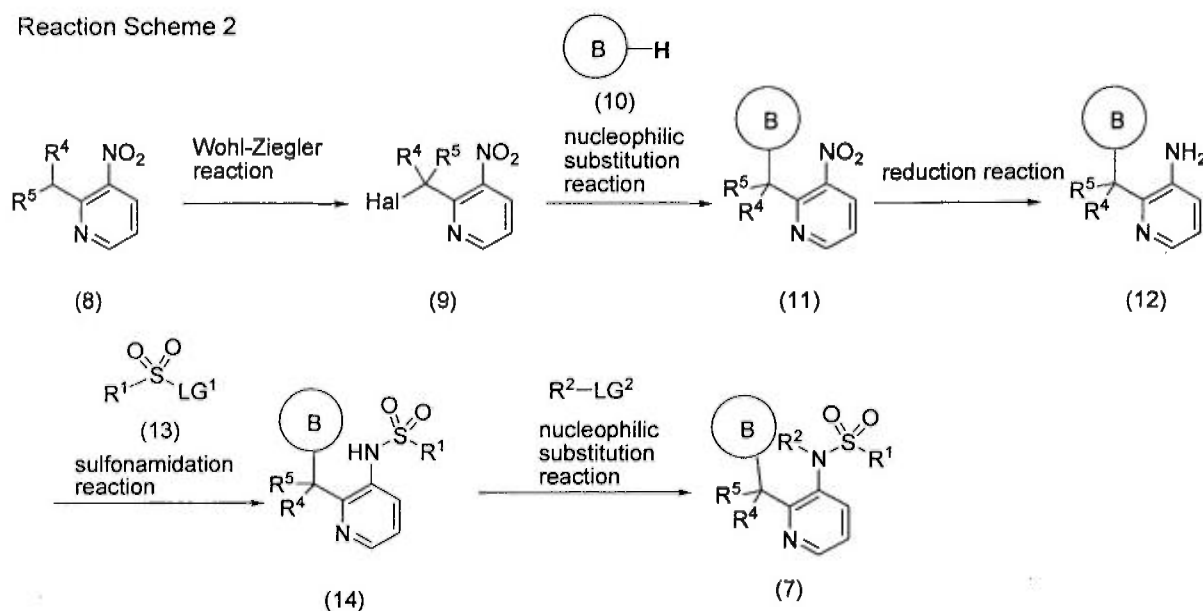
Compound (7) can be produced by subjecting compound (5) and compound (6) to a coupling reaction. Compound (6) may be commercially available, or can be produced according to a method known per se or a method analogous thereto.

[0198]

Compound (7) can also be produced from compound (8) according to the method shown in the following Reaction Scheme 2. As used herein, Hal is a halogen atom, LG¹ and LG² are each independently a leaving group, and the other symbols are as defined above.

[0199]

Reaction Scheme 2



[0200]

Examples of the "leaving group" represented by LG¹ or LG² include halogen atoms, optionally halogenated C₁₋₆ alkylsulfonyloxy groups (e.g., methanesulfonyloxy, ethanesulfonyloxy, trifluoromethanesulfonyloxy), C₆₋₁₄ arylsulfonyloxy groups optionally substituted by C₁₋₆ alkyl (e.g., benzenesulfonyloxy, toluenesulfonyloxy) and the like.

[0201]

Compound (8) may be commercially available, or can be produced according to a method known per se or a method analogous thereto.

[0202]

Compound (11) can be produced by subjecting compound (9) to a nucleophilic substitution reaction with compound (10). Examples of the compound (10) to be used include cyclic amines (e.g., pyrrolidine, piperidine), pyrazole and the like. In addition, a base may be added to the reaction system. Examples of the base include inorganic bases, organic bases, alkali metal hydrides and the like.

[0203]

Compound (14) can be produced by subjecting compound (12) to a sulfonamidation reaction with compound (13) in the presence of a base. Examples of the base to be used include

organic bases and the like. Compound (13) may be commercially available, or can be produced according to a method known per se.

[0204]

5 Compound (7) can be produced by subjecting compound (14) to a nucleophilic substitution reaction with an electrophile in the presence of a base. Examples of the electrophile to be used include alkyl halides and the like. Examples of the base to be used include alkali metal hydrides and the like.

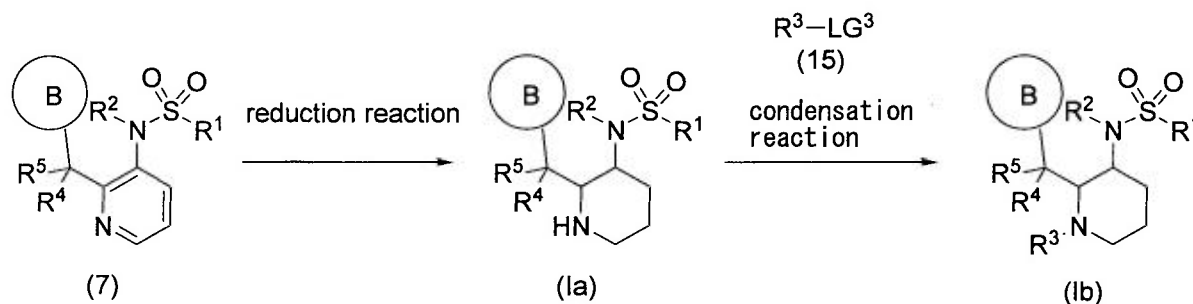
10 [0205]

Compound (Ia) and compound (Ib), which are compound (I) wherein Ring A is a piperidine ring, can be produced from compound (7) according to the method shown in the following Reaction Scheme 3. As used herein, LG³ is a leaving group, and

15 the other symbols are as defined above.

[0206]

Reaction Scheme 3



[0207]

Examples of the "leaving group" represented by LG³ include those exemplified as the "leaving group" represented by LG¹ or LG².

[0208]

Compound (Ia) can be produced by subjecting compound (7) to a reduction reaction. Examples of the reducing agent to be used include catalysts such as palladium carbon, rhodium carbon, platinum carbon and the like.

[0209]

Compound (Ib) can be produced by subjecting compound (Ia) and compound (15) to a condensation reaction. Examples of the

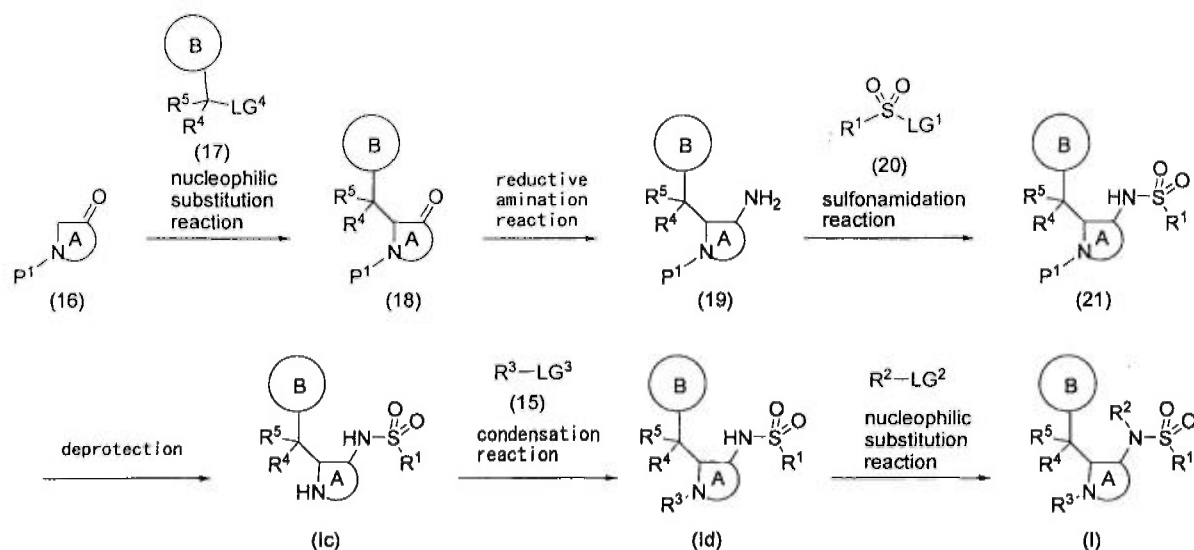
compound (15) to be used include acyl halides such as acid chlorides, acid bromides, alkyl chloroformates, carbamoyl chlorides and the like; activated carboxylic acids such as acid anhydrides, activated esters, sulfate esters and the like.

5 Examples of the activating agent for carboxylic acid include carbodiimide condensing agents such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD) and the like; triazine condensing agents such as 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride-n-hydrate
10 (DMT-MM) and the like; carbonate ester condensing agents such as 1,1-carbonyldiimidazole (CDI) and the like; diphenylphosphoryl azide (DPPA); benzotriazol-1-yloxy-trisdimethylaminophosphonium salt (BOP reagent); 2-chloro-1-methyl-pyridinium iodide (Mukaiyama reagent); thionyl chloride;
15 lower alkyl haloformates such as ethyl chloroformate and the like; O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU); sulfuric acid; combinations thereof, and the like. In addition, a base may be added to the reaction system. Examples of the base include inorganic bases,
20 organic bases and the like. When a carbodiimide condensing agent is used, an additive such as 1-hydroxybenzotriazole (HOBT), N-hydroxysuccinimide (HOSu), dimethylaminopyridine (DMAP) and the like may be further added to the reaction system.
[0210]

25 Compound (Ic) and compound (Id), which are compound (I) wherein R^2 is a hydrogen atom, and compound (I) can be produced from compound (16) according to the method shown in the following Reaction Scheme 4. As used herein, P^1 is a protecting group, LG^4 is a leaving group, and other symbols are
30 as defined above.

[0211]

Reaction Scheme 4



[0212]

Examples of the "protecting group" represented by P^1 include those exemplified as the above-mentioned "protecting group for an amino group and an aromatic heterocycle such as imidazole, pyrrole, indole and the like".

Examples of the "leaving group" represented by LG^4 include those exemplified as the "leaving group" represented by LG^1 or LG^2 .

10 [0213]

Compound (16) and compound (17) may be commercially available, or can be produced according to a method known per se or a method analogous thereto.

[0214]

15 Compound (18) can be produced by subjecting compound (16) to a nucleophilic substitution reaction with compound (17) in the presence of a base. Examples of the base to be used include alkali metal hydrides, organic lithiums and the like. Alternatively, compound (18) can also be produced by two step
20 reaction, i.e., by converting compound (16) to the corresponding enamine, and then reacting the enamine with compound (17).

Examples of the amine to be used for the enamine formation include pyrrolidine, morpholine, N,N-
25 dimethylhydrazine and the like. A base may be added to the

reaction system of the enamine and compound (17). Examples of the base include alkali metal hydrides, organic lithiums and the like. In addition, a catalyst may be added to the reaction system in order to promote the reaction. Examples of the catalyst to be used include tetrabutylammonium iodide and the like.

[0215]

Compound (19) can be produced by subjecting compound (18) to a reductive amination reaction. Examples of the reducing agent to be used include sodium triacetoxyborohydride, sodium cyanoborohydride, hydrogen, formic acid and the like. Examples of the amine to be used include ammonia and the like. In addition, a metal catalyst may be added to the reaction system. Examples of the catalyst to be used include iridium catalysts and the like. Alternatively, Compound (19) can also be produced by two step reaction, i.e., by converting compound (18) to the corresponding oxime, and then subjecting the oxime to a reduction reaction. Examples of the amines to be used for the oxime formation include hydroxylamine, O-methylhydroxylamine and the like. Examples of the reducing agent to be used include boranes such as borane tetrahydrofuran complex and the like, sodium borohydride and the like. In addition, a metal catalyst may be added to the reaction system. Examples of the catalyst to be used include molybdenum trioxide and the like.

[0216]

Compound (21) can be produced by subjecting compound (19) to a sulfonamidation reaction with compound (20) in the presence of a base. Examples of the base to be used include organic bases and the like. Compound (20) may be commercially available, or can be produced according to a method known per se.

[0217]

Compound (Id) can be produced by subjecting compound (Ic) and compound (15) to a condensation reaction. Examples of the

compound (15) to be used include acyl halides such as acid chlorides, acid bromides, alkyl chloroformates, carbamoyl chlorides and the like; activated carboxylic acids such as acid anhydrides, activated esters, sulfate esters and the like.

5 Examples of the activating agent for carboxylic acid include carbodiimide condensing agents such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD) and the like; triazine condensing agents such as 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride-n-hydrate
10 (DMT-MM) and the like; carbonate ester condensing agents such as 1,1-carbonyldiimidazole (CDI) and the like; diphenylphosphoryl azide (DPPA); benzotriazol-1-yloxy-trisdimethylaminophosphonium salt (BOP reagent); 2-chloro-1-methyl-pyridinium iodide (Mukaiyama reagent); thionyl chloride;
15 lower alkyl haloformates such as ethyl chloroformate and the like; O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU); sulfuric acid; combinations thereof, and the like. In addition, a base may be added to the reaction system. Examples of the base include inorganic bases,
20 organic bases and the like. When a carbodiimide condensing agent is used, an additive such as 1-hydroxybenzotriazole (HOBT), N-hydroxysuccinimide (HOSu), dimethylaminopyridine (DMAP) and the like may be further added to the reaction system.
[0218]

25 Compound (I) can be produced by subjecting compound (Id) to a nucleophilic substitution reaction with an electrophile in the presence of a base. Examples of the electrophile to be used include alkyl halide and the like. Examples of the base to be used include alkali metal hydrides and the like.

30 [0219]

In the thus-obtained compound (I), an intramolecular functional group can also be converted to an object functional group by a combination of chemical reactions known per se. Examples of the chemical reaction include oxidation reaction,
35 reduction reaction, alkylation reaction, acylation reaction,

ureation reaction, hydrolysis reaction, amination reaction, esterification reaction, aryl coupling reaction, deprotection reaction and the like.

[0220]

5 In the above-mentioned production method, when a starting compound has an amino group, a carboxyl group, a hydroxy group, a carbonyl group or a mercapto group as a substituent, a protecting group generally used in the peptide chemistry may be introduced into these groups, and the object compound can be
10 obtained by removing the protecting group as necessary after the reaction.

[0221]

Compound (I) obtained by the above-mentioned production method can be isolated and purified by a known means, such as
15 solvent extraction, liquid conversion, phase transfer, crystallization, recrystallization, chromatography and the like.

When compound (I) contains optical isomer, stereoisomer, regio isomer and rotamer, these compounds are also included in compound (I), and each can be obtained as a single product by a
20 synthesis method or a separation method known per se. For example, when an optical isomer exists in compound (I), an optical isomer resolved from the compound is also encompassed in compound (I).

Here, an optical isomer can be produced by a method known
25 per se.

Compound (I) may be a crystal.

A crystal of compound (I) (hereinafter sometimes to be abbreviated as the crystal of the present invention) can be produced by crystallizing compound (I), by applying a
30 crystallization method known per se.

[0222]

In the present specification, the melting point means a melting point measured, for example, by micro melting point apparatus (Yanako, MP-500D or Buchi, B-545), DSC (differential
35 scanning calorimetry analysis) apparatus (METTLER TOLEDO, DSC1)

and the like.

Generally, the melting point sometimes varies depending on the measurement device, measurement condition and the like. The crystal in the present specification may be a crystal
5 showing a melting point different from the values described in the present specification as long as the difference is within a general error range.

The crystal of the present invention is superior in the physicochemical properties (e.g., melting point, solubility,
10 stability) and biological properties (e.g., pharmacokinetics (absorbability, distribution, metabolism, excretion), efficacy expression), and is extremely useful as a medicament.

[0223]

Compound (I) may be used as a prodrug. A prodrug of the
15 compound (I) means a compound which is converted to the compound (I) of the present invention with a reaction due to an enzyme, an gastric acid, etc. under the physiological condition in the living body, that is, a compound which is converted to the compound (I) of the present invention with oxidation,
20 reduction, hydrolysis, etc. according to an enzyme; a compound which is converted to the compound (I) of the present invention by hydrolysis etc. due to gastric acid, etc.

A prodrug of compound (I) may be a compound obtained by subjecting an amino group in compound
25 (I) to an acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting an amino group in compound (I) to an eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation,
30 pivaloyloxymethylation and tert-butylation, etc.); a compound obtained by subjecting a hydroxy group in compound (I) to an acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting an hydroxy group in compound (I) to an acetylation, palmitoylation, propanoylation,
35 pivaloylation, succinylation, fumarylation, alanylation,

dimethylaminomethylcarbonylation, etc.);

a compound obtained by subjecting a carboxyl group in compound (I) to an esterification or amidation (e.g., a compound obtained by subjecting a carboxyl group in compound (I) to an ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification and methylamidation, etc.) and the like. Any of these compounds can be produced from compound (I) by a method known *per se*.

[0224]

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

In the present specification, a prodrug may form a salt, and as such salt, those exemplified as a salt of the compound represented by the above-mentioned formula (I) can be mentioned.

Compound (I) may be labeled with an isotope (e.g., ^3H , ^{13}C , ^{14}C , ^{18}F , ^{35}S , ^{125}I) and the like.

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

Furthermore, compound (I) may be a hydrate or a non-hydrate, or a non-solvate (e.g., anhydride), or a solvate (e.g., hydrate).

Compound (I) also encompasses a deuterium conversion form wherein ^1H is converted to $^2\text{H}(\text{D})$.

Furthermore, compound (I) may be a pharmaceutically acceptable cocrystal or cocrystal salt. The cocrystal or cocrystal salt means a crystalline substance constituted with

two or more special solids at room temperature, each having different physical properties (e.g., structure, melting point, melting heat, hygroscopicity, solubility and stability). The cocrystal or cocrystal salt can be produced by a
5 cocrystallization method known per se.

[0225]

Compound (I) or a prodrug thereof (hereinafter sometimes to be simply abbreviated as the compound of the present invention) can be used as it is or in the form of a
10 pharmaceutical composition (also referred to as a medicament) by mixing with a pharmacologically acceptable carrier etc. to mammals (e.g., human, mouse, rat, rabbit, dog, cat, bovine, horse, swine, monkey) as an agent for the prophylaxis or treatment of various diseases mentioned below.

15 As pharmacologically acceptable carriers, various organic or inorganic carrier substances conventionally used as preparation materials can be used. These are incorporated as excipient, lubricant, binder and disintegrant for solid preparations; or solvent, solubilizing agent, suspending agent,
20 isotonicity agent, buffer and soothing agent for liquid preparations; and the like; and preparation additives such as preservative, antioxidant, colorant, sweetening agent and the like can be added as necessary.

[0226]

25 Preferable examples of the excipient include lactose, sucrose, D-mannitol, D-sorbitol, starch, gelatinated starch, dextrin, crystalline cellulose, low-substituted hydroxypropylcellulose, sodium carboxymethylcellulose, gum arabic, pullulan, light anhydrous silicic acid, synthetic
30 aluminum silicate and magnesium alumino metasilicate.

Preferable examples of the lubricant include magnesium stearate, calcium stearate, talc and colloidal silica.

Preferable examples of the binder include gelatinated starch, sucrose, gelatin, gum arabic, methylcellulose,
35 carboxymethylcellulose, sodium carboxymethylcellulose,

crystalline cellulose, sucrose, D-mannitol, trehalose, dextrin, pullulan, hydroxypropylcellulose, hydroxypropylmethylcellulose and polyvinylpyrrolidone.

Preferable examples of the disintegrant include lactose,
5 sucrose, starch, carboxymethylcellulose, calcium carboxymethylcellulose, croscarmellose sodium, sodium carboxymethyl starch, light anhydrous silicic acid and low-substituted hydroxypropylcellulose.

Preferable examples of the solvent include water for
10 injection, physiological brine, Ringer's solution, alcohol, propylene glycol, polyethylene glycol, sesame oil, corn oil, olive oil and cottonseed oil.

Preferable examples of the solubilizing agent include polyethylene glycol, propylene glycol, D-mannitol, trehalose,
15 benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, sodium salicylate and sodium acetate.

Preferable examples of the suspending agent include surfactants such as stearyltriethanolamine, sodium lauryl
20 sulfate, lauryl aminopropionate, lecithin, benzalkonium chloride, benzethonium chloride, glycerol monostearate and the like; hydrophilic polymers such as poly(vinyl alcohol), polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose,
25 hydroxypropylcellulose and the like, polysorbates; and polyoxyethylene hydrogenated castor oil.

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

Preferable examples of the buffer include buffers of
30 phosphate, acetate, carbonate, citrate etc.

Preferable examples of the soothing agent include benzyl alcohol.

Preferable examples of the preservative include p-oxybenzoate esters, chlorobutanol, benzyl alcohol, phenethyl
35 alcohol, dehydroacetic acid and sorbic acid.

Preferable examples of the antioxidant include sulfite salts and ascorbate salts.

Preferable examples of the colorant include aqueous food tar colors (e.g., food colors such as Food Color Red Nos. 2 and 3, Food Color Yellow Nos. 4 and 5, Food Color Blue Nos. 1 and 2 and the like food colors), water insoluble lake dyes (e.g., aluminum salt of the above-mentioned aqueous food tar color), natural dyes (e.g., β -carotene, chlorophyll, red iron oxide) and the like.

Preferable examples of the sweetening agent include saccharin sodium, dipotassium glycyrrhizinate, aspartame and stevia.

[0227]

Examples of the dosage form of the above-mentioned pharmaceutical composition include oral preparations such as tablet (including sugar-coated tablet, film-coated tablet, sublingual tablet, orally disintegrating tablet, buccal tablet), capsule (including soft capsule, microcapsule), pill, granule, powder, troche, syrup, liquid, emulsion, suspension, aerosol, films (e.g., orally disintegrable films, oral mucosa-adhesive film) and the like; and parenteral agents such as injection (e.g., subcutaneous injection, intravenous injection, intramuscular injection, intraperitoneal injection, drip infusion), external preparation (e.g., transdermal absorption type preparation, ointment, lotion, adhesive preparation), suppository (e.g., rectal suppository, vaginal suppository), pellet, nasal preparation, pulmonary preparation (inhalant), eye drop and the like. The compound and medicament of the present invention can be respectively safely administered orally or parenterally (e.g., intrarectal, intravenous, intraarterial, intramuscular, subcutaneous, intraorgan, intranasal, intradermal, instillation, intracerebral, intravaginal, intraperitoneal, intratumoral, proximal tumor administrations, and administration to the lesion).

These preparations may be a release control preparation

(e.g., sustained-release microcapsule) such as an immediate-release preparation, a sustained-release preparation and the like.

[0228]

5 The pharmaceutical composition can be produced according to a method conventionally used in the field of pharmaceutical formulation, for example, the method described in the Japanese Pharmacopoeia, and the like.

 While the content of the compound of the present
10 invention in the pharmaceutical composition of the present invention varies depending on the dosage form, dose of the compound of the present invention and the like, it is, for example, about 0.1 to 100 wt%.

 When an oral preparation is produced, coating may be
15 applied where necessary for the purpose of taste masking, enteric solubility or sustainability.

[0229]

 Examples of the coating base used for coating include sugar coating base, water-soluble film coating base, enteric
20 film coating base, and sustained-release film coating base.

 As the sugar coating base, sucrose is used, and one or more kinds selected from talc, and the precipitated calcium carbonate, gelatin, gum arabic, pullulan, carnauba wax and the like may be further used in combination.

25 Examples of the water-soluble film coating base include cellulose polymers such as hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, methylhydroxyethylcellulose and the like; synthetic polymers such as polyvinyl acetal diethylaminoacetate,
30 aminoalkylmethacrylate copolymer E [Eudragit E (trade name)], polyvinylpyrrolidone and the like; and polysaccharides such as pullulan and the like.

 Examples of the enteric film coating base include cellulose polymers such as hydroxypropylmethylcellulose
35 phthalate, hydroxypropylmethylcellulose acetate succinate,

carboxymethylethylcellulose, cellulose acetate phthalate and the like; acrylic acid polymers such as methacrylic acid copolymer L [Eudragit L (trade name)], methacrylic acid copolymer LD [Eudragit L-30D-55 (trade name)], methacrylic acid
5 copolymer S [Eudragit S (trade name)] and the like; and naturally-occurring substances such as shellac and the like.

Examples of the sustained-release film coating base include cellulose polymers such as ethylcellulose and the like; and acrylic acid polymers such as aminoalkylmethacrylate
10 copolymer RS [Eudragit RS (trade name)], ethyl acrylate-methyl methacrylate copolymer suspension [Eudragit NE (trade name)] and the like.

Two or more kinds of the above-mentioned coating bases may be used in a mixture at an appropriate ratio. In addition,
15 for example, light shielding agents such as titanium oxide, red ferric oxide and the like may also be used during coating.

[0230]

Since the compound of the present invention shows low toxicity (e.g., acute toxicity, chronic toxicity, genetic
20 toxicity, reproductive toxicity, cardiotoxicity, carcinogenicity) and less side effects, it can be used as a prophylactic or therapeutic agent, or diagnostic agent for various diseases in mammals (e.g., human, bovine, horse, dog, cat, monkey, mouse, rat).

25 [0231]

The compound of the present invention has an excellent an orexin type 2 receptor agonist activity, and may treat, prevent or ameliorate the risk of various neurological and psychiatric diseases associated with an orexin type 2 receptor. The
30 compound of the present invention is useful as an agent for the prophylaxis or treatment of various diseases such as narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome accompanied by narcolepsy-like symptoms, hypersomnia syndrome accompanied by daytime hypersomnia (e.g.,
35 Kleine Levin syndrome, major depression with hypersomnia, Lewy

body dementia, Parkinson's disease, progressive supranuclear
paralysis, Prader-Willi syndrome, Mobius syndrome,
hypoventilation syndrome, Niemann-Pick disease type C, brain
contusion, cerebral infarction, brain tumor, muscular dystrophy,
5 multiple sclerosis, acute disseminated encephalomyelitis,
Guillain-Barre syndrome, Rasmussen's encephalitis, Wernicke's
encephalitis, limbic encephalitis, Hashimoto's encephalopathy),
coma, loss of consciousness, obesity (e.g., malignant
mastocytosis, exogenous obesity, hyperinsular obesity,
10 hyperplasmic obesity, hypop hyseal adiposity, hypoplastic
obesity, hypothyroid obesity, hypothalamic obesity, symptomatic
obesity, infantile obesity, upper body obesity, alimentary
obesity, hypogonadal obesity, systemic mastocytosis, simple
obesity, central obesity), insulin resistance syndrome,
15 Alzheimer's disease, disturbance of consciousness such as coma
and the like, side effects and complications due to anesthesia,
sleep disturbance, sleep problem, insomnia, Intermittent sleep,
nocturnal myoclonus, REM sleep interruption, jet lag, jet lag
syndrome, sleep disorder of alternating worker, sleep disorder,
20 night terror, depression, major depression, sleepwalking
disease, enuresis, sleep disorder, Alzheimer's dusk, diseases
associated with circadian rhythm, fibromyalgia, condition
arising from decline in the quality of sleep, overeating,
obsessive compulsive eating disorder, obesity-related disease,
25 hypertension, diabetes, elevated plasma insulin concentration
and insulin resistance, hyperlipidemia, hyperlipemia,
endometrial cancer, breast cancer, prostate cancer, colorectal
cancer, cancer, osteoarthritis, obstructive sleep apnea,
cholelithiasis, gallstones, cardiac disease, abnormal heartbeat,
30 arrhythmia, myocardial infarction, congestive cardiac failure,
cardiac failure, coronary heart disease, cardiovascular
disorder, sudden death, polycysticovarian disease,
craniopharingioma, Froelich's syndrome, growth hormone
deficient, normal mutant short stature, Turner's syndrome,
35 children suffering from acute lymphoblastic leukemia, syndrome

X, reproductive hormone abnormality, declining fertility, infertility, male gonadal function decline, sexual and reproductive dysfunction such as female male hirsutism, fetal defects associated with pregnant women obesity,

5 gastrointestinal motility disorders such as obesity-related gastroesophageal reflux, obesity hypoventilation syndrome (Pickwick syndrome), respiratory diseases such as dyspnea, inflammation such as systemic inflammation of the vascular system, arteriosclerosis, hypercholesterolemia, hyperuricemia,

10 lower back pain, gall bladder disease, gout, kidney cancer, risk of secondary outcomes of obesity, such as lowering the risk of left ventricular hypertrophy, migraine pain, headache, neuropathic pain, Parkinson's disease, psychosis, schizophrenia, facial flushing, night sweats, diseases of the genital/urinary

15 system, diseases related to sexual function or fertility, dysthymic disorder, bipolar disorder, bipolar I disorder, bipolar II disorder, cyclothymic disorder, acute stress disorder, agoraphobia, generalized anxiety disorder, obsessive disorder, panic attack, panic disorder, posttraumatic stress

20 disorder, separation anxiety disorder, social phobia, anxiety disorder, acute neurological and psychiatric disorders such as cardiac bypass surgery and post-transplant cerebral deficit, stroke, ischemic stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic

25 nerve injury, Huntington's chorea, amyotrophic lateral sclerosis, multiple sclerosis, eye damage, retinopathy, cognitive impairment, muscle spasm, tremor, epilepsy, disorders associated with muscle spasticity, delirium, amnestic disorder, age-related cognitive decline, schizoaffective disorder,

30 delusional disorder, drug addiction, dyskinesia, chronic fatigue syndrome, fatigue, medication-induced Parkinsonism syndrome, Jill-do La Tourette's syndrome, chorea, myoclonus, tic, restless legs syndrome, dystonia, dyskinesia, attention deficit hyperactivity disorder (ADHD), behavior disorder,

35 urinary incontinence, withdrawal symptoms, trigeminal neuralgia,

hearing loss, tinnitus, nerve damage, retinopathy, macular degeneration, vomiting, cerebral edema, pain, bone pain, arthralgia, toothache, cataplexy, and traumatic brain injury (TBI).

5 [0232]

Particularly, the compound of the present invention is useful as an agent for the prophylaxis or treatment of narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome accompanied by narcolepsy-like
10 symptoms, hypersomnia syndrome accompanied by daytime hypersomnia (e.g., Parkinson's disease, Guillain-Barre syndrome and Kleine Levin syndrome), Alzheimer's disease, obesity, insulin resistance syndrome, cardiac failure, diseases related to bone loss, sepsis, disturbance of consciousness such as coma
15 and the like, side effects and complications due to anesthesia, and the like, or anesthetic antagonist.

[0233]

While the dose of the compound of the present invention varies depending on the subject of administration,
20 administration route, target disease, symptom and the like, for example, when the compound of the present invention is administered orally or parenterally to an adult patient, its dose is for example, about 0.01 to 100 mg/kg body weight per dose, preferably 0.1 to 50 mg/kg body weight per dose and more
25 preferably 0.5 to 20 mg/kg body weight per dose. This amount is desirably administered in one to 3 portions daily.

[0234]

The compound of the present invention can be used in combination with other drugs (hereinafter to be abbreviated as
30 concomitant drug).

By combining the compound of the present invention and a concomitant drug, a superior effect, for example,
(1) the dose can be reduced as compared to single administration of the compound of the present invention or a
35 concomitant drug,

(2) the drug to be combined with the compound of the present invention can be selected according to the condition of patients (mild case, severe case and the like),

(3) the period of treatment can be set longer by selecting a concomitant drug having different action and mechanism from the compound of the present invention,

(4) a sustained treatment effect can be designed by selecting a concomitant drug having different action and mechanism from the compound of the present invention,

(5) a synergistic effect can be afforded by a combined use of the compound of the present invention and a concomitant drug, and the like, can be achieved.

[0235]

In the present specification, the compound of the present invention and a concomitant drug used in combination are referred to as the "combination agent of the present invention".

When using the combination agent of the present invention, the administration time of the compound of the present invention and the concomitant drug is not restricted, and the compound of the present invention or a pharmaceutical composition thereof, or the concomitant drug or a pharmaceutical composition thereof can be administered to an administration subject simultaneously, or may be administered at different times. The dosage of the concomitant drug may be determined according to the dose clinically used, and can be appropriately selected depending on an administration subject, administration route, disease, combination and the like.

The administration mode of the combination agent of the present invention and the concomitant drug is not particularly limited, and the compound of the present invention and the concomitant drug only need to be combined on administration. Examples of such administration mode include the following:

(1) administration of a single preparation obtained by simultaneously processing the compound of the present invention and the concomitant drug, (2) simultaneous administration of

two kinds of preparations of the compound of the present invention and the concomitant drug, which have been separately produced, by the same administration route, (3) administration of two kinds of preparations of the compound of the present invention and the concomitant drug, which have been separately produced, by the same administration route in a staggered manner, (4) simultaneous administration of two kinds of preparations of the compound of the present invention and the concomitant drug, which have been separately produced, by different administration routes, (5) administration of two kinds of preparations of the compound of the present invention and the concomitant drug, which have been separately produced, by different administration routes in a staggered manner (e.g., administration in the order of the compound of the present invention and the concomitant drug, or in the reverse order) and the like.

The dose of the concomitant drug can be appropriately determined based on the dose employed in clinical situations. The mixing ratio of the compound of the present invention and a concomitant drug can be appropriately determined depending on the administration subject, administration route, target disease, symptom, combination and the like.

For example, the content of the compound of the present invention in the combination agent of the present invention differs depending on the form of a preparation, and usually from about 0.01 to about 100 wt%, preferably from about 0.1 to about 50 wt%, further preferably from about 0.5 to about 20 wt%, based on the whole preparation.

The content of the concomitant drug in the combination agent of the present invention differs depending on the form of a preparation, and usually from about 0.01 to about 100 wt%, preferably from about 0.1 to about 50 wt%, further preferably from about 0.5 to about 20 wt%, based on the whole preparation.

The content of additives such as a carrier and the like in the combination agent of the present invention differs

depending on the form of a preparation, and usually from about 1 to about 99.99 wt%, preferably from about 10 to about 90 wt%, based on the preparation.

Similar contents may be employed even when the compound
5 of the present invention and a concomitant drug are separately formulated into preparations.

[0236]

Examples of the concomitant drug include the followings.
A therapeutic drug for narcolepsy (e.g., methylphenidate,
10 amphetamine, pemoline, phenelzine, protriptyline, sodium oxybate, modafinil, caffeine), antiobesity drug (amphetamine, benzphetamine, bromocriptine, bupropion, diethylpropion, exenatide, fenfluramine, liothyronine, liraglutide, mazindol, methamphetamine, octreotide, orlistat,
15 phendimetrazine, phendimetrazine, phenmetrazine, phentermine, Qnexa (registered trade mark), phenylpropanolamine, pramlintide, propylhexedrine, recombinant leptin, sibutramine, topiramate, zimeclidine, zonisamide, Lorcaserin, metformin), acetylcholine esterase inhibitor (e.g., donepezil, rivastigmine, galanthamine,
20 zanzapril, idebenone, tacrine), antidementia agent (e.g., memantine), inhibitor of β amyloid protein production, secretion, accumulation, aggregation and/or deposition, β secretase inhibitor (e.g., 6-(4-biphenyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin, 6-(4-biphenyl)methoxy-2-(N,N-dimethylamino)methyltetralin, 6-(4-biphenyl)methoxy-2-(N,N-dipropylamino)methyltetralin, 2-(N,N-dimethylamino)methyl-6-(4'-methoxybiphenyl-4-yl)methoxytetralin, 6-(4-biphenyl)methoxy-2-[2-(N,N-diethylamino)ethyl]tetralin, 2-[2-(N,N-dimethylamino)ethyl]-6-(4'-methylbiphenyl-4-yl)methoxytetralin, 2-[2-(N,N-dimethylamino)ethyl]-6-(4'-methoxybiphenyl-4-yl)methoxytetralin, 6-(2',4'-dimethoxybiphenyl-4-yl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin, 6-[4-(1,3-benzodioxol-5-yl)phenyl]methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin, 6-(3',4'-dimethoxybiphenyl-4-yl)methoxy-2-[2-(N,N-

dimethylamino)ethyl]tetralin, an optically active form thereof, a salt thereof and a hydrate thereof, OM99-2 (WO01/00663)), γ secretase inhibitor, β amyloid protein aggregation inhibitor (e.g., PTI-00703, ALZHEMED (NC-531), PPI-368 (National
5 Publication of International Patent Application No. 11-514333), PPI-558 (National Publication of International Patent Application No. 2001-500852), SKF-74652 (Biochem. J. (1999), 340(1), 283-289)), β amyloid vaccine, β amyloid-degrading enzyme and the like, brain function enhancer (e.g., aniracetam,
10 nicergoline), therapeutic drug for Parkinson's disease [(e.g., dopamine receptor agonist (e.g., L-DOPA, bromocriptine, pergolide, talipexole, pramipexole, cabergoline, amantadine), monoamine oxidase enzyme (MAO) inhibitor (e.g., deprenyl, selegiline, remacemide, riluzole), anticholinergic agent (e.g.,
15 trihexyphenidyl, biperiden), COMT inhibitor (e.g., entacapone)], therapeutic drug for amyotrophic lateral sclerosis (e.g., riluzole etc., neurotrophic factor), therapeutic drug for abnormal behavior accompanying progress of dementia, wandering and the like (e.g., sedative, anti-anxiety drug), apoptosis
20 inhibitor (e.g., CPI-1189, IDN-6556, CEP-1347), neuronal differentiation • regenerate promoter (e.g., leteprinim, xaliproden; SR-57746-A), SB-216763, Y-128, VX-853, prosaptide, 5,6-dimethoxy-2-[2,2,4,6,7-pentamethyl-3-(4-methylphenyl)-2,3-dihydro-1-benzofuran-5-yl]isoindoline, 5,6-dimethoxy-2-[3-(4-
25 isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl]isoindoline, 6-[3-(4-isopropylphenyl)-2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl]-6,7-dihydro-5H-[1,3]dioxolo[4,5-f]isoindole and an optically active form, salt or hydrate thereof), non-steroidal antiinflammatory
30 agents (meloxicam, tenoxicam, indomethacin, ibuprofen, celecoxib, rofecoxib, aspirin, indomethacin etc.), steroid drug (dexamethasone, hexestrol, cortisone acetate etc.), disease-modifying anti-rheumatic drug (DMARDs), anti-cytokine drug (e.g., TNF inhibitor, MAP kinase inhibitor), therapeutic agent
35 for incontinence, frequent urination (e.g., flavoxate

hydrochloride, oxybutynin hydrochloride, propiverine hydrochloride), phosphodiesterase inhibitor (e.g., sildenafil(citrate)), dopamine agonist (e.g., apomorphine), antiarrhythmic drugs (e.g., mexiletine), sex hormone or a derivative thereof (e.g., progesterone, estradiol, estradiol benzoate), therapeutic agent for osteoporosis (e.g., alfacalcidol, calcitriol, elcatonin, calcitonin salmon, estriol, ipriflavone, pamidronate disodium, alendronate sodium hydrate, incadronate disodium), parathyroid hormone (PTH), calcium receptor antagonists, therapeutic drug for insomnia (e.g., benzodiazepines medicament, non-benzodiazepines medicament, melatonin agonist, orexin receptor antagonists), therapeutic drug for schizophrenia (e.g., typical antipsychotic agents such as haloperidol and the like; atypical antipsychotic agents such as clozapine, olanzapine, risperidone, aripiprazole and the like; medicament acting on metabotropic glutamate receptor or ion channel conjugated-type glutamate receptor; phosphodiesterase inhibitor), benzodiazepines medicament (chlordiazepoxide, diazepam, potassium clorazepate, lorazepam, clonazepam, alprazolam etc.), L-type calcium channel inhibitor (pregabalin etc.), tricyclic or tetracyclic antidepressant (imipramine hydrochloride, amitriptyline hydrochloride, desipramine hydrochloride, clomipramine hydrochloride etc.), selective serotonin reuptake inhibitor (fluvoxamine maleate, fluoxetine hydrochloride, citalopram hydrobromide, sertraline hydrochloride, paroxetine hydrochloride, escitalopram oxalate etc.), serotonin-noradrenaline reuptake inhibitor (venlafaxine hydrochloride, duloxetine hydrochloride, desvenlafaxine hydrochloride etc.), noradrenaline reuptake inhibitor (reboxetine mesylate etc.), mirtazapine, trazodone hydrochloride, nefazodone hydrochloride, bupropion hydrochloride, setiptiline maleate, 5-HT_{1A} agonist, (buspirone hydrochloride, tandospirone citrate, osemozotan hydrochloride etc.), 5-HT_{2A} antagonist, 5-HT_{2A} inverse agonist, 5-HT₃ antagonist (cyamemazine etc.), heart non-selective β inhibitor

(propranolol hydrochloride, oxprenolol hydrochloride etc.), histamine H₁ antagonist (hydroxyzine hydrochloride etc.), CRF antagonist, other antianxiety drug (meprobamate etc.), tachykinin antagonist (MK-869, saredutant etc.), medicament
5 that acts on metabotropic glutamate receptor, CCK antagonist, β 3 adrenaline antagonist (amibegron hydrochloride etc.), GAT-1 inhibitor (tiagabine hydrochloride etc.), N-type calcium channel inhibitor, carbonic anhydrase II inhibitor, NMDA glycine moiety agonist, NMDA antagonist (memantine etc.),
10 peripheral benzodiazepine receptor agonist, vasopressin antagonist, vasopressin V1b antagonist, vasopressin V1a antagonist, phosphodiesterase inhibitor, opioid antagonist, opioid agonist, uridine, nicotinic acid receptor agonist, thyroid hormone (T3, T4), TSH, TRH, MAO inhibitor (phenelzine
15 sulfate, tranylcypromine sulfate, moclobemide etc.), therapeutic drug for bipolar disorder (lithium carbonate, sodium valproate, lamotrigine, riluzole, felbamate etc.), cannabinoid CB1 antagonist (rimonabant etc.), FAAH inhibitor, sodium channel inhibitor, anti-ADHD drug (methylphenidate
20 hydrochloride, methamphetamine hydrochloride etc.), therapeutic drug for alcoholism, therapeutic drug for autism, therapeutic drug for chronic fatigue syndrome, therapeutic drug for spasm, therapeutic drug for fibromyalgia syndrome, therapeutic drug for headache, therapeutic drug for quitting smoking,
25 therapeutic drug for myasthenia gravis, therapeutic drug for cerebral infarction, therapeutic drug for mania, therapeutic drug for hypersomnia, therapeutic drug for pain, therapeutic drug for dysthymia, therapeutic drug for autonomic ataxia, therapeutic drug for male and female sexual dysfunction,
30 therapeutic drug for migraine, therapeutic drug for pathological gambler, therapeutic drug for restless legs syndrome, therapeutic drug for substance addiction, therapeutic drug for alcohol-related syndrome, therapeutic drug for irritable bowel syndrome, therapeutic drug for lipid
35 abnormality such as cholesterol-lowering drug (statin series

(pravastatin sodium, atorvastatin, simvastatin, rosuvastatin etc.), fibrate (clofibrate etc.), squalene synthetase inhibitor), therapeutic drug for abnormal behavior or suppressant of dromomania due to dementia (sedatives, antianxiety drug etc.), therapeutic drug for diabetes, therapeutic agent for diabetic complications, therapeutic drug for hypertension, therapeutic drug for hypotension, diuretic, chemotherapeutic agent, immunotherapeutic agent, antithrombotic agent, anti-cancer agent and the like.

10 [0237]

Two or more kinds of the above-mentioned concomitant drug may be used in a mixture at an appropriate ratio.

When the compound of the present invention is applied to each of the above-mentioned diseases, it can also be used in combination with biologics (e.g., antibody drug, nucleic acid or nucleic acid derivative, aptamer drug, vaccine preparation), or can be used in combination with a gene therapy method and the like, or can also be used in combination with a treatment in psychiatric field without using drugs.

20 Examples of the antibody drug and vaccine preparation include vaccine preparation against angiotensin II, vaccine preparation against CETP, CETP antibody, antibody against TNF α antibody and other cytokines, amyloid β vaccine preparation, vaccine for type 1 diabetes (e.g., DIAPEP-277 of Peptor), anti-HIV antibody and HIV vaccine preparation, as well as antibodies or vaccine preparations against cytokines, renin-angiotensin type enzymes and products thereof, antibodies or vaccine preparations against enzymes or proteins involved in blood lipid metabolism, antibodies or vaccines relating to enzymes and proteins involved in blood coagulation or fibrinolysis system, antibodies or vaccine preparations against proteins involved in sugar metabolism and insulin resistance, and the like. In addition, it can be used in combination with biologics relating to growth factors such as GH, IGF and the like.

35

Examples of the gene therapy method include a treatment method using gene relating to cytokine, renin-angiotensin type enzyme and product thereof, G protein, G protein conjugated receptor and phosphorylating enzyme thereof, a treatment method using a DNA decoy such as NF κ B decoy and the like, a treatment method using antisense, a treatment method using a gene relating to a enzyme or protein involved in blood lipid metabolism (e.g., a gene relating to metabolism, excretion and absorption of cholesterol or triglyceride or HDL-cholesterol or blood phospholipid), a treatment method using a gene relating to a enzyme or protein involved in angiogenesis therapy for peripheral vascular obstruction and the like (e.g., growth factors such as HGF, VEGF etc.), a treatment method using a gene relating to a protein involved in glucose metabolism and insulin resistance, antisense against cytokines such as TNF etc., and the like.

Examples of the treatment method in the psychiatric field without using drug include modified electroconvulsive therapy, deep brain stimulation therapy, repetitive transcranial magnetic stimulation therapy, psychotherapy including cognitive behavioral therapy and the like.

The compound of the present invention can also be used in combination with various organ regeneration methods such as cardiac regeneration, renal regeneration, pancreatic regeneration, revascularization and the like, cell transplantation therapy utilizing bone marrow cells (bone marrow-derived mononuclear cell, myelogenic stem cell), or artificial organ utilizing tissue engineering (e.g., artificial blood vessel, cardiomyocyte sheet).

Examples

[0238]

The present invention is explained in detail in the following by referring to Examples, Experimental Examples and Formulation Examples. However, the examples do not limit the present invention and the examples can be modified within the

scope of the present invention.

The "room temperature" in the following Examples is generally about 10°C to about 35°C. The ratio for mixed solvent is, unless otherwise specified, a volume mixing ratio
5 and % means wt% unless otherwise specified.

[0239]

The elution by column chromatography in the Examples was performed under the observation by TLC (Thin Layer Chromatography) unless otherwise specified. In the observation
10 by TLC, 60 F₂₅₄ manufactured by Merck was used as a TLC plate, the solvent used as an elution solvent in column chromatography was used as an eluent, and UV detector was used for the detection. In silica gel column chromatography, the indication of NH means use of aminopropylsilane-bonded silica gel and the
15 indication of Diol means use of 3-(2,3-dihydroxypropoxy)propylsilane-bonded silica gel. In preparative HPLC (high performance liquid chromatography), the indication of C18 means use of octadecyl-bonded silica gel. The ratio for elution solvent is, unless otherwise specified, a
20 volume mixing ratio.

¹H NMR was measured by Fourier transform NMR. For the analysis of ¹H NMR, ACD/SpecManager (trade name) software and the like were used. Peaks of a hydroxyl group, an amino group and the like, having very mild proton peak, are not sometimes
25 described.

MS was measured by LC/MS. As the ionization method, ESI method, or APCI method was used. The data indicates actual measured value (found). While molecular ion peak is generally observed, a fragment ion is sometimes observed. In the case of
30 a salt, a molecular ion peak or fragment ion peak of free form is generally observed.

[0240]

The unit of sample concentration (c) for optical rotation ([α]_D) is g/100 mL.

35 Elemental analysis value (Anal.) is described as

calculated value (Calcd) and actual measured value (Found).

In Example, the cis/trans expression contained in compound name basically means a cis or trans mixture of two kinds of optical isomers when the corresponding partial
5 structure contains two asymmetric centers. Exceptionally, the cis/trans expression means a single optical isomer when indicated as "optional active".

Peaks by powder X-ray diffraction in the Examples mean peaks measured at room temperature by using Ultima IV (Rigaku
10 Corporation, Japan) using Cu K α radiation as a radiation source. The measurement conditions are as follows.

Electric pressure/Electric current: 40 kV/50 mA

Scan speed: 6 degrees/min

Scan range of 2 Theta: 2-35 degrees

15 The crystallinity by powder X-ray diffraction in the Examples was calculated by the Hermans method.

[0241]

In the following Examples, the following abbreviations are used.

20 mp: melting point

MS: mass spectrum

M: mol concentration

N: normality

CDCl₃: deuteriochloroform

25 DMSO-d₆: deuterodimethyl sulfoxide

¹H NMR: proton nuclear magnetic resonance

LC/MS: liquid chromatograph mass spectrometer

ESI: electrospray ionization, Electron Spray Ionization

30 APCI: atmospheric pressure chemical ionization, atmospheric pressure chemical ionization

Pd₂(dba)₃: tris(dibenzylideneacetone)dipalladium(0)

TFA: trifluoroacetic acid

DIPEA: N-ethyl-N-isopropylpropan-2-amine

DMF: N,N-dimethylformamide

35 THF: tetrahydrofuran

CH₃CN: acetonitrile
DME: 1,2-dimethoxyethane
MeOH: methanol
EtOH: ethanol
5 t-AmOH: 2-methyl-2-butanol
Pd(PPh₃)₄: palladium-triphenylphosphine (1:4)
tBuXphos: 2-di-tert-butylphosphino-2',4',6'-
triisopropylbiphenyl
XPhos Pd G3: (2-dicyclohexylphosphino-2',4',6'-triisopropyl-
10 1,1'-biphenyl) [2-(2'-amino-1,1'-biphenyl)]palladium(II)
methanesulfonate
PPh₃: triphenylphosphine
AcOH: acetic acid
TBAI: tetrabutylammonium iodide
15 TEA: triethylamine
(A-taPhos)₂PdCl₂: 4-(di-tert-butylphosphino)-N,N-
dimethylaniline-dichloropalladium (2:1)
T3P: 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-
trioxide
20 HATU: O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium
hexafluorophosphate
DMAP: N,N-dimethyl-4-aminopyridine
CPME: methoxycyclopentane
tBu: tert-butyl

25 Boc: tert-butoxycarbonyl
[0242]

Example 1

cis-2-(3-benzylbenzyl)-N-ethyl-3-
((methylsulfonyl)amino)piperidine-1-carboxamide

30 [0243]

A) 1-benzyl-3-bromobenzene

A mixture of (chloromethyl)benzene (3.78 g), (3-bromophenyl)boronic acid (6.00 g), Pd(PPh₃)₄ (1.73 g), sodium carbonate (3.16 g), DME (60 mL) and water (30 mL) was stirred
35 at 100°C for 15 hr. The reaction mixture was added to water,

and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether) to give the title compound (4.50 g).

^1H NMR (400 MHz, CDCl_3) δ 3.94 (2H, s), 7.10–7.25 (5H, m), 7.28–7.40 (4H, m).

[0244]

10 B) (3-benzylphenyl)(3-bromopyridin-2-yl)methanol

To a mixture of magnesium (147 mg) and THF (10 mL) were added iodine (catalytic amount) and 1-benzyl-3-bromobenzene (1.49 g). The mixture was heated under reflux for 1 hr, and cooled to 20°C. To the mixture was added 3-bromopyridine-2-carbaldehyde (750 mg), and the mixture was stirred under nitrogen atmosphere at 20°C for 15 hr. The reaction mixture was added to saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give the title compound (900 mg).

^1H NMR (400 MHz, CDCl_3) δ 3.97 (2H, s), 5.23 (1H, d, $J = 6.8$ Hz), 5.94 (1H, d, $J = 5.2$ Hz), 7.03–7.08 (1H, m), 7.10–7.31 (9H, m), 7.83–7.90 (1H, m), 8.59 (1H, dd, $J = 4.4, 1.2$ Hz).

[0245]

C) 2-(3-benzylbenzyl)-3-bromopyridine

To a mixture of (3-benzylphenyl)(3-bromopyridin-2-yl)methanol (900 mg) and TFA (5 mL) was added triethylsilane (10 mL). The mixture was stirred at 60°C for 40 hr, and the reaction mixture was concentrated under reduced pressure. The obtained residue was basified to pH 7 to 8 with saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed

with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give the title compound (1.10 g).

5 ¹H NMR (400 MHz, CDCl₃) δ3.95 (2H, s), 4.32 (2H, s), 7.00-7.08 (2H, m), 7.10-7.23 (6H, m), 7.25-7.30 (2H, m), 8.83 (1H, dd, J = 8.0, 1.6 Hz), 8.50 (1H, dd, J = 4.8, 1.6 Hz).

[0246]

D) N-(2-(3-benzylbenzyl)pyridin-3-yl)methanesulfonamide

10 A mixture of 2-(3-benzylbenzyl)-3-bromopyridine (1.10 g), methanesulfonamide (464 mg), tBuXphos (166 mg), Pd₂(dba)₃ (149 mg), cesium carbonate (1.59 g) and DME (20 mL) was stirred under nitrogen atmosphere at 85°C for 15 hr. The reaction mixture was added to water, and the mixture was extracted with
15 ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether) to give the title compound (260 mg).

20 ¹H NMR (400 MHz, CDCl₃) δ2.39 (3H, s), 3.93 (2H, s), 4.22 (2H, s), 6.21 (1H, brs), 7.00-7.35 (10H, m), 8.87 (1H, d, J = 7.2 Hz), 8.44 (1H, d, J = 3.6 Hz).

[0247]

E) N-(cis-2-(3-benzylbenzyl)piperidin-3-yl)methanesulfonamide

25 A mixture of N-(2-(3-benzylbenzyl)pyridin-3-yl)methanesulfonamide (200 mg), 5% rhodium on carbon (350 mg), THF (9 mL) and AcOH (1 mL) was stirred under hydrogen atmosphere of 35 psi at 20°C for 15 hr. The reaction mixture was filtered, and the filtrate was added to water. The mixture
30 was neutralized with saturated aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column
35 chromatography (dichloromethane/methanol) and preparative thin

layer chromatography to give the title compound (30 mg).

MS: [M+H]⁺ 359.0.

[0248]

F) cis-2-(3-benzylbenzyl)-N-ethyl-3-

5 ((methylsulfonyl)amino)piperidine-1-carboxamide

A mixture of N-(cis-2-(3-benzylbenzyl)piperidin-3-yl)methanesulfonamide (30 mg), TEA (25 mg) and isocyanatoethane (8 mg) in THF (5 mL) was stirred at 20°C for 15 hr. The reaction mixture was added to water, and the mixture was
10 extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by preparative HPLC (Fuji C18 (300x25), YMC 250x20, mobile phase: water/acetonitrile (0.1% aqueous ammonia solution)).
15 The obtained fraction was concentrated under reduced pressure, and freeze-dried to give the title compound (6 mg).
¹H NMR (400 MHz, CDCl₃) δ 0.72 (3H, t, J = 7.2 Hz), 1.60-1.90 (4H, m), 2.75-3.00 (8H, m), 3.50-3.60 (2H, m), 3.93 (2H, s), 4.05-4.15 (1H, m), 4.22-4.32 (1H, m), 4.59 (1H, d, J = 7.2 Hz),
20 7.03-7.08 (3H, m), 7.15-7.35 (6H, m).

[0249]

Example 19

tert-butyl cis-2-(biphenyl-3-ylmethyl)-3-

((methylsulfonyl)amino)piperidine-1-carboxylate

25 [0250]

A) tert-butyl 2-(biphenyl-3-ylmethyl)-3-oxopiperidine-1-carboxylate

To a mixture of tert-butyl 3-oxopiperidine-1-carboxylate (3.49 g) and toluene (38 mL) was added pyrrolidine (1.87 g) at
30 room temperature. The mixture was stirred at room temperature for 30 min, heated under reflux for 1 hr using Dean-Stark apparatus, and concentrated under reduced pressure. The obtained residue was mixed with CH₃CN (38 mL), and 3-(bromomethyl)biphenyl (5.19 g) was added thereto at room
35 temperature. The mixture was heated under reflux for 1 hr, and

the reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure.

5 The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (3.42 g).

MS: $[M+H-(tBu)]^+ 310.2$.

[0251]

B) tert-butyl cis-3-amino-2-(biphenyl-3-ylmethyl)piperidine-1-
10 carboxylate

To a mixture of tert-butyl 2-(biphenyl-3-ylmethyl)-3-oxopiperidine-1-carboxylate (3.41 g), THF (25 mL) and MeOH (25 mL) was added ammonium acetate (7.19 g) at room temperature. The mixture was stirred at room temperature for 1 hr, and
15 sodium triacetoxyborohydride (3.56 g) was added thereto. The mixture was stirred at room temperature for 18 hr. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution at 0°C, and the mixture was
20 extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (1.67 g).
MS: $[M+H]^+ 367.2$.

25 [0252]

C) tert-butyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate

To a mixture of tert-butyl cis-3-amino-2-(biphenyl-3-ylmethyl)piperidine-1-carboxylate (1.66 g), THF (15 mL) and TEA
30 (0.917 g) was added methanesulfonyl chloride (0.623 g) at 0°C. The mixture was stirred at room temperature for 1 hr, poured into ice water, and extracted with ethyl acetate. The organic layer was separated, washed with aqueous sodium hydrogencarbonate solution and saturated brine, dried over
35 anhydrous magnesium sulfate, and concentrated under reduced

pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.75 g).

¹H NMR (300 MHz, CDCl₃) δ 1.11 (9H, s), 1.61-1.74 (2H, m),
5 1.75-1.84 (1H, m), 1.88-1.97 (1H, m), 2.83-2.98 (3H, m), 3.00
(3H, s), 3.57-3.68 (1H, m), 4.04-4.12 (1H, m), 4.41 (1H, d, J =
7.9 Hz), 4.73-4.83 (1H, m), 7.17 (1H, d, J = 7.2 Hz), 7.30-7.39
(3H, m), 7.39-7.46 (3H, m), 7.52-7.58 (2H, m).

[0253]

10 Example 24

methyl cis-2-(3-iodobenzyl)-3-
((methylsulfonyl)amino)piperidine-1-carboxylate
[0254]

A) tert-butyl 2-(3-iodobenzyl)-3-oxopiperidine-1-carboxylate

15 To a mixture of tert-butyl 3-oxopiperidine-1-carboxylate
(10 g) and toluene (100 mL) was added pyrrolidine (4.28 g) at
room temperature. The mixture was stirred at room temperature
for 30 min, and concentrated under reduced pressure. The
residue was mixed with CH₃CN (100 mL), and 1-(bromomethyl)-3-
20 iodobenzene (17.9 g) was added to the mixture. The mixture was
stirred overnight at 80°C, and the reaction mixture was
concentrated under reduced pressure. The residue was dissolved
in ethyl acetate and 1M hydrochloric acid, and the solution was
stirred for 30 min, and extracted with ethyl acetate. The
25 separated organic layer was washed with saturated brine, dried
over anhydrous magnesium sulfate, and concentrated under
reduced pressure. The residue was purified by silica gel
column chromatography (ethyl acetate/hexane) to give the title
compound (14.7 g).

30 MS: [M+H-Boc]⁺ 316.0.

[0255]

B) tert-butyl cis-3-amino-2-(3-iodobenzyl)piperidine-1-
carboxylate

To a mixture of tert-butyl 2-(3-iodobenzyl)-3-
35 oxopiperidine-1-carboxylate (3.9 g), MeOH (40 mL) and THF (40

mL) was added ammonium acetate (7.24 g) at room temperature. The mixture was stirred at room temperature for 1 hr, sodium triacetoxyborohydride (3.58 g) was added thereto, and the mixture was stirred at room temperature for 18 hr. The
5 reaction mixture was added to saturated aqueous sodium hydrogencarbonate solution under ice-cooling, and the mixture was extracted with ethyl acetate. The separated organic layer washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure.
10 The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (2.14 g).
MS: [M+H]⁺417.1.

[0256]

C) tert-butyl cis-2-(3-iodobenzyl)-3-
15 ((methylsulfonyl)amino)piperidine-1-carboxylate

To a mixture of tert-butyl cis-3-amino-2-(3-iodobenzyl)piperidine-1-carboxylate (2.00 g) and THF (20 mL) were added TEA (0.972 g) and methanesulfonyl chloride (0.660 g) at 0°C. The mixture was stirred at room temperature for 1 hr.
20 To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue
25 was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.66 g).
MS: [M-H]⁻ 493.1.

[0257]

D) N-(cis-2-(3-iodobenzyl)piperidin-3-yl)methanesulfonamide
30 hydrochloride

To a mixture of tert-butyl cis-2-(3-iodobenzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate (1.66 g) and THF (8 mL) was added 4M hydrogen chloride/ethyl acetate solution (8.39 mL) at room temperature. The mixture was
35 stirred overnight at room temperature, and concentrated under

reduced pressure. The residue was suspended in ethyl acetate, and the solid was collected by filtration. The obtained solid was washed with ethyl acetate to give the title compound (1.29 g).

5 MS: [M+H]⁺ 395.0.

[0258]

E) methyl cis-2-(3-iodobenzyl)-3-

((methylsulfonyl)amino)piperidine-1-carboxylate

To a mixture of N-(cis-2-(3-iodobenzyl)piperidin-3-yl)methanesulfonamide hydrochloride (1.3 g), TEA (1.22 g) and THF (20 mL) was added methyl carbonochloridate (0.570 g) at room temperature. The mixture was stirred at room temperature for 10 min, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.30 g).

¹H NMR (300 MHz, DMSO-d₆) δ 1.35-1.56 (1H, m), 1.59-1.76 (3H, m), 2.78-2.87 (2H, m), 2.89-3.04 (4H, m), 3.05-3.23 (2H, m), 3.33-3.52 (2H, m), 3.67-3.87 (1H, m), 4.37-4.65 (1H, m), 7.00-7.10 (1H, m), 7.12-7.21 (1H, m), 7.34 (1H, s), 7.48-7.56 (2H, m).

[0259]

Example 27

methyl cis-3-((methylsulfonyl)amino)-2-(3-(pyrrolidin-1-yl)benzyl)piperidine-1-carboxylate

25 A mixture of methyl cis-2-(3-iodobenzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate (40 mg), pyrrolidine (12.6 mg), Pd₂(dba)₃ (8.10 mg), dicyclohexyl(2',6'-diisopropoxybiphenyl-2-yl)phosphine (12.4 mg), cesium carbonate (86 mg) and t-AmOH (1 mL) was subjected to microwave irradiation at 100°C for 1 hr. The mixture was poured into water, and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (19.0 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.32-1.57 (1H, m), 1.61-1.76 (3H, m), 1.86-1.99 (4H, m), 2.68-2.84 (2H, m), 2.90-3.03 (4H, m), 3.08-3.23 (5H, m), 3.34-3.52 (2H, m), 3.61-3.89 (1H, m), 4.39-4.71 (1H, m), 6.23-6.47 (3H, m), 6.92-7.06 (1H, m), 7.28-7.40 (1H, m).

[0260]

Example 64

isopropyl cis-3-((methylsulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate

10 [0261]

A) (6-phenylpyridin-2-yl)methanol

A mixture of (6-bromopyridin-2-yl)methanol (5.10 g), phenylboronic acid (4.96 g), Pd(PPh₃)₄ (1.25 g), 2M aqueous sodium carbonate solution (33.9 mL) and DME (55 mL) was heated under reflux for 15 hr under argon atmosphere. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate-THF. The insoluble substance was removed by filtration, and the organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) and silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (3.76 g).

MS: [M+H]⁺ 186.1.

25 [0262]

B) 2-(bromomethyl)-6-phenylpyridine

To a mixture of (6-phenylpyridin-2-yl)methanol (3.74 g), PPh₃ (6.36 g) and benzotrifluoride (150 mL) was added tetrabromomethane (8.04 g) at 0°C. The mixture was stirred at 0°C for 3 hr, and the insoluble substance was removed by filtration, and washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (4.03 g).

35 MS: [M+H]⁺ 248.0.

[0263]

C) tert-butyl 3-oxo-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate

To a mixture of tert-butyl 3-oxopiperidine-1-carboxylate
5 (2.69 g) and toluene (29 mL) was added pyrrolidine (1.44 g) at
room temperature. The mixture was stirred at room temperature
for 30 min, heated under reflux for 1 hr using Dean-Stark
apparatus, and concentrated under reduced pressure. The
residue was mixed with CH₃CN (29 mL), and 2-(bromomethyl)-6-
10 phenylpyridine (4.02 g) was added to the mixture at room
temperature. The mixture was stirred at room temperature for
15 hr, and the reaction mixture was poured into water, and the
mixture was extracted with ethyl acetate. The organic layer
was separated, washed with water and saturated brine, dried
15 over anhydrous magnesium sulfate, and concentrated under
reduced pressure. The residue was purified by silica gel
column chromatography (ethyl acetate/hexane) to give the title
compound (2.56 g).

MS: [M+H]⁺ 367.2.

20 [0264]

D) tert-butyl cis-3-amino-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate

To a mixture of tert-butyl 3-oxo-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate (2.55 g), MeOH (19 mL) and
25 THF (19 mL) was added ammonium acetate (5.36 g) at room
temperature. The mixture was stirred at room temperature for 1
hr, and sodium triacetoxyborohydride (2.65 g) was added thereto.
The mixture was stirred at room temperature for 3 hr. The
reaction mixture was poured into saturated aqueous sodium
30 hydrogencarbonate solution under ice-cooling, and the mixture
was extracted with ethyl acetate. The organic layer was
separated, washed with water and saturated brine, dried over
anhydrous magnesium sulfate, and concentrated under reduced
pressure. The residue was purified by silica gel column
35 chromatography (methanol/ethyl acetate) to give the title

compound (977 mg).

MS: [M+H]⁺ 368.2.

[0265]

E) tert-butyl cis-3-((methanesulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate

To a mixture of tert-butyl cis-3-amino-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate (973 mg), TEA (536 mg) and THF (9 mL) was added methanesulfonyl chloride (364 mg) at 0°C. The mixture was stirred at room temperature for 1 hr, and the reaction mixture was poured into ice water, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.05 g).

MS: [M+H]⁺ 446.2.

[0266]

F) N-(cis-2-((6-phenylpyridin-2-yl)methyl)piperidin-3-yl)methanesulfonamide

To a mixture of tert-butyl cis-3-((methanesulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate (991 mg) and toluene (11 mL) was added TFA (11 mL) at room temperature. The mixture was stirred at room temperature for 1 hr, and the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution under ice-cooling. The mixture was basified to pH=8 with potassium carbonate, and extracted with ethyl acetate/THF. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained solid was collected by filtration, and washed with diisopropyl ether to give the title compound (671 mg).

MS: [M+H]⁺ 346.1.

[0267]

G) isopropyl cis-3-((methylsulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate

To a mixture of N-(cis-2-((6-phenylpyridin-2-yl)methyl)piperidin-3-yl)methanesulfonamide (150 mg) and THF (2.17 mL) were added TEA (132 mg) and isopropyl carbonochloridate (0.326 mL) at room temperature. The mixture was stirred at room temperature for 1 hr, and the reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (157 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.12 (6H, d, J = 6.4 Hz), 1.75 (4H, brs), 2.05-2.19 (1H, m), 2.67-2.90 (3H, m), 2.88-3.06 (2H, m), 3.35 (1H, dd, J = 13.9, 5.7 Hz), 3.53-3.68 (1H, m), 3.96-4.14 (1H, m), 4.84 (2H, d, J = 5.7 Hz), 7.14-7.22 (1H, m), 7.38-7.52 (3H, m), 7.55-7.59 (1H, m), 7.66-7.74 (1H, m), 7.90-7.98 (2H, m).

[0268]

Example 75

ethyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate

[0269]

A) tert-butyl 2-(biphenyl-3-ylmethyl)-3-oxopyrrolidine-1-carboxylate

To a mixture of tert-butyl 3-oxopyrrolidine-1-carboxylate (3.5 g) and toluene (30 mL) was added pyrrolidine (1.61 g) at room temperature. The mixture was stirred at 100°C for 3 hr, and concentrated. CH₃CN (30 mL) and 3-(bromomethyl)biphenyl (4.67 g) were added thereto at room temperature. The mixture was stirred overnight under nitrogen atmosphere at 80°C, and concentrated. The obtained residue was diluted with water, and the mixture was extracted with ethyl acetate. The organic

layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (2.92 g).

5 MS: $[M+H-Boc]^+$ 252.2.

[0270]

B) tert-butyl cis-2-(biphenyl-3-ylmethyl)-3-((1-phenylethyl)amino)pyrrolidine-1-carboxylate

A mixture of tert-butyl 2-(biphenyl-3-ylmethyl)-3-oxopyrrolidine-1-carboxylate (2.38 g), 1-phenylethanamine (0.903 g), ytterbium(3+) tris(trifluoromethanesulfonate) (0.420 g) and toluene (20 mL) was stirred at 100°C for 4 hr. The reaction mixture was partitioned between ethyl acetate-water, and the organic layer was washed with saturated brine, and concentrated under reduced pressure. To a mixture of the obtained residue (3.08 g), CH₃CN (30 mL) and AcOH (5 mL) was added sodium triacetoxyborohydride (4.30 g) at 0°C. The mixture was stirred at room temperature for 1 hr, and neutralized with 4M aqueous sodium hydroxide solution. The obtained mixture was partitioned between ethyl acetate-aqueous sodium hydrogencarbonate solution, and the organic layer was washed with saturated brine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (2.29 g).

25 MS: $[M+H]^+$ 457.3.

[0271]

C) tert-butyl cis-3-amino-2-(biphenyl-3-ylmethyl)pyrrolidine-1-carboxylate

30 A mixture of tert-butyl cis-2-(biphenyl-3-ylmethyl)-3-((1-phenylethyl)amino)pyrrolidine-1-carboxylate (2.29 g), 20% palladium hydroxide on carbon (3.52 g), 1M hydrochloric acid (10.0 mL) and MeOH (50 mL) was stirred overnight under normal hydrogen atmosphere at room temperature. The catalyst was removed by filtration, and the filtrate was concentrated under

reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (865 mg).

MS, found: 297.2.

5 [0272]

D) tert-butyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate

To a mixture of tert-butyl cis-3-amino-2-(biphenyl-3-ylmethyl)pyrrolidine-1-carboxylate (865 mg), TEA (497 mg) and
10 THF (50 mL) was added methanesulfonyl chloride (337 mg) at 0°C. The mixture was stirred at room temperature for 1 hr, poured into ice water, and extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried over
15 anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (750 mg).

MS: [M-H]⁻ 429.2.

20 [0273]

E) N-(cis-2-(biphenyl-3-ylmethyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride

A mixture of tert-butyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate (750 mg) and
25 4M hydrogen chloride/ethyl acetate solution (20 mL) was stirred at room temperature for 3 days. The precipitate was collected by filtration to give the title compound (500 mg).

MS: [M+H]⁺ 331.1.

[0274]

30 F) ethyl cis-2-(biphenyl-3-ylmethyl)-3-

((methylsulfonyl)amino)pyrrolidine-1-carboxylate

To a mixture of N-(cis-2-(biphenyl-3-ylmethyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (40 mg), TEA (33.1 mg) and THF (3 mL) was added ethyl carbonochloridate (23.7 mg) at
35 room temperature. The mixture was stirred at room temperature

for 30 min, the reaction solution was poured into saturated aqueous sodium hydrogencarbonate solution at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained solid was crystallized from ethyl acetate-heptane to give the title compound (32.0 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.64-1.23 (3H, m), 1.72-2.25 (2H, m), 2.60-3.48 (8H, m), 3.54-4.25 (3H, m), 7.11-7.69 (10H, m).

10 [0275]

Example 76

optically active isopropyl cis-3-((methanesulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate

A racemate (120 mg) of isopropyl cis-3-((methanesulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate was resolved by HPLC (column: CHIRALPAK AD-H(UG065), 4.6 mmID×250 mmL, Manufactured by Daicel Chemical Industries, mobile phase: hexane/2-propanol = 700/300) to give the title compound (49.4 mg) having a shorter retention time. The title compound was purified by HPLC (C18, mobile phase: water/acetonitrile (containing 0.1% TFA)), and to the obtained fraction was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the title compound (43.0 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.47 (2H, brs), 0.64-1.12 (4H, m), 1.48 (1H, brs), 1.74 (3H, brs), 2.93-3.24 (6H, m), 3.43 (1H, d, J = 6.1 Hz), 3.86 (1H, brs), 4.31 (1H, brs), 4.76 (1H, brs), 7.11-7.22 (1H, m), 7.34-7.54 (4H, m), 7.73 (2H, brs), 8.00-8.11 (2H, m).

[0276]

Example 81

N-(cis-2-(biphenyl-3-ylmethyl)pyrrolidin-3-yl)methanesulfonamide

A mixture of tert-butyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate (0.950 g), TFA (3.08 g) and dichloromethane (10 mL) was stirred under nitrogen atmosphere at 15°C for 2 hr. The reaction solution was
5 neutralized (pH=7) with saturated aqueous sodium hydrogencarbonate solution. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue
10 was purified by silica gel column chromatography (EtOH/ethyl acetate) to give the title compound (0.378 g).
¹H NMR (400 MHz, CDCl₃) δ 1.85-1.96 (1H, m), 2.22-2.34 (1H, m), 2.74-2.86 (2H, m), 2.94 (3H, s), 3.00-3.15 (2H, m), 3.25-3.33 (1H, m), 3.90-3.96 (1H, m), 7.18-7.25 (1H, m), 7.30-7.48 (6H,
15 m), 7.54-7.63 (2H, m).

[0277]

Example 88

tert-butyl cis-3-((methylsulfonyl)amino)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)piperidine-1-carboxylate

20 [0278]

A) 4-(chloromethyl)-2-phenyl-1,3-thiazole

A mixture of benzenecarbothioamide (6.86 g), 1,3-dichloroacetone (6.35 g) and toluene (50 mL) was heated under reflux for 3 hr. The reaction mixture was cooled, and water
25 was added thereto. The mixture was extracted with ethyl acetate, and the extract was washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title
30 compound (9.77 g).

MS: [M+H]⁺ 210.1.

[0279]

B) tert-butyl 3-oxo-2-((2-phenyl-1,3-thiazol-4-yl)methyl)piperidine-1-carboxylate

35 To a mixture of tert-butyl 3-oxopiperidine-1-carboxylate

(0.950 g) and toluene (10 mL) was added pyrrolidine (0.509 g) at room temperature. The mixture was stirred at room temperature for 30 min, and concentrated. The residue was mixed with CH₃CN (10 mL), and 4-(chloromethyl)-2-phenyl-1,3-thiazole (1 g) and TBAI (0.352 g) were added to the mixture at room temperature. The mixture was stirred overnight at 80°C, and the reaction mixture was concentrated. The obtained residue was partitioned between ethyl acetate-water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (0.580 g). MS: [M+H]⁺ 373.1.

[0280]

C) tert-butyl cis-3-amino-2-((2-phenyl-1,3-thiazol-4-yl)methyl)piperidine-1-carboxylate

To a mixture of tert-butyl 3-oxo-2-((2-phenyl-1,3-thiazol-4-yl)methyl)piperidine-1-carboxylate (580 mg), ammonium acetate (1200 mg), MeOH (5 mL) and THF (5 mL) was added sodium triacetoxyborohydride (495 mg) at room temperature. The mixture was stirred overnight at room temperature, and concentrated. The obtained residue was mixed with saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (213 mg).

MS: [M+H]⁺ 374.2.

[0281]

D) tert-butyl cis-3-((methylsulfonyl)amino)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)piperidine-1-carboxylate

To a mixture of tert-butyl cis-3-amino-2-((2-phenyl-1,3-thiazol-4-yl)methyl)piperidine-1-carboxylate (212 mg), TEA (86

mg) and THF (5 mL) was added methanesulfonic anhydride (119 mg) at room temperature. The mixture was stirred at room temperature for 10 min, and the reaction mixture was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (212 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.33 (9H, s), 1.58-1.83 (3H, m), 2.00-2.11 (1H, m), 2.75-3.07 (5H, m), 3.27 (1H, dd, J = 14.4, 6.1 Hz), 3.54-3.69 (1H, m), 4.01 (1H, d, J = 11.4 Hz), 4.75 (1H, q, J = 5.8 Hz), 6.14 (1H, brs), 7.01 (1H, s), 7.39-7.49 (3H, m), 7.86-8.01 (2H, m).

[0282]

Example 89

isopropyl cis-3-((methanesulfonyl)amino)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)piperidine-1-carboxylate

[0283]

A) N-(cis-2-((2-phenyl-1,3-thiazol-4-yl)methyl)piperidin-3-yl)methanesulfonamide dihydrochloride

To a mixture of tert-butyl cis-3-((methanesulfonyl)amino)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)piperidine-1-carboxylate (207 mg) and ethyl acetate (5 mL) was added 4M hydrogen chloride/ethyl acetate solution (2 mL) at room temperature. The mixture was stirred overnight at room temperature, and the reaction mixture was concentrated to give the title compound (200 mg).

MS: [M+H]⁺ 352.1.

[0284]

B) isopropyl cis-3-((methanesulfonyl)amino)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)piperidine-1-carboxylate

To a mixture of N-(cis-2-((2-phenyl-1,3-thiazol-4-yl)methyl)piperidin-3-yl)methanesulfonamide dihydrochloride (60 mg), TEA (71.5 mg) and THF (2 mL) was added 2M isopropyl carbonochloridate/toluene solution (0.106 mL) at room temperature. The mixture was stirred at room temperature for 3 hr, and the reaction mixture was directly purified by silica

gel column chromatography (ethyl acetate/hexane) to give the title compound (43.0 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.04-1.21 (6H, m), 1.59-1.83 (3H, m), 2.03-2.15 (1H, m), 2.81-3.05 (5H, m), 3.30 (1H, dd, J = 14.8, 6.4 Hz), 3.53-3.71 (1H, m), 3.98-4.09 (1H, m), 4.69-4.91 (2H, m), 6.38 (1H, brs), 7.02 (1H, s), 7.38-7.53 (3H, m), 7.90-8.02 (2H, m).

[0285]

Example 93

10 N-(cis-2-(biphenyl-3-ylmethyl)-1-

(cyclopropylcarbonyl)piperidin-3-yl)methanesulfonamide

To a mixture of N-(cis-2-(biphenyl-3-ylmethyl)piperidin-3-yl)methanesulfonamide (100 mg), TEA (58.8 mg) and dichloromethane (1 mL) was added cyclopropanecarbonyl chloride (45.5 mg) under nitrogen atmosphere at 0°C. The mixture was stirred at 0°C for 1 hr. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with dichloromethane. The organic layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by HPLC (column: Phenomenex Gemini, mobile phase: water/CH₃CN (containing 0.05% NH₃-H₂O)) to give the title compound (56.0 mg).

¹H NMR (400 MHz, DMSO-d₆) δ 0.53-0.40 (4H, m), 1.26-1.76 (5H, m), 2.90-3.05 (6H, m), 3.23-3.52 (1H, m), 4.28-4.66 (1H, m), 4.88-5.18 (1H, m), 7.16 (1H, d, J = 7.6 Hz), 7.27-7.47 (7H, m), 7.57-7.62 (2H, m).

[0286]

Example 100

30 isopropyl cis-2-((6-(2,5-difluorophenyl)pyridin-2-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate

[0287]

A) isopropyl 3-oxopiperidine-1-carboxylate

To a mixture of 1-benzyl piperidin-3-one hydrochloride (15.0 g), TEA (7.40 g) and CH₃CN (100 mL) was added dropwise 2M

isopropyl carbonochloridate/toluene solution (59.8 mL) at 0°C. The mixture was stirred at room temperature for 2 hr, and the insoluble substance was removed by filtration, and washed with CH₃CN. The filtrate was concentrated under reduced pressure.

5 The residue was diluted with saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified
10 by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (11.0 g).

¹H NMR (300 MHz, CDCl₃) δ 1.25 (6H, d, J = 6.4 Hz), 1.95-2.04 (2H, m), 2.48 (2H, t, J = 6.6 Hz), 3.60-3.66 (2H, m), 4.04 (2H, s), 4.94 (1H, spt, J = 6.2 Hz).

15 [0288]

B) 2-bromo-6-(bromomethyl)pyridine

To a mixture of (6-bromopyridin-2-yl)methanol (5.22 g), PPh₃ (8.74 g) and benzotrifluoride (210 mL) was added tetrabromomethane (11.1 g) at 0°C. The mixture was stirred at
20 0°C for 2 hr, and the insoluble substance was removed by filtration, and washed with ethyl acetate/diethyl ether. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (7.33 g).

25 ¹H NMR (300 MHz, CDCl₃) δ 4.50 (2H, s), 7.39-7.45 (2H, m), 7.52-7.60 (1H, m).

[0289]

C) isopropyl 2-((6-bromopyridin-2-yl)methyl)-3-oxopiperidine-1-carboxylate

30 To a mixture of isopropyl 3-oxopiperidine-1-carboxylate (4.50 g) and toluene (52 mL) was added pyrrolidine (2.59 g) at room temperature. The mixture was stirred at room temperature for 30 min, and concentrated. Toluene and CH₃CN were added thereto, and the mixture was concentrated. The residue was
35 mixed with CH₃CN (52 mL), and 2-bromo-6-(bromomethyl)pyridine

(7.32 g) was added thereto at room temperature. The mixture was heated under reflux for 15 hr, and the reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (2.72 g).
MS: [M+H]⁺ 355.0.

10 [0290]

D) isopropyl cis-3-amino-2-((6-bromopyridin-2-yl)methyl)piperidine-1-carboxylate

To a mixture of isopropyl 2-((6-bromopyridin-2-yl)methyl)-3-oxopiperidine-1-carboxylate (2.71 g), MeOH (23 mL) and THF (23 mL) was added ammonium acetate (5.88 g) at room temperature. The mixture was stirred at room temperature for 1 hr, and sodium triacetoxyborohydride (3.23 g) was added thereto. The mixture was stirred at room temperature for 15 hr. The mixture was poured into saturated aqueous sodium hydrogencarbonate solution under ice-cooling, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (373 mg).

MS: [M+H]⁺ 356.0.

[0291]

E) isopropyl cis-2-((6-bromopyridin-2-yl)methyl)-3-((methanesulfonyl)amino)piperidine-1-carboxylate
30

To a mixture of isopropyl cis-3-amino-2-((6-bromopyridin-2-yl)methyl)piperidine-1-carboxylate (369 mg), TEA (210 mg) and THF (3.5 mL) was added methanesulfonyl chloride (142 mg) at room temperature. The mixture was stirred at room temperature for 1 hr, and the reaction solution was poured into water, and

the mixture was extracted with ethyl acetate. The organic layer was separated, washed with aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (340 mg).

MS: [M+H]⁺ 434.0.

[0292]

10 F) isopropyl cis-2-((6-(2,5-difluorophenyl)pyridin-2-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate

A mixture of isopropyl cis-2-((6-bromopyridin-2-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate (73 mg), (2,5-difluorophenyl)boronic acid (39.8 mg), 2M aqueous sodium carbonate solution (0.210 mL) and DME (1.1 mL) was heated under reflux under argon atmosphere for 9 hr. The mixture was poured into water, and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (58.6 mg).

¹H NMR (300 MHz, CDCl₃) δ 0.92-1.12 (6H, m), 1.60-1.83 (3H, m), 2.02-2.07 (1H, m), 2.91 (3H, s), 2.94-3.06 (2H, m), 3.30 (1H, dd, J = 14.0, 5.7 Hz), 3.57-3.68 (1H, m), 3.99-4.13 (1H, m), 4.73 (1H, spt, J = 6.2 Hz), 4.84-4.92 (1H, m), 5.64 (1H, brs), 7.01-7.16 (2H, m), 7.22-7.26 (1H, m), 7.62-7.74 (3H, m).

[0293]

Example 101

30 ethyl (2S,3S)-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate

A racemate (146 mg) of ethyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate was resolved by HPLC (column: CHIRALCEL OD(IK001), 50 mmID×500 mmL, Manufactured by Daicel Chemical Industries, mobile phase:

hexane/2-propanol = 450/550) to give the title compound (47 mg) having a shorter retention time.

¹H NMR (300 MHz, DMSO-d₆) δ 0.62-1.16 (3H, m), 1.71-2.23 (2H, m), 2.67-3.50 (8H, m), 3.55-4.26 (3H, m), 7.10-7.68 (10H, m).

5 [0294]

Example 116

isopropyl cis-2-((2',3'-difluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate

A mixture of isopropyl cis-2-(3-iodobenzyl)-3-
10 ((methylsulfonyl)amino)piperidine-1-carboxylate (96 mg), (2,3-difluorophenyl)boronic acid (95 mg), XPhos Pd G3 (8.46 mg), 1M aqueous tripotassium phosphate solution (0.6 mL) and THF (1 mL) was heated under reflux for 1 hr. The mixture was diluted with ethyl acetate, washed with water and saturated brine, dried
15 over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (71.0 mg).

¹H NMR (300 MHz, CDCl₃) δ 0.82 (3H, brs), 1.03 (3H, d, J = 6.4
20 Hz), 1.59-1.99 (4H, m), 2.98 (6H, s), 3.56-3.73 (1H, m), 4.01-4.13 (1H, m), 4.38 (1H, d, J = 7.6 Hz), 4.54-4.69 (1H, m), 4.74-4.89 (1H, m), 7.07-7.25 (4H, m), 7.30-7.42 (3H, m)

[0295]

Example 117

25 isopropyl cis-2-(3-iodobenzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate

To a mixture of N-(cis-2-(3-iodobenzyl)piperidin-3-yl)methanesulfonamide hydrochloride (1.29 g), TEA (0.909 g) and THF (15 mL) was added 2M isopropyl carbonochloridate/toluene
30 solution (1.80 mL) at room temperature. To the mixture was added saturated aqueous sodium hydrogencarbonate solution at room temperature, and the mixture was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.16 g).

35 ¹H NMR (300 MHz, CDCl₃) δ 0.83-1.00 (3H, m), 1.10 (3H, d, J =

6.1 Hz), 1.58-1.98 (4H, m), 2.70-2.92 (3H, m), 3.00 (3H, s), 3.51-3.68 (1H, m), 4.03-4.14 (1H, m), 4.22-4.38 (1H, m), 4.58-4.82 (2H, m), 6.92-7.07 (1H, m), 7.15 (1H, d, J = 7.6 Hz), 7.48-7.58 (2H, m)

5 [0296]

Example 122

isopropyl cis-3-((methylsulfonyl)amino)-2-((3-phenyl-1H-pyrazol-1-yl)methyl)piperidine-1-carboxylate

[0297]

10 A) 3-nitro-2-((3-phenyl-1H-pyrazol-1-yl)methyl)pyridine

A mixture of 2-(bromomethyl)-3-nitropyridine (100 mg), 3-phenyl-1H-pyrazole (69.8 mg) and DMF (2 mL) was stirred at 60°C for 17 hr. The mixture was partitioned between ethyl acetate-water, and the organic layer was washed with saturated brine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (87 mg).

MS: [M+H]⁺ 281.0.

[0298]

20 B) 2-((3-phenyl-1H-pyrazol-1-yl)methyl)pyridin-3-amine

A mixture of 3-nitro-2-((3-phenyl-1H-pyrazol-1-yl)methyl)pyridine (793 mg), 10% palladium on carbon (301 mg) and EtOH (35 mL) was stirred under normal hydrogen atmosphere at room temperature for 1 hr. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (509 mg).

MS: [M+H]⁺ 251.0.

30 [0299]

C) N-(2-((3-phenyl-1H-pyrazol-1-yl)methyl)pyridin-3-yl)methanesulfonamide

A mixture of 2-((3-phenyl-1H-pyrazol-1-yl)methyl)pyridin-3-amine (550 mg), TEA (667 mg), methanesulfonyl chloride (629 mg) and THF (10 mL) was stirred at room temperature for 1 hr.

To the mixture were added MeOH (5 mL) and 2M aqueous sodium hydroxide solution (2.20 mL). The mixture was stirred at 50°C for 3 hr. The reaction solution was partitioned between ethyl acetate-water, and the organic layer was washed with saturated
5 brine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (650 mg).

MS: [M+H]⁺ 329.0.

[0300]

10 D) N-(cis-2-((3-phenyl-1H-pyrazol-1-yl)methyl)piperidin-3-yl)methanesulfonamide

A mixture of N-(2-((3-phenyl-1H-pyrazol-1-yl)methyl)pyridin-3-yl)methanesulfonamide (648 mg), 5% platinum on carbon (150 mg), 35% hydrochloric acid (411 mg), MeOH (23
15 mL) and water (7 mL) was stirred under hydrogen atmosphere of 3MPa at 50°C for 2 hr. To the mixture was added 5% platinum on carbon (75 mg), and the mixture was stirred under hydrogen atmosphere of 3MPa at 50°C for 2 hr. The catalyst was removed by filtration, and the filtrate was concentrated under reduced
20 pressure. The obtained residue was partitioned between THF-aqueous sodium hydrogencarbonate solution, and the organic layer was washed with saturated brine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane), and
25 crystallized from ethyl acetate to give the title compound (110 mg).

MS: [M+H]⁺ 335.1.

[0301]

30 E) isopropyl cis-3-((methylsulfonyl)amino)-2-((3-phenyl-1H-pyrazol-1-yl)methyl)piperidine-1-carboxylate

A mixture of N-(cis-2-((3-phenyl-1H-pyrazol-1-yl)methyl)piperidin-3-yl)methanesulfonamide (110 mg), TEA (66.6 mg), 2 M isopropyl carbonochloridate/toluene solution (0.247 mL) and THF (3 mL) was stirred at room temperature for 30 min.
35 The mixture was partitioned between ethyl acetate-aqueous

sodium hydrogencarbonate solution, and the organic layer was washed with saturated brine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title

5 compound (93 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.62 (6H, d, J = 5.3 Hz, minor), 0.81-1.12 (6H, m, major), 1.41-1.83 (4H, m), 3.03 (3H, s), 3.06-3.21 (1H, m), 3.41-3.54 (1H, m), 3.74-3.96 (1H, m), 4.26-4.59 (3H, m), 4.60-4.80 (1H, m), 6.62 (1H, d, J = 1.5 Hz),
10 7.21-7.30 (1H, m), 7.32-7.41 (2H, m), 7.47 (1H, brs), 7.60 (1H, d, J = 2.3 Hz), 7.76 (2H, d, J = 7.6 Hz).

[0302]

Example 178

isopropyl cis-3-((cyclopropylsulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate

15 [0303]

A) tert-butyl cis-3-(((benzyloxy)carbonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate

To a mixture of tert-butyl cis-3-amino-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate (1.05 g), sodium hydrogencarbonate (0.360 g), THF (7 mL) and water (7 mL) was added 1-(((benzyloxy)carbonyl)oxy)pyrrolidine-2,5-dione (0.748 g) at room temperature. The mixture was vigorously stirred at room temperature for 2 hr, poured into water, and
25 extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.37 g).

30 MS: [M+H]⁺ 502.2.

[0304]

B) benzyl (cis-2-((6-phenylpyridin-2-yl)methyl)piperidin-3-yl)carbamate

To a mixture of tert-butyl cis-3-(((benzyloxy)carbonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate (1.05 g), sodium hydrogencarbonate (0.360 g), THF (7 mL) and water (7 mL) was added 1-(((benzyloxy)carbonyl)oxy)pyrrolidine-2,5-dione (0.748 g) at room temperature. The mixture was vigorously stirred at room temperature for 2 hr, poured into water, and
35 extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.37 g).

yl)methyl)piperidine-1-carboxylate (1.37 g) and toluene (15 mL) was added TFA (15 mL) at room temperature. The mixture was stirred at room temperature for 1 hr, and added to saturated aqueous sodium hydrogencarbonate solution under ice-cooling.
5 The mixture was basified to pH=8 with potassium carbonate, and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography
10 (NH, ethyl acetate/hexane) to give the title compound (966 mg).
MS: [M+H]⁺ 402.1.

[0305]

C) isopropyl cis-3-(((benzyloxy)carbonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate

15 To a mixture of benzyl (cis-2-((6-phenylpyridin-2-yl)methyl)piperidin-3-yl)carbamate (960 mg), TEA (726 mg) and THF (20 mL) was added 2M isopropyl carbonochloridate/toluene solution (2.39 mL) at room temperature. The mixture was stirred at room temperature for 1 hr, added to aqueous sodium
20 hydrogencarbonate solution, and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to
25 give the title compound (1.11 g).

MS: [M+H]⁺ 488.2.

[0306]

D) isopropyl cis-3-amino-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate

30 A mixture of isopropyl cis-3-(((benzyloxy)carbonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate (1.09 g), 10% palladium hydroxide on carbon (0.36 g) and MeOH (22 mL) was stirred under normal hydrogen atmosphere at room temperature for 1.5 hr. The
35 catalyst was removed by filtration, and the filtrate was

concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (703 mg).

MS: [M+H]⁺ 354.1.

5 [0307]

E) isopropyl cis-3-((cyclopropylsulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate

To a mixture of isopropyl cis-3-amino-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate (28 mg), TEA
10 (0.00971 mg) and THF (1.0 mL) was added cyclopropanesulfonyl chloride (13.5 mg). The mixture was stirred at room temperature for 3 hr, and the reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The organic layer was filtered using Top-Phase Separation Filter
15 Tube, and the filtrate was concentrated by blowing of air at 60°C. The residue was purified by HPLC (YMCTriartC18, mobile phase: water/MeCN (10 mM ammonium bicarbonate)). The obtained fraction was concentrated by blowing of air at 60°C to give the title compound (12.7 mg).

20 MS: [M+H]⁺ 458.1.

[0308]

Example 206

N-(cis-2-(biphenyl-3-ylmethyl)-1-

(cyclopropylcarbonyl)pyrrolidin-3-yl)methanesulfonamide

25 To a mixture of N-(cis-2-(biphenyl-3-ylmethyl)pyrrolidin-3-yl)methanesulfonamide (52.0 mg), TEA (47.8 mg) and THF (1.2 mL) was added cyclopropanecarbonyl chloride (32.9 mg) at room temperature. The mixture was stirred at room temperature for 50 min, and poured into aqueous sodium hydrogencarbonate
30 solution, and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give a solid. The
35 solid was collected by filtration, and washed with isopropyl

ether/hexane to give the title compound (38.0 mg).

¹H NMR (300 MHz, CDCl₃) δ 0.07-0.62 (2H, m), 0.72-1.08 (3H, m), 1.71-1.91 (1H, m), 2.23-2.36 (1H, m), 2.49-2.74 (2H, m), 2.92-3.06 (2H, m), 3.22 (1H, td, J = 13.1, 3.0 Hz), 3.47-3.76 (2H, m), 3.96-4.10 (1H, m), 4.52-4.80 (2H, m), 7.17 (1H, d, J = 7.6 Hz), 7.30-7.49 (6H, m), 7.52-7.58 (2H, m).

[0309]

Example 209

N-(cis-2-(biphenyl-3-ylmethyl)-1-isobutyryl pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-(cis-2-(biphenyl-3-ylmethyl)pyrrolidin-3-yl)methanesulfonamide (51.2 mg), TEA (47.0 mg) and THF (2 mL) was added 2-methylpropanoyl chloride (24.8 mg) at 0°C. The mixture was stirred at 0°C for 30 min, and to the mixture was added water at 0°C, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate). The obtained solid was recrystallized from ethyl acetate/hexane to give the title compound (29.0 mg).

¹H NMR (300 MHz, CDCl₃) δ 0.50-1.19 (6H, m), 1.71-2.51 (4H, m), 2.54-2.74 (1H, m), 2.87-3.09 (2H, m), 3.11-3.27 (1H, m), 3.38-3.84 (2H, m), 3.91-4.09 (1H, m), 4.23-4.55 (1H, m), 4.57-4.74 (1H, m), 7.09-7.62 (9H, m).

[0310]

Example 210

optically active isopropyl cis-3-((methylsulfonyl)amino)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)piperidine-1-carboxylate

A racemate (82 mg) of isopropyl cis-3-((methylsulfonyl)amino)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)piperidine-1-carboxylate was resolved by SFC (column: CHIRALCEL ODH (TB001), 4.6 mmID×150 mmL, Manufactured by Daicel Chemical Industries, mobile phase: carbon dioxide/methanol = 770/230) to give the title compound (381 mg) having a longer

retention time.

¹H NMR (300 MHz, CDCl₃) δ 0.96-1.24 (6H, m), 1.60-1.87 (3H, m),
2.08 (1H, d, J = 9.5 Hz), 2.78-3.07 (5H, m), 3.30 (1H, dd, J =
14.6, 6.2 Hz), 3.52-3.76 (1H, m), 4.05 (1H, d, J = 14.8 Hz),
5 4.67-4.90 (2H, m), 6.31 (1H, brs), 7.02 (1H, s), 7.38-7.52 (3H,
m), 7.89-8.04 (2H, m).

[0311]

Example 213

isopropyl cis-3-((methylsulfonyl)amino)-2-(pyridin-3-
10 ylmethyl)piperidine-1-carboxylate

[0312]

A) tert-butyl 2-((6-chloropyridin-3-yl)methyl)-3-oxopiperidine-
1-carboxylate

To a mixture of tert-butyl 3-oxopiperidine-1-carboxylate
15 (2.00 g) and toluene (20 mL) was added pyrrolidine (0.857 g) at
room temperature. The mixture was stirred for 15 min, and
concentrated under reduced pressure. The residue was dissolved
in CH₃CN (20 mL), and 2-chloro-5-(chloromethyl)pyridine (1.63
g) and TBAI (0.742 g) were added thereto. The mixture was
20 heated under reflux for 1 hr, and the reaction mixture was
diluted with water. The mixture was extracted with ethyl
acetate, and the extract was concentrated under reduced
pressure. The residue was purified by silica gel column
chromatography (ethyl acetate/hexane) to give the title
25 compound (1.61 g).

MS: [M+H]⁺ 325.3.

[0313]

B) tert-butyl cis-3-amino-2-((6-chloropyridin-3-
yl)methyl)piperidine-1-carboxylate

30 To a mixture of tert-butyl 2-((6-chloropyridin-3-
yl)methyl)-3-oxopiperidine-1-carboxylate (1.61 g), THF (15 mL)
and MeOH (15 mL) was added ammonium acetate (3.82 g) at room
temperature. The mixture was stirred at room temperature for 1
hr, and sodium triacetoxyborohydride (2.10 g) was added thereto.
35 The mixture was stirred overnight at room temperature, poured

into saturated aqueous sodium hydrogencarbonate solution under ice-cooling, and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under
5 reduced pressure. The residue was purified by silica gel column chromatography (NH, methanol/ethyl acetate) to give the title compound (567 mg).

MS: [M+H]⁺ 326.2.

[0314]

- 10 C) tert-butyl cis-2-((6-chloropyridin-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate

To a mixture of tert-butyl cis-3-amino-2-((6-chloropyridin-3-yl)methyl)piperidine-1-carboxylate (567 mg), TEA (264 mg) and THF (8 mL) was added methanesulfonic anhydride
15 (364 mg) at room temperature. The mixture was stirred at room temperature for 2 hr, and the reaction solution was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (650 mg).

- 20 MS: [M+H]⁺ 404.2.

[0315]

- D) N-(cis-2-((6-chloropyridin-3-yl)methyl)piperidin-3-yl)methanesulfonamide dihydrochloride

A mixture of tert-butyl cis-2-((6-chloropyridin-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate
25 (645 mg) and hydrogen chloride/methanol solution (776 mg) was stirred overnight at room temperature. The mixture was concentrated under reduced pressure to give the title compound (557 mg).

- 30 MS: [M+H]⁺ 304.1.

[0316]

- E) isopropyl cis-2-((6-chloropyridin-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate

To a mixture of N-(cis-2-((6-chloropyridin-3-yl)methyl)piperidin-3-yl)methanesulfonamide dihydrochloride
35

(200 mg), TEA (215 mg) and THF (5 mL) was added 2M isopropyl carbonochloridate/toluene solution (0.319 mL) at room temperature. The mixture was stirred overnight at room temperature. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (222 mg).

MS: [M+H]⁺390.2.

[0317]

F) isopropyl cis-3-((methylsulfonyl)amino)-2-(pyridin-3-ylmethyl)piperidine-1-carboxylate

A mixture of isopropyl cis-2-((6-chloropyridin-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate (91.0 mg), 5.5% palladium on carbon (30 mg) and EtOH (5 mL) was stirred under normal hydrogen atmosphere at room temperature for 2 days. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The similar reaction was carried out using isopropyl cis-2-((6-chloropyridin-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate (117 mg) and 5.5% palladium on carbon (40 mg) and EtOH (5 mL). The combined residues were purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (144 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.49-1.13 (6H, m), 1.49 (1H, brs), 1.60-1.82 (3H, m), 2.81-2.91 (2H, m), 2.92-3.07 (4H, m), 3.35-3.50 (1H, m), 3.85 (1H, d, J = 14.4 Hz), 4.26-4.67 (2H, m), 7.27 (1H, brs), 7.39 (1H, brs), 7.54 (1H, dt, J = 7.8, 2.0 Hz), 8.36 (2H, d, J = 2.3 Hz).

[0318]

Example 214

isopropyl cis-3-((methylsulfonyl)amino)-2-((1-phenylpiperidin-3-yl)methyl)piperidine-1-carboxylate

[0319]

A) isopropyl cis-3-((methylsulfonyl)amino)-2-(piperidin-3-ylmethyl)piperidine-1-carboxylate

A mixture of isopropyl cis-3-((methylsulfonyl)amino)-2-(pyridin-3-ylmethyl)piperidine-1-carboxylate (142 mg), 5% rhodium on carbon (50% wet, 30 mg), MeOH (25 mL) and AcOH (5 mL) was stirred under hydrogen atmosphere of 3MPa at 50°C for 3 hr. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified 10 by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (140 mg).

MS: [M+H]⁺ 362.2.

[0320]

B) isopropyl cis-3-((methylsulfonyl)amino)-2-((1-phenylpiperidin-3-yl)methyl)piperidine-1-carboxylate 15

To a mixture of isopropyl cis-3-((methylsulfonyl)amino)-2-(piperidin-3-ylmethyl)piperidine-1-carboxylate (28.6 mg), bromobenzene (24.8 mg), cesium carbonate (103 mg) and t-AmOH (1 mL) were added Pd₂(dba)₃ (7.24 mg) and dicyclohexyl(2',6'-diisopropoxybiphenyl-2-yl)phosphine (7.38 mg) at room 20 temperature. The mixture was heated under reflux under nitrogen atmosphere for 4 hr. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over 25 anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (23.6 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.92-2.04 (18H, m), 2.22-2.45 (1H, m), 2.55-2.87 (2H, m), 2.92 (3H, s), 3.20-3.64 (2H, m), 3.79 (1H, brs), 4.43 (1H, brs), 4.76 (1H, quin, J = 6.2 Hz), 6.72 (1H, t, J = 7.2 Hz), 6.90 (2H, dd, J = 8.5, 3.2 Hz), 7.09-7.27 (3H, m).

[0321]

35 Example 227

N-(cis-2-(biphenyl-3-ylmethyl)-1-(2,2-dimethylpropanoyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-(cis-2-(biphenyl-3-ylmethyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (40 mg), pivalic acid (13.4 mg), HATU (49.7 mg) and DMF (0.5 ml) was added TEA (33.1 mg) at 0°C. The mixture was stirred at room temperature for 30 min, and to the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (39 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.26 (9H, s), 1.89-2.05 (1H, m), 2.20-2.34 (1H, m), 2.45 (3H, s), 2.78-2.93 (1H, m), 3.19-3.29 (1H, m), 3.62-3.77 (2H, m), 3.89-4.04 (1H, m), 4.45 (1H, d, J = 8.3 Hz), 4.70-4.80 (1H, m), 7.30-7.49 (6H, m), 7.52-7.62 (3H, m).

[0322]

Example 254

N-(cis-1-(cyclobutylcarbonyl)-2-((2-(3-fluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

[0323]

A) 2-bromo-4-(bromomethyl)-1,3-thiazole

To a mixture of (2-bromo-1,3-thiazol-4-yl)methanol (5.0 g) and THF (50 ml) was added phosphorous tribromide (6.97 g) at 0°C. The mixture was stirred overnight under nitrogen atmosphere at room temperature. The mixture was poured into ice water at room temperature, and extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium hydrogencarbonate solution and water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (3.90 g).

MS: [M+H]⁺ 255.7.

[0324]

B) tert-butyl 2-((2-bromo-1,3-thiazol-4-yl)methyl)-3-oxopyrrolidine-1-carboxylate

5 To a mixture of tert-butyl 3-oxopyrrolidine-1-carboxylate (20.2 g) and toluene (200 mL) was added pyrrolidine (8.53 g) at room temperature. The mixture was heated under reflux overnight, and the reaction solution was concentrated. The residue was mixed with CH₃CN (200 mL), and a mixture of 2-
10 bromo-4-(bromomethyl)-1,3-thiazole (14.0 g), TBAI (4.03 g) and CH₃CN (200 mL) was added thereto at 80°C. The mixture was stirred under nitrogen atmosphere at 80°C for 3 hr, and concentrated under reduced pressure. The mixture was poured into water, and extracted with ethyl acetate. The organic
15 layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (13.5 g).

20 MS: [M-H]⁻ 358.8.

[0325]

C) tert-butyl cis-3-amino-2-((2-bromo-1,3-thiazol-4-yl)methyl)pyrrolidine-1-carboxylate

To a mixture of tert-butyl 2-((2-bromo-1,3-thiazol-4-yl)methyl)-3-oxopyrrolidine-1-carboxylate (13.6 g), ammonium
25 formate (25.0 g) and MeOH (40 mL) was added chloro[N-[4-(dimethylamino)phenyl]-2-pyridinecarboxamidato](pentamethylcyclopentadienyl)iridium(III) (0.454 g) at room temperature. The mixture was heated under
30 reflux for 2 hr. The reaction solution was concentrated. The obtained residue was diluted with ethyl acetate, and the mixture was washed with a mixture of saturated brine and saturated aqueous sodium hydrogencarbonate solution, dried over anhydrous sodium sulfate, and concentrated under reduced
35 pressure to give the title compound (6.18 g).

MS: [M+H]⁺ 362.1.

[0326]

D) tert-butyl cis-2-((2-bromo-1,3-thiazol-4-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate

5 A mixture of tert-butyl cis-3-amino-2-((2-bromo-1,3-thiazol-4-yl)methyl)pyrrolidine-1-carboxylate (145 mg), TEA (81 mg) and THF (2 ml) was stirred at 0°C, and methanesulfonic anhydride (91 mg) was added thereto at 0°C. The reaction mixture was concentrated under reduced pressure, and the
10 residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (53 mg).

MS: [M+H]⁺ 440.0.

[0327]

E) N-(cis-2-((2-bromo-1,3-thiazol-4-yl)methyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)methanesulfonamide
15

tert-Butyl cis-2-((2-bromo-1,3-thiazol-4-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate (650 mg) and 4M hydrogen chloride/ethyl acetate solution (7.38 ml) were mixed at room temperature. After 30 min, and the reaction
20 solution was concentrated. The obtained residue was mixed with THF (7.5 ml), and TEA (747 mg) and cyclobutanecarbonyl chloride (262 mg) at 0°C were added thereto. The mixture was stirred at room temperature for 1 hr, to the reaction solution was added saturated brine, and the mixture was concentrated under reduced
25 pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (422 mg).

MS: [M+H]⁺ 422.1.

[0328]

30 F) N-(cis-1-(cyclobutylcarbonyl)-2-((2-(3-fluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-(cis-2-((2-bromo-1,3-thiazol-4-yl)methyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)methanesulfonamide (60.0 mg), (3-fluorophenyl)boronic acid
35 (29.8 mg), potassium carbonate (40.2 mg), water (0.40 ml) and

DME (1.2 ml) was added (A-taPhos)₂PdCl₂ (5.7 mg) at room temperature. The mixture was stirred under nitrogen atmosphere at 80°C for 3 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and silica
5 gel column chromatography (ethyl acetate/hexane), and the obtained compound was triturated in diethyl ether/hexane to give the title compound (35.2 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.33-1.52 (1H, m), 1.81-2.58 (7H, m), 2.94-3.45 (7H, m), 3.61 (1H, dd, J = 14.8, 6.1 Hz), 4.00-4.21
10 (1H, m), 4.30-4.59 (1H, m), 6.94-7.04 (1H, m), 7.10-7.20 (1H, m), 7.39-7.51 (1H, m), 7.59-7.68 (1H, m), 7.69-7.79 (1H, m), 8.12 (1H, d, J = 9.1 Hz).

[0329]

Example 255

15 N-(cis-1-(cyclobutylcarbonyl)-2-((2-(2-fluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-(cis-2-((2-bromo-1,3-thiazol-4-yl)methyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)methanesulfonamide (60.0 mg), (2-fluorophenyl)boronic acid
20 (30.0 mg), potassium carbonate (40.1 mg), water (0.40 ml) and DME (1.2 ml) was added (A-taPhos)₂PdCl₂ (6.0 mg) at room temperature. The mixture was stirred under nitrogen atmosphere at 80°C for 3 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and silica
25 gel column chromatography (ethyl acetate/hexane), and the obtained compound was triturated in diethyl ether/hexane to give the title compound (38.2 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.23-1.43 (1H, m), 1.82-2.59 (7H, m), 2.94-3.46 (7H, m), 3.66 (1H, dd, J = 14.8, 5.7 Hz), 4.01-4.19
30 (1H, m), 4.30-4.62 (1H, m), 7.02-7.12 (1H, m), 7.16-7.25 (1H, m), 7.28-7.36 (1H, m), 7.38-7.49 (1H, m), 8.14-8.29 (2H, m).

[0330]

Example 256

N-(cis-1-(cyclobutylcarbonyl)-2-((2-(2,3-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide
35

To a mixture of N-(cis-2-((2-bromo-1,3-thiazol-4-yl)methyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)methanesulfonamide (60.0 mg), (2,3-difluorophenyl)boronic acid (35.0 mg), potassium carbonate (40.1 mg), water (0.40 ml) and DME (1.2 ml) was added (A-taPhos)₂PdCl₂ (6.0 mg) at room temperature. The mixture was stirred under nitrogen atmosphere at 80°C for 3 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and silica gel column chromatography (ethyl acetate/hexane), and the obtained compound was triturated in diethyl ether/hexane to give the title compound (38.4 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.20-1.44 (1H, m), 1.81-2.03 (2H, m), 2.06-2.61 (5H, m), 2.94-3.44 (7H, m), 3.67 (1H, dd, J = 14.6, 5.9 Hz), 4.00-4.19 (1H, m), 4.30-4.60 (1H, m), 7.05-7.51 (3H, m), 7.89-8.12 (2H, m).

[0331]

Example 258

N-(cis-1-(cyclobutylcarbonyl)-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-(cis-2-((2-bromo-1,3-thiazol-4-yl)methyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)methanesulfonamide (51.1 mg), (3,5-difluorophenyl)boronic acid (25.3 mg), potassium carbonate (35.1 mg), water (0.40 ml) and DME (1.2 ml) was added (A-taPhos)₂PdCl₂ (3.7 mg) at room temperature. The mixture was stirred overnight under nitrogen atmosphere at 80°C. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and silica gel column chromatography (ethyl acetate/hexane), and the obtained compound was triturated in diethyl ether/hexane to give the title compound (30.2 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.33-1.52 (1H, m), 1.80-2.03 (2H, m), 2.06-2.58 (5H, m), 2.96-3.05 (3H, m), 3.07-3.45 (4H, m), 3.60 (1H, dd, J = 14.8, 6.4 Hz), 3.98-4.20 (1H, m), 4.30-4.57 (1H, m), 6.84-6.95 (1H, m), 6.99-7.10 (1H, m), 7.42-7.53 (2H, m), 7.94 (1H, d, J = 8.7 Hz).

[0332]

Example 259

N-(cis-1-(cyclobutylcarbonyl)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)cyclopropanesulfonamide

5 [0333]

A) tert-butyl 3-oxo-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidine-1-carboxylate

To a mixture of tert-butyl 3-oxopyrrolidine-1-carboxylate (185 mg) and toluene (2.00 ml) was added pyrrolidine (85 mg) at
10 room temperature. The mixture was stirred at room temperature for 15 min, and concentrated under reduced pressure. The residue was mixed with CH₃CN (2 ml), and 4-(chloromethyl)-2-phenyl-1,3-thiazole (105 mg) and TBAI (36.9 mg) were added thereto. The mixture was heated under reflux for 1.5 hr, and
15 the reaction mixture was diluted with water. The mixture was extracted with ethyl acetate, and the extract was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (45.3 mg).

20 MS: [M+H]⁺ 359.1.

[0334]

B) tert-butyl cis-3-amino-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidine-1-carboxylate

To a mixture of tert-butyl 3-oxo-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidine-1-carboxylate (3.66 g),
25 ammonium formate (6.44 g) and MeOH (30ml) was added chloro[N-[4-(dimethylamino)phenyl]-2-pyridinecarboxamidato](pentamethylcyclopentadienyl)iridium(III) (123 mg) at room temperature. The mixture was stirred under
30 argon atmosphere at 70°C for 2 hr. The mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate, and the mixture was washed with saturated aqueous sodium hydrogencarbonate solution and saturated brine, and concentrated under reduced pressure to
35 give the title compound (3.42 g).

MS: [M+H]⁺ 360.1.

[0335]

C) tert-butyl cis-3-((cyclopropylsulfonyl)amino)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidine-1-carboxylate

5 To a mixture of tert-butyl cis-3-amino-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidine-1-carboxylate (810 mg), TEA (0.81 ml), DMAP (91.0 mg), THF (5.0 ml) and DMF (6.0 ml) was added cyclopropanesulfonyl chloride (0.57 ml) at room temperature. The mixture was stirred at room temperature for 2
10 hr. To the reaction mixture was added 5% aqueous acetic acid solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified
15 by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (317 mg).

MS: [M+H]⁺ 464.3.

[0336]

D) N-(cis-1-(cyclobutylcarbonyl)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)cyclopropanesulfonamide
20

To a mixture of tert-butyl cis-3-((cyclopropylsulfonyl)amino)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidine-1-carboxylate (72.0 mg), cyclopentyl methyl ether (2.0 mL) and MeOH (2.0 mL) was added 4M hydrogen
25 chloride/cyclopentyl methyl ether solution (2.0 mL) at room temperature. The mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure. To the residue were added DMF (2.0 mL), THF (2.0 mL), TEA (0.088 mL) and cyclobutanecarbonyl chloride (0.050 mL), and the mixture was
30 stirred overnight at room temperature. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified
35 by silica gel column chromatography (NH, ethyl acetate/hexane)

and silica gel column chromatography (ethyl acetate/hexane). The obtained compound was purified by HPLC (C18, mobile phase: water/acetonitrile (containing 0.1% TFA)), and to the obtained fraction was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The extract was dried over sodium sulfate, and concentrated under reduced pressure, and the obtained compound was triturated in diethyl ether/hexane to give the title compound (15.5 mg).

¹H NMR (300 MHz, CDCl₃) δ 0.81-1.44 (6H, m), 1.80-2.53 (7H, m), 3.03-3.53 (4H, m), 3.65 (1H, dd, J = 14.8, 5.7 Hz), 4.03-4.21 (1H, m), 4.45-4.58 (1H, m), 6.88-6.98 (1H, m), 7.41-7.52 (3H, m), 7.88-8.00 (2H, m), 8.11 (1H, d, J = 9.5 Hz).
[0337]

Example 261

N-((2S,3S)-2-(biphenyl-3-ylmethyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)methanesulfonamide
[0338]

A) tert-butyl 2-(3-bromobenzyl)-3-oxopyrrolidine-1-carboxylate
To a mixture of tert-butyl 3-oxopyrrolidine-1-carboxylate (5.4 g) and toluene (50.0 ml) was added pyrrolidine (2.49 g) at room temperature. The mixture was stirred for 15 min, and concentrated. The residue was mixed with CH₃CN (50 ml), and 1-bromo-3-(bromomethyl)benzene (7.29 g) and TBAI (2.15 g) were added thereto. The mixture was heated under reflux for 1 hr, and the reaction mixture was diluted with water. The mixture was extracted with ethyl acetate, and the extract was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (4.00 g).

MS, found: 254.2.

[0339]

B) tert-butyl cis-3-amino-2-(3-bromobenzyl)pyrrolidine-1-carboxylate

To a mixture of tert-butyl 2-(3-bromobenzyl)-3-

oxopyrrolidine-1-carboxylate (1.54 g), ammonium formate (1.37 g) and MeOH (25 ml) was added chloro[N-[4-(dimethylamino)phenyl]-2-pyridinecarboxamidato](pentamethylcyclopentadienyl)iridium(III) (0.026 g) at room temperature. The mixture was stirred under nitrogen atmosphere at 70°C for 2 hr. The mixture was neutralized with saturated aqueous sodium hydrogencarbonate solution at 0°C, and concentrated under reduced pressure. The mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (565 mg).

MS, found: 299.2.

[0340]

C) tert-butyl (2S,3S)-3-amino-2-(3-bromobenzyl)pyrrolidine-1-carboxylate

A racemate (1.5 g) of tert-butyl cis-3-amino-2-(3-bromobenzyl)pyrrolidine-1-carboxylate was resolved by HPLC (column: CHIRALPAK AD(AK001), 50 mmID×500 mmL, Manufactured by Daicel Chemical Industries, mobile phase: hexane/ethanol/diethylamine = 850/150/1) to give the title compound (650 mg) having a shorter retention time.

MS, found: 299.0.

[0341]

D) tert-butyl (2S,3S)-2-(3-bromobenzyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate

A mixture of tert-butyl (2S,3S)-3-amino-2-(3-bromobenzyl)pyrrolidine-1-carboxylate (920 mg), TEA (786 mg) and THF (10 ml) was stirred, and methanesulfonic anhydride (541 mg) was added thereto at room temperature. After 0.5 hr, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.05 g).

MS, found: 333.1.

[0342]

E) N-((2S,3S)-2-(3-bromobenzyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride

5 To 4M hydrogen chloride/ethyl acetate solution (5.42 mL) was added tert-butyl ((2S,3S)-2-(3-bromobenzyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate (470 mg) at room temperature. The mixture was stirred for 1 hr, and the reaction solution was concentrated to give the title compound
10 (370 mg).

MS: [M+H]⁺ 333.1.

[0343]

F) N-((2S,3S)-2-(3-bromobenzyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)methanesulfonamide

15 To a mixture of N-((2S,3S)-2-(3-bromobenzyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (200 mg), TEA (274 mg) and THF (5 ml) was added cyclobutanecarbonyl chloride (96 mg) at room temperature. The mixture was stirred at room temperature for 2 hr. To the mixture was added saturated aqueous sodium
20 hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to
25 give the title compound (220 mg).

MS: [M+H]⁺ 415.2.

[0344]

G) N-((2S,3S)-2-(biphenyl-3-ylmethyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)methanesulfonamide

30 A mixture of N-((2S,3S)-2-(3-bromobenzyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)methanesulfonamide (55 mg), phenylboronic acid (48.4 mg), XPhos Pd G3 (5.60 mg), 1M aqueous tripotassium phosphate solution (0.397 ml) and THF (1 ml) was heated under reflux for 1 hr. The reaction mixture was
35 concentrated under reduced pressure, and the residue was

diluted with ethyl acetate. The mixture was washed with saturated aqueous sodium hydrogencarbonate solution, and purified by silica gel column chromatography (methanol/ethyl acetate). The obtained solid was crystallized from ethyl acetate-diisopropyl ether-hexane to give the title compound (31 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.31-3.01 (11H, m), 3.04-3.79 (4H, m), 3.89-4.74 (3H, m), 7.07-7.63 (10H, m).

[0345]

10 Example 262

N-((2S,3S)-1-(cyclobutylcarbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

[0346]

A) tert-butyl (2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate

A mixture of tert-butyl (2S,3S)-2-(3-bromobenzyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate (2.38 g), (3-fluorophenyl)boronic acid (1.15 g), XPhos Pd G3 (0.139 g), 1M aqueous tripotassium phosphate solution (16.5 ml) and THF (50 ml) was stirred at 70°C for 2 hr. The mixture was concentrated under reduced pressure, and the residue was diluted with saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (2.37 g).

MS: [M+H-Boc]⁺ 349.3.

[0347]

30 B) N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride

To a mixture of tert-butyl (2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate (2.37 g) and ethyl acetate (10 ml) was added 4M hydrogen chloride/ethyl acetate solution (26.4 ml) at room temperature.

The mixture was stirred at room temperature for 2 hr. The mixture was concentrated under reduced pressure, and the obtained solid was collected by filtration with ethyl acetate. The obtained solid was washed with ethyl acetate, and dried to
5 give the title compound (1.88 g).

MS: [M+H]⁺ 349.3.

[0348]

C) N-((2S,3S)-1-(cyclobutylcarbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

10 To a mixture of N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (1.10 g), TEA (1.45 g) and THF (20 ml) was added dropwise cyclobutanecarbonyl chloride (0.508 g) at 0°C. The mixture was stirred at room temperature for 1 hr. To the mixture was added
15 saturated aqueous sodium hydrogencarbonate solution, and the mixture was concentrated under reduced pressure to remove THF. The remaining aqueous layer was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under
20 reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane). The residue was crystallized from ethyl acetate-hexane to give the title compound (1.10 g).

¹H NMR (300 MHz, DMSO-d₆) δ 0.91-2.41 (9H, m), 2.53-3.05 (5H, m), 3.09-3.58 (2H, m), 3.75-3.96 (1H, m), 4.04-4.46 (1H, m), 7.03-7.77 (9H, m).

[0349]

Example 266

N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-1-((1-fluorocyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide
30 [0350]

A) N-((2S,3S)-2-(3-bromobenzyl)-1-((1-fluorocyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-((2S,3S)-2-(3-bromobenzyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (100 mg), 1-
35

fluorocyclobutanecarboxylic acid (50 mg) and DMF (2 ml) were added HATU (154 mg) and DIPEA (105 mg) at room temperature. The mixture was stirred at room temperature for 2 hr. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (109 mg).

MS: [M+H]⁺ 433.1.

[0351]

B) N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-1-((1-fluorocyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide

A mixture of N-((2S,3S)-2-(3-bromobenzyl)-1-((1-fluorocyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide (54.4 mg), (3-fluorophenyl)boronic acid (52.7 mg), XPhos Pd G3 (5.31 mg), 1M tripotassium phosphate (0.377 ml) and THF (1 ml) was stirred at 70°C for 2 hr. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane). The residue was crystallized from ethyl acetate-hexane to give the title compound (42.4 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.28-2.41 (7H, m), 2.52-2.64 (1H, m), 2.70-2.86 (4H, m), 3.00 (1H, dd, J = 13.8, 6.6 Hz), 3.38-3.63 (2H, m), 3.81-4.00 (1H, m, J = 10.2 Hz), 4.37-4.58 (1H, m), 7.12-7.23 (1H, m), 7.24-7.41 (2H, m), 7.43-7.63 (6H, m).

[0352]

Example 269

N-(cis-1-(cyclobutylcarbonyl)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide

[0353]

A) tert-butyl cis-3-(((fluoromethyl)sulfonyl)amino)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidine-1-carboxylate

To a mixture of tert-butyl cis-3-amino-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidine-1-carboxylate (108 mg), DIPEA (58.2 mg) and THF (1 ml) was added fluoromethanesulfonyl chloride (31.8 mg) at 0°C. To the reaction mixture was added water, and the mixture was concentrated under reduced pressure. The residue was diluted with ethyl acetate, and the mixture was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (62.5 mg). MS: [M+H]⁺ 456.1.

[0354]

B) N-(cis-1-(cyclobutylcarbonyl)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide

To a mixture of tert-butyl cis-3-(((fluoromethyl)sulfonyl)amino)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidine-1-carboxylate (31.2 mg) and MeOH (0.200 ml) was added 4M hydrogen chloride/cyclopentyl methyl ether solution (0.342 ml) at room temperature. The mixture was stirred at room temperature for 1 hr, and the reaction solution was concentrated. The residue was mixed with THF (0.7 ml), and TEA (34.7 mg) and cyclobutanecarbonyl chloride (12.2 mg) were added thereto at 0°C. The mixture was stirred at room temperature for 1 hr, and to the mixture was added saturated brine, and the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (22.2 mg). ¹H NMR (300 MHz, CDCl₃) δ ppm 1.35-1.53 (1H, m), 1.81-2.02 (2H, m), 2.14 (5H, br. s.), 3.03-3.39 (4H, m), 3.67 (1H, dd, J = 14.8, 5.7 Hz), 4.13-4.28 (1H, m), 4.42-4.59 (1H, m), 4.92-5.32 (2H, m), 6.98 (1H, s), 7.41-7.51 (3H, m), 7.90-8.03 (2H, m), 8.96 (1H, d, J = 8.7 Hz)

[0355]

Example 293

N-(cis-2-((2-fluorobiphenyl-3-yl)methyl)-1-isobutyryl
pyrrolidin-3-yl)methanesulfonamide

5 [0356]

A) 1-bromo-3-(bromomethyl)-2-fluorobenzene

To a mixture of (3-bromo-2-fluorophenyl)methanol (5.13 g),
PPh₃ (7.88 g) and trifluoromethylbenzene (180 ml) was added
tetrabromomethane (9.96 g) at 0°C. The mixture was stirred at
10 0°C for 2 hr, and the insoluble substance was removed by
filtration, and washed with diethyl ether. The filtrate was
concentrated under reduced pressure. The residue was purified
by silica gel column chromatography (ethyl acetate/hexane) to
give the title compound (6.70 g).

15 ¹H NMR (300 MHz, CDCl₃) δ 4.51 (2H, d, J = 1.1 Hz), 7.02 (1H,
td, J = 8.0, 1.4 Hz), 7.30-7.37 (1H, m), 7.51 (1H, ddd, J = 8.1,
6.4, 1.7 Hz).

[0357]

B) tert-butyl 2-(3-bromo-2-fluorobenzyl)-3-oxopyrrolidine-1-
20 carboxylate

To a mixture of tert-butyl 3-oxopyrrolidine-1-carboxylate
(3.30 g) and toluene (28 ml) was added pyrrolidine (1.52 g) at
room temperature. The mixture was stirred at room temperature
for 30 min, heated under reflux using Dean-Stark apparatus for
25 30 min, and concentrated under reduced pressure. The residue
was mixed with CH₃CN (28 ml), and 1-bromo-3-(bromomethyl)-2-
fluorobenzene (4.77 g) and TBAI (1.32 g) were added to the
mixture at room temperature. The mixture was heated under
reflux for 4.5 hr, and the reaction mixture was poured into
30 water, and the mixture was extracted with ethyl acetate. The
organic layer was washed with water and saturated brine, dried
over anhydrous magnesium sulfate, and concentrated under
reduced pressure. The residue was purified by silica gel
column chromatography (ethyl acetate/hexane) to give the title
35 compound (1.71 g).

^1H NMR (300 MHz, CDCl_3) δ 1.45 (9H, s), 2.12-2.30 (1H, m), 2.44-2.59 (1H, m), 2.97-3.40 (3H, m), 3.74-4.02 (1H, m), 4.21 (1H, t, $J = 5.1$ Hz), 6.89-6.96 (1H, m), 7.05 (1H, t, $J = 6.7$ Hz), 7.43 (1H, ddd, $J = 8.0, 6.4, 1.9$ Hz).

5 [0358]

C) tert-butyl cis-3-amino-2-(3-bromo-2-fluorobenzyl)pyrrolidine-1-carboxylate

A mixture of tert-butyl 2-(3-bromo-2-fluorobenzyl)-3-oxopyrrolidine-1-carboxylate (941 mg), ammonium formate (1.28
10 g), chloro[N-[4-(dimethylamino)phenyl]-2-pyridinecarboxamidato](pentamethylcyclopentadienyl)iridium(III) (30.5 mg) and MeOH (20 ml) was stirred under argon atmosphere at 70°C for 2.5 hr. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution under ice-
15 cooling, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the
20 title compound (427 mg).

MS: $[\text{M}+\text{H}-(\text{tBu})]^+$ 316.9.

[0359]

D) tert-butyl cis-2-(3-bromo-2-fluorobenzyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate

25 To a mixture of tert-butyl cis-3-amino-2-(3-bromo-2-fluorobenzyl)pyrrolidine-1-carboxylate (421 mg), TEA (228 mg) and THF (4 ml) was added methanesulfonyl chloride (155 mg) at room temperature. The mixture was stirred at room temperature for 1 hr, and the reaction mixture was poured into water, and
30 the mixture was extracted with ethyl acetate. The organic layer was washed with aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give crystals. The crystals were collected by filtration, and washed with
35 diisopropyl ether-hexane to give the title compound (437 mg).

MS: [M-H]⁻ 448.9.

[0360]

E) N-(cis-2-(3-bromo-2-fluorobenzyl)pyrrolidin-3-yl)methanesulfonamide

5 To a mixture of tert-butyl cis-2-(3-bromo-2-fluorobenzyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate (434 mg) and toluene (4.8 ml) was added TFA (4.8 ml) at room temperature. The mixture was stirred at room temperature for 1 hr, and the reaction mixture was poured into
10 saturated aqueous sodium hydrogencarbonate solution under ice-cooling. The mixture was basified to pH=8 with potassium carbonate, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to
15 give crystals. The crystals were collected by filtration, and washed with diisopropyl ether-hexane to give the title compound (245 mg).

MS: [M+H]⁺ 350.9.

[0361]

20 F) N-(cis-2-(3-bromo-2-fluorobenzyl)-1-isobutyryl pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-(cis-2-(3-bromo-2-fluorobenzyl)pyrrolidin-3-yl)methanesulfonamide (120 mg), TEA (104 mg) and THF (3 ml) was added 2-methylpropanoyl chloride
25 (72.8 mg) at room temperature. The mixture was stirred at room temperature for 1 hr, added to aqueous sodium hydrogencarbonate solution, and extracted with THF-ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced
30 pressure to give crystals. The crystals were collected by filtration, and washed with diisopropyl ether-hexane to give the title compound (132 mg).

MS: [M+H]⁺ 421.0.

[0362]

35 G) N-(cis-2-((2-fluorobiphenyl-3-yl)methyl)-1-isobutyryl

pyrrolidin-3-yl)methanesulfonamide

A mixture of N-(cis-2-(3-bromo-2-fluorobenzyl)-1-isobutyryl pyrrolidin-3-yl)methanesulfonamide (63 mg), phenylboronic acid (36.5 mg), XPhos Pd G3 (6.33 mg), 1 M aqueous tripotassium phosphate solution (0.449 ml) and THF (1.5 ml) was stirred under argon atmosphere at 70°C for 1 hr. The mixture was poured into aqueous sodium hydrogencarbonate solution, and extracted with THF-ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (52.8 mg).

¹H NMR (300 MHz, CDCl₃) δ 0.57-1.14 (6H, m), 1.83-2.13 (1H, m), 2.27-2.41 (1H, m), 2.53-3.20 (6H, m), 3.40-3.55 (2H, m), 3.65-4.11 (1H, m), 4.35-4.67 (1H, m), 4.81-4.89 (1H, m), 7.10-7.20 (1H, m), 7.28-7.54 (7H, m).

[0363]

Example 294

N-(cis-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-isobutyryl pyrrolidin-3-yl)methanesulfonamide

A mixture of N-(cis-2-(3-bromo-2-fluorobenzyl)-1-isobutyryl pyrrolidin-3-yl)methanesulfonamide (62 mg), (3-fluorophenyl)boronic acid (41.2 mg), Xphos Pd G3 (6.23 mg), 1 M aqueous tripotassium phosphate solution (0.441 ml) and THF (1.5 ml) was stirred under argon atmosphere at 70°C for 1 hr. The mixture was poured into aqueous sodium hydrogencarbonate solution, and extracted with THF-ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (53.2 mg).

¹H NMR (300 MHz, CDCl₃) δ 0.56-1.13 (6H, m), 1.86-2.08 (1H, m), 2.29-2.43 (1H, m), 2.55-3.21 (6H, m), 3.41-3.78 (2H, m), 3.97-

4.11 (1H, m), 4.36-4.67 (1H, m), 4.77-4.86 (1H, m), 7.03-7.11 (1H, m), 7.14-7.23 (2H, m), 7.27-7.51 (4H, m).

[0364]

Example 299

5 N-(cis-1-(cyclobutylcarbonyl)-2-((5-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

[0365]

A) tert-butyl 2-(3-bromo-5-fluorobenzyl)-3-oxopyrrolidine-1-carboxylate

10 To a mixture of tert-butyl 3-oxopyrrolidine-1-carboxylate (3.44 g) and toluene (30 ml) was added pyrrolidine (1.59 g) at room temperature. The mixture was stirred at room temperature for 20 min, heated under reflux for 20 min using Dean-Stark apparatus, and concentrated under reduced pressure. The
15 residue was mixed with CH₃CN (30 ml), and 1-bromo-3-(bromomethyl)-5-fluorobenzene (4.98 g) and TBAI (1.37 g) were added to the mixture at room temperature. The mixture was heated under reflux for 4.5 hr, and the reaction mixture was poured into water, and the mixture was extracted with ethyl
20 acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (2.83 g).

25 MS: [M+H-Boc]⁺ 271.9.

[0366]

B) tert-butyl cis-3-amino-2-(3-bromo-5-fluorobenzyl)pyrrolidine-1-carboxylate

A mixture of tert-butyl 2-(3-bromo-5-fluorobenzyl)-3-oxopyrrolidine-1-carboxylate (2.82 g), ammonium formate (3.82 g), chloro[N-[4-(dimethylamino)phenyl]-2-pyridinecarboxamidato](pentamethylcyclopentadienyl)iridium(III) (0.069 g) and MeOH (60 ml) was stirred under argon atmosphere at 70°C for 2.5 hr. The reaction mixture was poured into
35 saturated aqueous sodium hydrogencarbonate solution under ice-

cooling, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel
5 column chromatography (methanol/ethyl acetate) to give the title compound (1.07 g).

MS: $[M+H-(tBu)]^+ 316.9$.

[0367]

C) tert-butyl cis-2-(3-bromo-5-fluorobenzyl)-3-
10 ((methylsulfonyl)amino)pyrrolidine-1-carboxylate

To a mixture of tert-butyl cis-3-amino-2-(3-bromo-5-fluorobenzyl)pyrrolidine-1-carboxylate (1.06 g), TEA (0.575 g) and THF (10 ml) was added methanesulfonyl chloride (0.390 g) at room temperature. The mixture was stirred at room temperature
15 for 1 hr, and the reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The organic layer was washed with aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give crystals. The
20 crystals were collected by filtration, and washed with diisopropyl ether-hexane to give the title compound (1.09 g).

MS: $[M-H]^- 448.8$.

[0368]

D) N-(cis-2-(3-bromo-5-fluorobenzyl)pyrrolidin-3-
25 yl)methanesulfonamide

To a mixture of tert-butyl cis-2-(3-bromo-5-fluorobenzyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate (1.09 g) and toluene (12 ml) was added TFA (12 ml) at room temperature. The mixture was stirred at room
30 temperature for 1 hr, and poured into saturated aqueous sodium hydrogencarbonate solution under ice-cooling. The mixture was basified to pH=8 with potassium carbonate, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and
35 concentrated under reduced pressure to give crystals. The

crystals were collected by filtration, and washed with diisopropyl ether-hexane to give the title compound (245 mg).

MS: [M+H]⁺ 350.9.

[0369]

- 5 E) N-(cis-2-(3-bromo-5-fluorobenzyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-(cis-2-(3-bromo-5-fluorobenzyl)pyrrolidin-3-yl)methanesulfonamide (229 mg), TEA (198 mg) and THF (5.6 ml) was added cyclobutanecarbonyl chloride (155 mg) at room temperature. The mixture was stirred at room temperature for 1 hr, added to aqueous sodium hydrogencarbonate solution, and extracted with THF-ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give crystals. The crystals were collected by filtration, and washed with diisopropyl ether-hexane to give the title compound (261 mg).

MS: [M+H]⁺ 433.0.

[0370]

- 20 F) N-(cis-1-(cyclobutylcarbonyl)-2-((5-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

A mixture of N-(cis-2-(3-bromo-5-fluorobenzyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)methanesulfonamide (128 mg), phenylboronic acid (72.0 mg), XPhos Pd G3 (12.5 mg), 1 M aqueous tripotassium phosphate solution (0.886 ml) and THF (3 ml) was stirred under argon atmosphere at 70°C for 1 hr. The mixture was poured into aqueous sodium hydrogencarbonate solution, and extracted with THF-ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (107 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.66-2.39 (8H, m), 2.47-3.22 (6H, m), 3.28-3.78 (2H, m), 3.89-4.04 (1H, m), 4.23-4.81 (2H, m), 6.84-

7.10 (1H, m), 7.11-7.19 (1H, m), 7.31-7.48 (4H, m), 7.50-7.57 (2H, m).

[0371]

Example 300

5 N-(cis-1-(cyclobutylcarbonyl)-2-((3',5-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

A mixture of N-(cis-2-(3-bromo-5-fluorobenzyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)methanesulfonamide (126 mg), (3-fluorophenyl)boronic acid (81 mg), XPhos Pd G3 (12.3 mg), 1
10 M aqueous tripotassium phosphate solution (0.872 ml) and THF (2.9 ml) was stirred under argon atmosphere at 70°C for 1 hr. The mixture was poured into aqueous sodium hydrogencarbonate solution, and extracted with THF-ethyl acetate. The organic layer was washed with water and saturated brine, dried over
15 anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (118 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.67-2.38 (8H, m), 2.43-3.22 (6H, m),
20 3.28-3.82 (2H, m), 3.89-4.06 (1H, m), 4.22-4.66 (1H, m), 4.68-4.84 (1H, m), 6.88-7.24 (4H, m), 7.27-7.45 (3H, m).

[0372]

Example 303

N-(cis-1-(cyclobutylcarbonyl)-2-((6-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide
25

[0373]

A) tert-butyl 2-(3-bromo-4-fluorobenzyl)-3-oxopyrrolidine-1-carboxylate

To a mixture of tert-butyl 3-oxopyrrolidine-1-carboxylate
30 (3.46 g) and toluene (30 ml) was added pyrrolidine (1.59 g) at room temperature. The mixture was stirred at room temperature for 30 min, heated under reflux for 30 min using Dean-Stark apparatus, and concentrated under reduced pressure. The residue was mixed with CH₃CN (30 ml), and 2-bromo-4-
35 (bromomethyl)-1-fluorobenzene (5.00 g) and TBAI (1.38 g) were

added to the mixture at room temperature. The mixture was heated under reflux for 4 hr, and the reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.59 g).

MS: [M+H-Boc]⁺ 271.9.

10 [0374]

B) tert-butyl cis-3-amino-2-(3-bromo-4-fluorobenzyl)pyrrolidine-1-carboxylate

A mixture of tert-butyl 2-(3-bromo-4-fluorobenzyl)-3-oxopyrrolidine-1-carboxylate (1.59 g), ammonium formate (1.35 g), chloro[N-[4-(dimethylamino)phenyl]-2-pyridinecarboxamidato](pentamethylcyclopentadienyl)iridium(III) (0.026 g) and MeOH (25 ml) was stirred under argon atmosphere at 70°C for 2.5 hr. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution under ice-cooling, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (548 mg).

MS: [M+H-(tBu)]⁺ 317.0.

[0375]

C) tert-butyl cis-2-(3-bromo-4-fluorobenzyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate

30 To a mixture of tert-butyl cis-3-amino-2-(3-bromo-4-fluorobenzyl)pyrrolidine-1-carboxylate (542 mg), TEA (294 mg) and THF (5.1 ml) was added methanesulfonyl chloride (200 mg) at room temperature. The mixture was stirred at room temperature for 1 hr, and the reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The organic

layer was washed with aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl
5 acetate/hexane) to give the title compound (482 mg).

MS: $[M-H]^-$ 448.8.

[0376]

D) N-(cis-2-(3-bromo-4-fluorobenzyl)pyrrolidin-3-yl)methanesulfonamide

10 To a mixture of tert-butyl cis-2-(3-bromo-4-fluorobenzyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate (477 mg) and toluene (5.3 ml) was added TFA (5.3 ml) at room temperature. The mixture was stirred at room temperature for 1 hr, and poured into saturated aqueous sodium
15 hydrogencarbonate solution under ice-cooling. The mixture was basified to pH=8 with potassium carbonate, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give crystals. The
20 crystals were collected by filtration, and washed with diisopropyl ether-hexane to give the title compound (323 mg).
MS: $[M+H]^+$ 350.9.

[0377]

E) N-(cis-2-(3-bromo-4-fluorobenzyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)methanesulfonamide
25

To a mixture of N-(cis-2-(3-bromo-4-fluorobenzyl)pyrrolidin-3-yl)methanesulfonamide (160 mg), TEA (138 mg) and THF (3.9 ml) was added cyclobutanecarbonyl chloride (108 mg) at room temperature. The mixture was stirred
30 at room temperature for 1 hr, added to aqueous sodium hydrogencarbonate solution, and extracted with THF-ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give crystals. The crystals were
35 collected by filtration, and washed with diisopropyl ether-

hexane to give the title compound (149 mg).

MS: $[M+H]^+$ 433.0.

[0378]

F) N-(cis-1-(cyclobutylcarbonyl)-2-((6-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

A mixture of N-(cis-2-(3-bromo-4-fluorobenzyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)methanesulfonamide (72 mg), phenylboronic acid (40.5 mg), XPhos Pd G3 (7.03 mg), 1 M aqueous tripotassium phosphate solution (0.498 ml) and THF (1.7 ml) was stirred under argon atmosphere at 70°C for 1 hr. The mixture was poured into aqueous sodium hydrogencarbonate solution, and extracted with THF-ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (61.3 mg).

^1H NMR (300 MHz, CDCl_3) δ 1.65-2.58 (9H, m), 2.60-3.20 (5H, m), 3.30-3.80 (2H, m), 3.88-4.04 (1H, m), 4.18-4.76 (2H, m), 7.06-7.21 (2H, m), 7.28-7.54 (6H, m).

[0379]

Example 304

N-(cis-1-(cyclobutylcarbonyl)-2-((3',6-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

A mixture of N-(cis-2-(3-bromo-4-fluorobenzyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)methanesulfonamide (71 mg), (3-fluorophenyl)boronic acid (45.9 mg), XPhos Pd G3 (6.93 mg), 1 M aqueous tripotassium phosphate solution (0.492 ml) and THF (1.7 ml) was stirred under argon atmosphere at 70°C for 1 hr. The mixture was poured into aqueous sodium hydrogencarbonate solution, and extracted with THF-ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give crystals. The

crystals were collected by filtration, and washed with diisopropyl ether-hexane to give the title compound (59.6 mg). ¹H NMR (300 MHz, CDCl₃) δ 1.68-2.57 (9H, m), 2.65-3.20 (5H, m), 3.28-3.81 (2H, m), 3.88-4.05 (1H, m), 4.19-4.74 (2H, m), 7.02-7.26 (4H, m), 7.28-7.45 (3H, m).

[0380]

Example 305

N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-1-((1-methylcyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide

10 To a mixture of N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (50 mg), 1-methylcyclobutanecarboxylic acid (17.8 mg), TEA (65.7 mg) and DMF (2 mL) was added HATU (59.3 mg) at room temperature, and the mixture was stirred at room temperature for 30 min. To 15 the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified 20 by silica gel column chromatography (ethyl acetate/hexane), and crystallized from ethanol and water to give the title compound (50 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.41 (3H, s), 1.60-2.06 (5H, m), 2.19-2.32 (1H, m), 2.33-2.49 (2H, m), 2.55 (3H, s), 2.85-3.02 25 (1H, m), 3.09-3.25 (1H, m), 3.26-3.49 (2H, m), 3.86-4.04 (1H, m), 4.35-4.49 (1H, m), 4.60-4.74 (1H, m), 6.92-7.13 (1H, m), 7.27-7.58 (7H, m).

[0381]

Example 306

30 N-((2S,3S)-1-(bicyclo[1.1.1]pent-1-ylcarbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (50 mg), bicyclo[1.1.1]pentane-1-carboxylic acid (17.5 mg), TEA 35 (65.7 mg) and DMF (2 mL) was added HATU (59.3 mg) at room

temperature, and the mixture was stirred at room temperature for 30 min. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with
5 saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane), and crystallized from ethyl acetate and hexane to give the title compound (10 mg).

10 ^1H NMR (300 MHz, CDCl_3) δ 1.66-1.94 (2H, m), 2.07-2.34 (6H, m), 2.46-2.60 (3H, m), 2.90-3.23 (2H, m), 3.32-3.82 (3H, m), 3.89-4.07 (1H, m), 4.30-4.47 (1H, m), 4.57-4.70 (1H, m), 6.98-7.10 (1H, m), 7.27-7.55 (7H, m).

[0382]

15 Example 307

N-((2S,3S)-1-(bicyclo[1.1.1]pent-1-ylcarbonyl)-2-((3',5'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide
[0383]

A) N-((2S,3S)-1-(bicyclo[1.1.1]pent-1-ylcarbonyl)-2-(3-bromobenzyl)pyrrolidin-3-yl)methanesulfonamide
20

To a mixture of N-((2S,3S)-2-(3-bromobenzyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (240 mg), bicyclo[1.1.1]pentane-1-carboxylic acid (80 mg), TEA (328 mg) and DMF (2 mL) was added HATU (296 mg) at room temperature, and
25 the mixture was stirred at room temperature for 30 min. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under
30 reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (270 mg).

MS: $[\text{M}+\text{H}]^+$ 427.2.

[0384]

35 B) N-((2S,3S)-1-(bicyclo[1.1.1]pent-1-ylcarbonyl)-2-((3',5'-

difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

A mixture of N-((2S,3S)-1-(bicyclo[1.1.1]pent-1-ylcarbonyl)-2-(3-bromobenzyl)pyrrolidin-3-yl)methanesulfonamide (55 mg), (3,5-difluorophenyl)boronic acid (61.0 mg), XPhos Pd G3 (5.45 mg), 1M aqueous tripotassium phosphate solution (0.356 mL) and THF (1 mL) was heated under reflux for 1 hr. The mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The mixture was washed with water and saturated brine, and purified by silica gel column chromatography (ethyl acetate/hexane), and the obtained product was crystallized from ethyl acetate and hexane to give the title compound (25 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.68-1.87 (2H, m), 2.08-2.35 (6H, m), 2.44-2.65 (3H, m), 2.67-3.87 (5H, m), 3.88-4.05 (1H, m), 4.36-4.51 (1H, m), 4.57-4.67 (1H, m), 6.73-6.86 (1H, m), 7.02-7.12 (2H, m), 7.28-7.50 (4H, m).

[0385]

Example 308

N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-1-((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (49.6 mg), 1-hydroxycyclobutanecarboxylic acid (18.0 mg) and DMF (1 mL) were added HATU (73.5 mg) and DIPEA (50.0 mg) at room temperature. The mixture was stirred overnight at room temperature. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (45.5 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.28 (1H, dd, J = 19.1, 8.5 Hz), 1.55-2.14 (5H, m), 2.36-2.46 (2H, m), 2.62-2.74 (3H, m), 2.80 (1H, dd, J = 13.6, 4.9 Hz), 2.91-3.06 (1H, m), 3.48-3.68 (2H,

m), 3.84 (1H, brs), 4.36-4.72 (1H, m), 5.63-6.07 (1H, m), 7.12-7.23 (1H, m), 7.31-7.42 (2H, m), 7.45-7.57 (5H, m), 7.64 (1H, s).

[0386]

5 Example 309

N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-1-((1-(trifluoromethyl)cyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (51.0 mg), 1-(trifluoromethyl)cyclobutanecarboxylic acid (26.7 mg) and DMF (1 ml) were added HATU (76 mg) and DIPEA (51.4 mg) at room temperature. The mixture was stirred overnight at room temperature. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (54.5 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.40 (1H, d, J = 10.6 Hz), 1.74-2.08 (2H, m), 2.11-2.37 (4H, m), 2.53-2.66 (1H, m), 2.68-2.83 (4H, m), 2.98 (1H, dd, J = 13.8, 6.6 Hz), 3.32-3.41 (1H, m), 3.45-3.61 (1H, m), 3.86 (1H, d, J = 9.8 Hz), 4.53 (1H, q, J = 7.3 Hz), 7.12-7.24 (1H, m), 7.30-7.41 (2H, m), 7.43-7.56 (4H, m), 7.59 (1H, s), 7.63 (1H, s).

[0387]

Example 310

N-((2S,3S)-1-(cyclobutylcarbonyl)-2-((3',5'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

A mixture of N-((2S,3S)-2-(3-bromobenzyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)methanesulfonamide (49.5 mg), (3,5-difluorophenyl)boronic acid (28.2 mg), 1M aqueous tripotassium phosphate solution (0.358 ml), XPhos Pd G3 (3.03 mg) and THF (2 ml) was stirred under nitrogen atmosphere at

70°C for 1 hr. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane). The obtained solid was crystallized from ethyl acetate/hexane to give the title compound (32.7 mg).
¹H NMR (300 MHz, DMSO-d₆) δ 0.86-2.40 (9H, m), 2.64-3.30 (6H, m), 3.33-3.58 (1H, m), 3.75-3.98 (1H, m), 4.02-4.46 (1H, m), 7.13-7.69 (8H, m).

[0388]

Example 311

N-((2S,3S)-1-(cyclobutylcarbonyl)-2-((3'-methylbiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

A mixture of N-((2S,3S)-2-(3-bromobenzyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)methanesulfonamide (51.4 mg), (3-methylphenyl)boronic acid (25.2 mg), 1M aqueous tripotassium phosphate solution (0.371 ml), XPhos Pd G3 (3.14 mg) and THF (2 ml) was stirred under nitrogen atmosphere at 70°C for 1 hr. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (52.0 mg).
¹H NMR (300 MHz, DMSO-d₆) δ 0.91-2.36 (8H, m), 2.37 (3H, s), 2.64-3.07 (5H, m), 3.11-3.60 (3H, m), 3.73-3.97 (1H, m), 4.01-4.45 (1H, m), 7.09-7.69 (9H, m).

[0389]

Example 312

N-((2S,3S)-1-(cyclobutylcarbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)-1-methoxymethanesulfonamide

[0390]

A) tert-butyl (2S,3S)-2-(3-bromobenzyl)-3-
(((bromomethyl)sulfonyl)amino)pyrrolidine-1-carboxylate

To a mixture of tert-butyl (2S,3S)-3-amino-2-(3-bromobenzyl)pyrrolidine-1-carboxylate (900 mg) and THF (3 ml) were added DIPEA (1.33 mL) and bromomethanesulfonyl chloride (0.392 mL) at 0°C. The mixture was stirred for 30 min, and to the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the title compound (1.35 g).

MS: [M-H]⁺510.8

[0391]

B) tert-butyl (2S,3S)-2-(3-bromobenzyl)-3-
(((methoxymethyl)sulfonyl)amino)pyrrolidine-1-carboxylate

A mixture of tert-butyl (2S,3S)-2-(3-bromobenzyl)-3-(((bromomethyl)sulfonyl)amino)pyrrolidine-1-carboxylate (1.20 g), silver(I) carbonate (3.23 g) and MeOH (3 ml) was heated in a sealed tube to 100°C. The mixture was stirred for 3 hr, and filtered, saturated aqueous sodium hydrogencarbonate solution was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (640 mg).

MS: [M-H]⁺460.9

[0392]

C) tert-butyl (2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-3-
(((methoxymethyl)sulfonyl)amino)pyrrolidine-1-carboxylate

A mixture of tert-butyl (2S,3S)-2-(3-bromobenzyl)-3-(((methoxymethyl)sulfonyl)amino)pyrrolidine-1-carboxylate (342 mg), (3-fluorophenyl)boronic acid (155 mg), XPhos Pd G3 (125 mg), 1M aqueous tripotassium phosphate solution (1 ml) and THF (1 ml) was stirred at 60°C for 1 hr. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the

mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (286 mg).

MS: [M-H]⁺477.0.

[0393]

D) N-((2S,3S)-1-(cyclobutylcarbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)-1-methoxymethanesulfonamide

To tert-butyl (2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-3-(((methoxymethyl)sulfonyl)amino)pyrrolidine-1-carboxylate (58 mg) was added 4M hydrogen chloride/ethyl acetate solution (1 ml), and the mixture was stirred for 1 hr. The reaction solution was concentrated, and to a mixture of the residue and THF (1 ml) were added TEA (0.084 mL) and cyclobutanecarbonyl chloride (17.2 mg) at room temperature. The mixture was stirred for 30 min, and to the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (28 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.63-2.01 (4H, m), 2.07-2.67 (5H, m), 3.00-3.23 (2H, m), 3.26-3.53 (2H, m), 3.55-3.71 (3H, m), 3.92-4.27 (3H, m), 4.50 (2H, s), 6.93-7.24 (2H, m), 7.29-7.55 (6H, m).

[0394]

Example 313

N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (50.2 mg) and THF (2 ml) were added bis(trichloromethyl) carbonate (31.0 mg) and DIPEA (33.7 mg) at 0°C. The mixture

was stirred at 0°C for 10 min, and the reaction solution was concentrated. To the obtained residue were added THF (2 ml) and azetidine (22.3 mg). The mixture was stirred at room temperature for 2 hr. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane). The obtained solid was crystallized from ethyl acetate/hexane to give the title compound (44.7 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.79-2.02 (3H, m), 2.08 (1H, dt, J = 7.5, 4.0 Hz), 2.68-2.79 (1H, m), 2.83 (3H, s), 2.86-2.97 (1H, m), 3.09-3.22 (1H, m), 3.26-3.38 (1H, m), 3.60 (2H, q, J = 7.6 Hz), 3.79 (3H, q, J = 7.6 Hz), 4.28 (1H, q, J = 6.7 Hz), 7.12-7.23 (1H, m), 7.26-7.32 (1H, m), 7.32-7.41 (1H, m), 7.44-7.55 (5H, m), 7.57 (1H, s).

[0395]

Example 314

N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-1-((1-methoxycyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (50 mg), 1-methoxycyclobutanecarboxylic acid (20.3 mg), TEA (65.7 mg) and DMF (2 mL) was added HATU (59.3 mg) at room temperature, and the mixture was stirred at room temperature for 30 min. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane), and crystallized from ethyl acetate, diisopropyl ether and hexane to give the title compound (53 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.60-2.03 (3H, m), 2.03-2.20 (2H, m), 2.20-2.37 (1H, m), 2.42-2.61 (5H, m), 2.85-2.98 (1H, m), 3.08 (3H, s), 3.19-3.30 (1H, m), 3.52-3.66 (2H, m), 3.91-4.09 (1H, m), 4.36-4.48 (1H, m), 4.68-4.80 (1H, m), 6.98-7.09 (1H, m),
5 7.26-7.48 (6H, m), 7.53-7.58 (1H, m).

[0396]

Example 315

N-(cis-1-(cyclobutylcarbonyl)-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide

10 [0397]

A) tert-butyl cis-2-((2-bromo-1,3-thiazol-4-yl)methyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate

To a mixture of tert-butyl cis-3-amino-2-((2-bromo-1,3-thiazol-4-yl)methyl)pyrrolidine-1-carboxylate (500 mg), TEA
15 (209 mg) and THF (5 mL) was added ethanesulfonyl chloride (213 mg) at room temperature. The mixture was stirred at room temperature for 1 hr, and diluted with ethyl acetate. The insoluble substance was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was
20 purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (610 mg).

MS: [M+H]⁺ 454.1.

[0398]

B) tert-butyl cis-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate
25

A mixture of tert-butyl cis-2-((2-bromo-1,3-thiazol-4-yl)methyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate (610 mg), (3,5-difluorophenyl)boronic acid (318 mg), (A-taPhos)₂PdCl₂ (90 mg), potassium carbonate (371 mg), DME (4.8
30 mL) and water (1.6 mL) was stirred under nitrogen atmosphere at 90°C for 30 min. The mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (595 mg).

MS: [M+H]⁺ 488.3.

35 [0399]

C) N-(cis-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide dihydrochloride

To a mixture of tert-butyl cis-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)-3-

5 ((ethylsulfonyl)amino)pyrrolidine-1-carboxylate (595 mg) and MeOH (2 mL) was added 4M hydrogen chloride/cyclopentyl methyl ether solution (8 mL) at room temperature. The mixture was stirred at room temperature for 30 min, and the reaction mixture was concentrated to give the title compound (560 mg).

10 MS: [M+H]⁺ 388.2.

[0400]

D) N-(cis-1-(cyclobutylcarbonyl)-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide

To a mixture of N-(cis-2-((2-(3,5-difluorophenyl)-1,3-
15 thiazol-4-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide dihydrochloride (100 mg), TEA (110 mg) and THF (2 mL) was added cyclobutanecarbonyl chloride (38.6 mg) at room temperature. The mixture was stirred at room temperature for 1 hr, and the reaction mixture was diluted with ethyl acetate. The insoluble
20 substance was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (73 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.16 (3H, s), 1.28-2.23 (8H, m),
25 2.65-3.47 (7H, m), 3.77-3.96 (1H, m), 4.15-4.49 (1H, m), 7.31-7.74 (5H, m).

[0401]

Example 316

N-(cis-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)-1-
30 ((1-methylcyclobutyl)carbonyl)pyrrolidin-3-yl)ethanesulfonamide

To a mixture of N-(cis-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide dihydrochloride (100 mg), 1-methylcyclobutanecarboxylic acid (29.8 mg), TEA (110 mg) and DMF (2 mL) was added HATU (99 mg)
35 at room temperature, and the mixture was stirred at room

temperature for 30 min. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane), and crystallized from ethyl acetate, diisopropyl ether and hexane to give the title compound (68 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 1.08-1.30 (6H, m), 1.35-1.51 (1H, m), 1.55-1.69 (2H, m), 1.70-1.93 (2H, m), 2.04-2.21 (2H, m), 2.24-2.39 (1H, m), 2.82-3.30 (6H, m), 3.75-3.94 (1H, m), 4.39-4.53 (1H, m), 7.31-7.44 (1H, m), 7.48 (1H, s), 7.52-7.69 (3H, m).

[0402]

Example 317

N-(cis-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)-1-((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-yl)ethanesulfonamide

To a mixture of N-(cis-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide dihydrochloride (100 mg), 1-hydroxycyclobutanecarboxylic acid (30.3 mg), TEA (110 mg) and DMF (2 mL) was added HATU (99 mg) at room temperature, and the mixture was stirred at room temperature for 30 min. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane), and crystallized from ethyl acetate, diisopropyl ether and hexane to give the title compound (56 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 1.16 (3H, t, J = 7.4 Hz), 1.22-1.49 (1H, m), 1.55-1.82 (2H, m), 1.83-2.17 (3H, m), 2.31-2.47 (2H, m), 2.87-3.28 (4H, m), 3.37-3.52 (1H, m), 3.54-3.71 (1H, m), 3.73-3.94 (1H, m), 4.39-4.57 (1H, m), 5.73 (1H, s), 7.31-7.43

(1H, m), 7.47 (1H, s), 7.51-7.58 (1H, m), 7.59-7.68 (2H, m).
[0403]

Example 318

N-(cis-1-(bicyclo[1.1.1]pent-1-ylcarbonyl)-2-((2-(3,5-
5 difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-
yl)ethanesulfonamide

To a mixture of N-(cis-2-((2-(3,5-difluorophenyl)-1,3-
thiazol-4-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide
dihydrochloride (100 mg), bicyclo[1.1.1]pentane-1-carboxylic
10 acid (29.2 mg), TEA (110 mg) and DMF (2 mL) was added HATU (99
mg) at room temperature, and the mixture was stirred at room
temperature for 30 min. To the mixture was added saturated
aqueous sodium hydrogencarbonate solution, and the mixture was
extracted with ethyl acetate. The organic layer was separated,
15 washed with saturated brine, dried over anhydrous magnesium
sulfate, and concentrated under reduced pressure. The residue
was purified by silica gel column chromatography (ethyl
acetate/hexane), and crystallized from ethyl acetate,
diisopropyl ether and hexane to give the title compound (41 mg).
20 ¹H NMR (300 MHz, DMSO-d₆) δ 1.11-1.21 (3H, m), 1.63-2.03 (7H,
m), 2.05-2.19 (1H, m), 2.22-2.42 (1H, m), 2.75-3.55 (6H, m),
3.75-3.96 (1H, m), 4.34-4.60 (1H, m), 7.27-7.69 (5H, m).

[0404]

Example 319

25 N-(cis-1-(cyclobutylcarbonyl)-2-((2-phenyl-1,3-thiazol-4-
yl)methyl)pyrrolidin-3-yl)methanesulfonamide

[0405]

A) tert-butyl cis-3-((methylsulfonyl)amino)-2-((2-phenyl-1,3-
thiazol-4-yl)methyl)pyrrolidine-1-carboxylate

30 To a mixture of tert-butyl cis-3-amino-2-((2-phenyl-1,3-
thiazol-4-yl)methyl)pyrrolidine-1-carboxylate (45.3 mg), TEA
(25.5 mg) and THF (1 mL) was added methanesulfonic anhydride
(28.5 mg) at 0°C, and the reaction solution was concentrated
under reduced pressure. The residue was purified by silica gel
35 column chromatography (ethyl acetate/hexane) to give the title

compound (44.3 mg).

MS: [M+H]⁺ 438.2.

[0406]

B) N-(cis-1-(cyclobutylcarbonyl)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

A mixture of tert-butyl cis-3-((methylsulfonyl)amino)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidine-1-carboxylate (44.3 mg), 4M hydrogen chloride/cyclopentyl methyl ether solution (0.506 mL) and MeOH (0.25 mL) was stirred at room temperature for 30 min, and the reaction solution was concentrated under reduced pressure. The residue was suspended in THF (0.8 mL), and TEA (51.2 mg) and cyclobutanecarbonyl chloride (18.0 mg) were added thereto at 0°C. The mixture was stirred at room temperature for 1 hr, saturated brine was added thereto, and the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (32.9 mg).

¹H NMR (400 MHz, CDCl₃) δ 1.32-1.51 (1H, m), 1.82-2.03 (2H, m), 2.07-2.59 (5H, m), 2.96-3.03 (3H, m), 3.07-3.41 (4H, m), 3.55-3.67 (1H, m), 4.02-4.09 (1H, m), 4.29-4.58 (1H, m), 6.84-7.04 (1H, m), 7.39-7.53 (3H, m), 7.88-8.00 (2H, m), 8.29 (1H, d, J = 9.5 Hz).

[0407]

Example 320

N-((2S,3S)-1-(cyclobutylcarbonyl)-2-((2-(3-fluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

A racemate (123 mg) of N-(cis-1-(cyclobutylcarbonyl)-2-((2-(3-fluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide was resolved by HPLC (column: CHIRALPAK OD (IK001), 50 mmID×500 mmL, Manufactured by Daicel Chemical Industries, mobile phase: hexane/ethanol = 600/400) to give a compound having a shorter retention time. The obtained compound was triturated in diethyl ether/hexane to give the title compound (43.2 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.35-1.50 (1H, m), 1.82-2.47 (7H, m), 2.95-3.40 (7H, m), 3.61 (1H, dd, J = 14.7, 6.0 Hz), 3.88-4.19 (1H, m), 4.30-4.57 (1H, m), 6.89-7.05 (1H, m), 7.10-7.20 (1H, m), 7.40-7.50 (1H, m), 7.59-7.68 (1H, m), 7.70-7.78 (1H, m),
5 8.12 (1H, d, J = 9.1 Hz).

[0408]

Example 321

N-((2S,3S)-1-(cyclobutylcarbonyl)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)cyclopropanesulfonamide

10 A racemate (234 mg) of N-(cis-1-(cyclobutylcarbonyl)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)cyclopropanesulfonamide was resolved by HPLC (column: CHIRALPAK AS (CC001), 50 mmID×500 mmL, Manufactured by Daicel Chemical Industries, mobile phase: hexane/ethanol = 700/300) to
15 give a compound having a longer retention time. The obtained compound was triturated in diethyl ether/hexane to give the title compound (42.6 mg).

¹H NMR (300 MHz, CDCl₃) δ 0.80-1.44 (5H, m), 1.81-2.50 (8H, m), 3.02-3.39 (4H, m), 3.65 (1H, dd, J = 14.8, 5.7 Hz), 4.03-4.21
20 (1H, m), 4.43-4.57 (1H, m), 6.89-6.97 (1H, m), 7.41-7.57 (3H, m), 7.90-7.96 (2H, m), 8.11 (1H, d, J = 9.8 Hz).

[0409]

Example 322

N-(cis-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)-1-
25 ((1-methylcyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide

[0410]

A) tert-butyl cis-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate

30 A mixture of tert-butyl cis-2-((2-bromo-1,3-thiazol-4-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate (430 mg), (3,5-difluorophenyl)boronic acid (231 mg), (A-taPhos)₂PdCl₂ (32.8 mg), potassium carbonate (270 mg), DME (4 mL) and water (1 mL) was stirred under nitrogen atmosphere at
35 80°C for 30 min. The reaction solution was concentrated under

reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (379 mg).

MS: [M+H]⁺ 474.1.

5 [0411]

B) N-(cis-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide dihydrochloride

A mixture of tert-butyl cis-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-10 1-carboxylate (379 mg), 4M hydrogen chloride/cyclopentyl methyl ether solution (4 mL) and MeOH (2 mL) was stirred at room temperature for 1 hr, and the reaction solution was concentrated under reduced pressure to give the title compound (420 mg).

15 MS: [M+H]⁺ 374.0.

[0412]

C) N-(cis-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)-1-((1-methylcyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide

20 To a mixture of N-(cis-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide dihydrochloride (80 mg) and DMF (1 mL) were added TEA (0.106 mL), 1-methylcyclobutanecarboxylic acid (20.9 mg) and HATU (69.5 mg) at room temperature. The mixture was stirred for 1
25 hr, and to the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified
30 by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (60.7 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.33 (3H, s), 1.64-1.85 (4H, m), 1.88-2.00 (1H, m), 2.06-2.20 (1H, m), 2.22-2.55 (2H, m), 2.98-3.31 (6H, m), 3.68 (1H, dd, J = 14.7, 6.4 Hz), 4.01-4.24 (1H, 35 m), 4.51 (1H, t, J = 6.6 Hz), 6.76-7.00 (1H, m), 7.08 (1H, s),

7.38-7.63 (2H, m), 8.21 (1H, d, J = 8.7 Hz).

[0413]

Example 323

N-(cis-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)-1-
5 ((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-
yl)methanesulfonamide

To a mixture of N-(cis-2-((2-(3,5-difluorophenyl)-1,3-
thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide
dihydrochloride (80 mg) and DMF (1 mL) were added TEA (0.106
10 mL), 1-hydroxycyclobutanecarboxylic acid (21.2 mg) and HATU
(69.5 mg) at room temperature. The mixture was stirred for 1
hr, and to the mixture was added saturated aqueous sodium
hydrogencarbonate solution, and the mixture was extracted with
ethyl acetate. The organic layer was separated, washed with
15 saturated brine, dried over anhydrous sodium sulfate, and
concentrated under reduced pressure. The residue was purified
by silica gel column chromatography (ethyl acetate/hexane) to
give the title compound (65 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.41-1.56 (1H, m), 1.63-1.74 (1H, m),
20 1.88-2.23 (4H, m), 2.35-2.40 (1H, m), 2.42-2.58 (1H, m), 2.58-
2.78 (1H, m), 3.02 (3H, s), 3.19 (1H, d, J = 14.7 Hz), 3.29-
3.43 (1H, m), 3.45-3.74 (2H, m), 3.98-4.27 (1H, m), 4.53 (1H, t,
J = 6.6 Hz), 6.79-6.95 (1H, m), 7.10 (1H, s), 7.41-7.54 (2H, m),
8.02 (1H, d, J = 9.0 Hz).

25 [0414]

Example 324

N-((2S,3S)-2-(biphenyl-3-ylmethyl)-1-
(cyclobutylcarbonyl)pyrrolidin-3-yl)-1-
methoxymethanesulfonamide

30 [0415]

A) tert-butyl (2S,3S)-2-(biphenyl-3-ylmethyl)-3-
((methoxymethyl)sulfonyl)amino)pyrrolidine-1-carboxylate

A mixture of tert-butyl (2S,3S)-2-(3-bromobenzyl)-3-
((methoxymethyl)sulfonyl)amino)pyrrolidine-1-carboxylate (200
35 mg), phenylboronic acid (79 mg), XPhos Pd G3 (73.2 mg), 1M

aqueous tripotassium phosphate solution (1 ml) and THF (1 ml) was stirred at 60°C for 30 min. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer
5 was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (188 mg).

MS: [M-H]⁺459.0.

10 [0416]

B) N-((2S,3S)-2-(biphenyl-3-ylmethyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)-1-methoxymethanesulfonamide

To tert-butyl (2S,3S)-2-(biphenyl-3-ylmethyl)-3-
15 (((methoxymethyl)sulfonyl)amino)pyrrolidine-1-carboxylate (70.2 mg) was added 4M hydrogen chloride/ethyl acetate solution (1 mL) at room temperature. The mixture was stirred for 1.5 hr, and the reaction solution was concentrated under reduced pressure. To the obtained residue were added THF (1 mL), TEA
20 (0.106 mL) and cyclobutanecarbonyl chloride (21.7 mg). The mixture was stirred at room temperature for 1 hr. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium
25 sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (12.3 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.62-2.03 (4H, m), 2.15 (4H, dd, J = 8.1, 4.7 Hz), 3.13 (2H, s), 3.27-3.38 (1H, m), 3.41-3.51 (1H, m), 3.52-3.72 (4H, m), 4.08 (2H, s), 4.19 (1H, s), 4.37-4.71
30 (2H, m), 7.32-7.67 (9H, m).

[0417]

Example 328

N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-1-(oxetan-2-ylcarbonyl)pyrrolidin-3-yl)methanesulfonamide
35

To a mixture of N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (50 mg), oxetane-2-carboxylic acid (15.9 mg), TEA (65.7 mg) and DMF (1 mL) was added HATU (59.3 mg) at room temperature, and the
5 mixture was stirred at room temperature for 30 min. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under
10 reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate), and crystallized from ethyl acetate, diisopropyl ether and hexane to give the title compound (40 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.75-2.44 (4H, m), 2.54-3.10 (6H, m), 3.15-4.04 (3H, m), 4.15-4.57 (3H, m), 7.11-7.69 (9H, m).
[0418]

Example 333

N-(cis-1-(azetidin-1-ylcarbonyl)-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)pyrrolidin-3-yl)methanesulfonamide
20 [0419]

A) (6-(3-fluorophenyl)pyridin-2-yl)methanol

A mixture of (6-bromopyridin-2-yl)methanol (10.0 g), (3-fluorophenyl)boronic acid (12.0 g), (A-taPhos)₂PdCl₂ (2.10 g), 2M aqueous sodium carbonate solution (100 mL) and DME (300 mL)
25 was stirred under nitrogen atmosphere at 70°C for 5 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure.
30 The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (10.8 g).
MS: [M+H]⁺ 204.2.

[0420]

B) 2-(bromomethyl)-6-(3-fluorophenyl)pyridine

35 To a mixture of (6-(3-fluorophenyl)pyridin-2-yl)methanol

(10.8 g) and THF (300 mL) was added phosphorous tribromide (43.2 g) at 0°C. The mixture was stirred under nitrogen atmosphere overnight at room temperature. The reaction mixture was poured into ice water, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium hydrogencarbonate solution and water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (13.5 g).

MS: $[M+H]^+$ 265.9.

[0421]

C) tert-butyl 2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)-3-oxopyrrolidine-1-carboxylate

A mixture of pyrrolidine (7.74 g), tert-butyl 3-oxopyrrolidine-1-carboxylate (17.5 g) and toluene (200 mL) was refluxed overnight. The mixture was concentrated under reduced pressure. To a mixture of the obtained residue, TBAI (3.75 g) and CH₃CN (200 mL) was added a solution of 2-(bromomethyl)-6-(3-fluorophenyl)pyridine (13.5 g) in CH₃CN (200 mL) at 80°C. The mixture was stirred under nitrogen atmosphere at 80°C for 3 hr. The reaction mixture was poured into water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (16.0 g).

MS: $[M+H]^+$ 371.1.

[0422]

D) tert-butyl cis-3-amino-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)pyrrolidine-1-carboxylate

A mixture of ammonium formate (40 g), chloro[N-[4-(dimethylamino)phenyl]-2-pyridinecarboxamidato](pentamethylcyclopentadienyl)iridium(III)

(0.521 g), tert-butyl 2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)-3-oxopyrrolidine-1-carboxylate (16.0 g) and MeOH (500 mL) was refluxed for 5 hr. The reaction mixture was concentrated, and the residue was poured into saturated brine at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogencarbonate solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (9.00 g). MS: [M+H]⁺ 372.1.

[0423]

E) tert-butyl cis-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate

To a mixture of tert-butyl cis-3-amino-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)pyrrolidine-1-carboxylate (1.10 g), TEA (653 mg) and THF (30 mL) was added methanesulfonic anhydride (690 mg) at 0°C. The mixture was stirred at room temperature for 30 min, and the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.14 g). MS: [M+H]⁺ 450.1.

[0424]

F) N-(cis-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)pyrrolidin-3-yl)methanesulfonamide dihydrochloride

To a mixture of tert-butyl cis-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate (1.10 g) and cyclopentyl methyl ether (10 mL) was added 4M hydrogen chloride/cyclopentyl methyl ether solution (10 mL) at 0°C. The mixture was stirred overnight under nitrogen atmosphere at room temperature, and the reaction mixture was concentrated to give the title compound (1.00 g).

MS: [M+H]⁺ 350.0.

[0425]

G) N-(cis-1-(azetidin-1-ylcarbonyl)-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

5 To a mixture of bis(trichloromethyl) carbonate (69.5 mg) and THF (7 mL) was added a mixture of N-(cis-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)pyrrolidin-3-yl)methanesulfonamide dihydrochloride (120 mg), DIPEA (148 mg) and THF (7 mL) at 0°C. The mixture was stirred at 0°C for 20
10 min, and concentrated under reduced pressure to give an intermediate. To a mixture of the obtained intermediate and THF (7 mL) was added azetidine (85 mg) at 0°C. The mixture was stirred under nitrogen atmosphere at room temperature for 1 hr, and concentrated under reduced pressure. The residue was
15 purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (85 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.24-1.46 (1H, m), 1.94-2.09 (1H, m), 2.11-2.30 (2H, m), 2.85 (3H, s), 2.97-3.19 (2H, m), 3.23-3.37 (1H, m), 3.43-3.60 (1H, m), 3.69-3.84 (2H, m), 3.91-4.15 (3H, m),
20 4.44-4.62 (1H, m), 7.05-7.25 (2H, m), 7.41-7.86 (5H, m), 8.47-8.67 (1H, m).

[0426]

Example 338

N-(cis-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)-1-((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide
25

To a mixture of N-(cis-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)pyrrolidin-3-yl)methanesulfonamide dihydrochloride (51.1 mg), 1-hydroxycyclobutanecarboxylic acid (24.3 mg), TEA (72.6 mg) and DMF (1.0 mL) was added HATU (54.2 mg) at room
30 temperature. The mixture was stirred at room temperature for 1 hr, to the reaction mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over sodium sulfate, and
35 concentrated under reduced pressure. The residue was purified

by silica gel column chromatography (ethyl acetate/hexane), triturated in diethyl ether and hexane to give the title compound (27.3 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.29-1.43 (1H, m), 1.58-1.74 (1H, m),
5 1.86-2.21 (5H, m), 2.38-2.53 (1H, m), 2.61-2.95 (4H, m), 3.21-3.37 (2H, m), 3.41-3.58 (1H, m), 3.72 (1H, dd, J = 14.0, 6.4 Hz), 4.05-4.21 (1H, m), 4.62 (1H, t, J = 6.6 Hz), 7.10-7.21 (2H, m), 7.43-7.83 (5H, m), 8.73 (1H, d, J = 8.7 Hz).

[0427]

10 Example 339

N-((2S,3S)-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)-1-((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide

[0428]

15 A) tert-butyl (2S,3S)-3-amino-2-((2-bromo-1,3-thiazol-4-yl)methyl)pyrrolidine-1-carboxylate

A racemate (550 mg) of tert-butyl cis-3-amino-2-((2-bromo-1,3-thiazol-4-yl)methyl)pyrrolidine-1-carboxylate was resolved by HPLC (column: CHIRALPAK AD (NF001), 50 mmID×500 mmL,
20 Manufactured by Daicel Chemical Industries, mobile phase: hexane/ethanol = 850/150) to give the title compound (207 mg) having a shorter retention time.

MS: [M+H]⁺ 362.1.

[0429]

25 B) tert-butyl (2S,3S)-2-((2-bromo-1,3-thiazol-4-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate

To a mixture of tert-butyl (2S,3S)-3-amino-2-((2-bromo-1,3-thiazol-4-yl)methyl)pyrrolidine-1-carboxylate (150 mg) and THF (1 mL) were added TEA (126 mg) and methanesulfonic
30 anhydride (87 mg) at room temperature. The mixture was stirred for 30 min, and to the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under
35 reduced pressure to give the title compound (184 mg).

MS: [M-H]⁺437.8.

[0430]

C) tert-butyl (2S,3S)-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)-3-((methanesulfonyl)amino)pyrrolidine-1-carboxylate

5 A mixture of tert-butyl (2S,3S)-2-((2-bromo-1,3-thiazol-4-yl)methyl)-3-((methanesulfonyl)amino)pyrrolidine-1-carboxylate (182 mg), (3,5-difluorophenyl)boronic acid (131 mg), potassium carbonate (114 mg), (A-taPhos)₂PdCl₂ (13.9 mg), DME (4 mL) and water (1 mL) was stirred at 60°C for 30 min. To the mixture
10 was added water, and the mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (172 mg).

15 MS: [M-H]⁻471.9.

[0431]

D) N-((2S,3S)-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide dihydrochloride

To a mixture of tert-butyl (2S,3S)-2-((2-(3,5-
20 difluorophenyl)-1,3-thiazol-4-yl)methyl)-3-((methanesulfonyl)amino)pyrrolidine-1-carboxylate (172 mg) and MeOH (2 mL) was added 4M hydrogen chloride/cyclopentyl methyl ether (1 mL) at room temperature. The mixture was stirred for 2 hr, and concentrated under reduced pressure to give the title
25 compound (173 mg).

MS: [M+H]⁺374.0.

[0432]

E) N-((2S,3S)-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)-1-((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-
30 yl)methanesulfonamide

To a mixture of N-((2S,3S)-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide dihydrochloride (72.6 mg) and DMF (1 mL) were added TEA (82 mg), 1-hydroxycyclobutanecarboxylic acid (22.7 mg) and HATU (74.2
35 mg) at room temperature. The mixture was stirred for 1 hr, and

to the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (68.5 mg).

^1H NMR (300 MHz, CDCl_3) δ 1.43-1.54 (1H, m), 1.62-1.73 (1H, m), 1.88-2.22 (5H, m), 2.40-2.57 (1H, m), 2.59-2.75 (1H, m), 3.02 (3H, s), 3.21 (1H, s), 3.30-3.45 (1H, m), 3.47-3.60 (1H, m), 3.66 (1H, dd, $J = 14.9, 6.6$ Hz), 4.00-4.21 (1H, m), 4.53 (1H, t, $J = 6.6$ Hz), 6.84-6.95 (1H, m), 7.10 (1H, s), 7.44-7.50 (2H, m), 8.02 (1H, d, $J = 9.0$ Hz).

[0433]

Example 340

N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-((2S,3S)-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide dihydrochloride (92.6 mg) and THF (1 mL) were added bis(trichloromethyl) carbonate (30.8 mg) and DIPEA (53.6 mg) at 0°C. The mixture was stirred for 30 min, and to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. To the obtained residue were added THF (1 mL) and azetidine (35.5 mg). The mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane), and crystallized from ethyl acetate/hexane to give the title compound (56 mg).

^1H NMR (300 MHz, CDCl_3) δ 1.26 (1H, t, $J = 7.2$ Hz), 2.06-2.27 (3H, m), 3.00 (3H, s), 3.10-3.24 (3H, m), 3.47 (1H, dd, $J = 14.7, 6.8$ Hz), 3.75 (2H, q, $J = 7.8$ Hz), 3.95-4.15 (3H, m),

4.28-4.52 (1H, m), 6.79-6.97 (1H, m), 7.13 (1H, s), 7.49 (2H, m), 8.02 (1H, d, J = 7.9 Hz).

[0434]

Example 341

5 N-((2S,3S)-1-((3-fluoroazetidin-1-yl)carbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide
[0435]

A) (2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carbonyl chloride

10 To a mixture of N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (101 mg) and THF (2 mL) were added bis(trichloromethyl) carbonate (62.3 mg) and DIPEA (67.8 mg) at 0°C. The mixture was stirred at 0°C for 15 min, and the reaction solution was concentrated
15 under reduced pressure to give the title compound (152 mg).
MS: [M+H]⁺ 411.2.

[0436]

B) N-((2S,3S)-1-((3-fluoroazetidin-1-yl)carbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

20 To a mixture of (2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carbonyl chloride (50 mg) and THF (1 mL) were added 3-fluoroazetidine hydrochloride (19.3 mg) and DIPEA (33.5 mg) at room temperature. The mixture was stirred at room temperature for 1 hr. To the
25 mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel
30 column chromatography (NH, ethyl acetate/hexane), and the obtained solid was crystallized from ethyl acetate/hexane to give the title compound (37.8 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.80-1.98 (1H, m), 2.02-2.19 (1H, m), 2.70-2.79 (1H, m), 2.82 (3H, s), 2.92 (1H, dd, J = 13.8,
35 6.2 Hz), 3.12-3.25 (1H, m), 3.32-3.39 (1H, m), 3.55-3.74 (1H,

m), 3.75-4.01 (3H, m), 4.03-4.19 (1H, m), 4.28 (1H, q, $J = 6.4$ Hz), 5.00-5.37 (1H, m), 7.11-7.23 (1H, m), 7.25-7.32 (1H, m), 7.32-7.39 (1H, m), 7.43-7.55 (5H, m), 7.58 (1H, s).

[0437]

5 Example 342

N-((2S,3S)-1-((3,3-difluoroazetidin-1-yl)carbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of 3,3-difluoroazetidine hydrochloride (22.4 mg), DIPEA (33.5 mg) and THF (0.5 mL) was added a mixture of
10 (2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carbonyl chloride (50 mg) and THF (0.5 mL) at room temperature. The mixture was stirred at room temperature for 2 hr. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the
15 mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane), and the obtained
20 solid was crystallized from ethyl acetate/hexane to give the title compound (28.4 mg).

^1H NMR (300 MHz, DMSO- d_6) δ 1.84-2.02 (1H, m), 2.07-2.20 (1H, m), 2.74 (1H, dd, $J = 13.4, 7.4$ Hz), 2.84 (3H, s), 2.87-2.99 (1H, m), 3.16-3.27 (1H, m), 3.32-3.42 (1H, m), 3.76-3.90 (1H, m),
25 3.99 (2H, td, $J = 13.1, 10.6$ Hz), 4.20 (2H, td, $J = 13.3, 10.6$ Hz), 4.31 (1H, q, $J = 6.6$ Hz), 7.12-7.23 (1H, m), 7.24-7.31 (1H, m), 7.31-7.38 (1H, m), 7.43-7.55 (5H, m), 7.58 (1H, s).

[0438]

30 Example 343

N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-1-((2-methylazetidin-1-yl)carbonyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of 2-methylazetidine hydrochloride (46.5 mg), DIPEA (112 mg) and THF (0.5 mL) was added a mixture of (2S,3S)-
35 2-((3'-fluorobiphenyl-3-yl)methyl)-3-

((methylsulfonyl)amino)pyrrolidine-1-carbonyl chloride (50 mg) and THF (0.5 mL) at room temperature. The mixture was stirred at room temperature for 5 hr. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (31.1 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.03-1.24 (3H, m), 1.55-1.94 (2H, m), 1.97-2.23 (2H, m), 2.68-2.89 (4H, m), 2.90-3.05 (1H, m), 3.14 (1H, t, J = 8.9 Hz), 3.23-3.39 (1H, m), 3.40-3.75 (1H, m), 3.75-3.91 (2H, m), 3.97-4.40 (2H, m), 7.13-7.23 (1H, m), 7.23-7.41 (2H, m), 7.44-7.63 (6H, m).

[0439]

Example 344

N-((2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-1-((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide [0440]

A) N-((2S,3S)-2-(3-bromobenzyl)-1-((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-((2S,3S)-2-(3-bromobenzyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (101 mg), 1-hydroxycyclobutanecarboxylic acid (38.1 mg) and DMF (1 mL) were added HATU (156 mg) and DIPEA (106 mg) at room temperature. The mixture was stirred at room temperature for 2 hr. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (105 mg).

MS: [M+H]⁺ 431.1.

[0441]

B) N-((2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-1-((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide

A mixture of N-((2S,3S)-2-(3-bromobenzyl)-1-((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide (49.5 mg), (3,5-difluorophenyl)boronic acid (27.2 mg), XPhos Pd G3 (2.91 mg), 1M aqueous tripotassium phosphate solution (0.344 mL) and THF (2 mL) was stirred at 70°C for 1 hr. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane), and the obtained solid was collected by filtration with hexane to give the title compound (33.2 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.16-1.37 (2H, m), 1.57-1.72 (1H, m), 1.82-1.97 (2H, m), 2.08 (1H, brs), 2.35-2.47 (2H, m), 2.63-2.75 (3H, m), 2.75-2.86 (1H, m), 2.91-3.04 (1H, m), 3.45-3.67 (2H, m), 3.75-3.93 (1H, m), 4.33-4.72 (1H, m), 5.71-6.02 (1H, m), 7.20 (1H, tt, J = 9.2, 2.3 Hz), 7.37 (1H, d, J = 7.2 Hz), 7.39-7.47 (3H, m), 7.48-7.57 (2H, m), 7.65 (1H, s).

[0442]

Example 345

25 N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((3',5'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

[0443]

A) N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-(3-bromobenzyl)pyrrolidin-3-yl)methanesulfonamide

30 To a mixture of N-((2S,3S)-2-(3-bromobenzyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (101 mg) and THF (2 mL) were added bis(trichloromethyl) carbonate (64.9 mg) and DIPEA (70.6 mg) at 0°C. The mixture was stirred at 0°C for 15 min, and the reaction solution was concentrated under reduced pressure. To the residue were added THF (2 mL) and azetidine

(46.8 mg), and the mixture was stirred at room temperature for 2 hr. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (78.4 mg). MS: [M+H]⁺ 416.2.

10 [0444]

B) N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((3',5'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

A mixture of N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-(3-bromobenzyl)pyrrolidin-3-yl)methanesulfonamide (46.8 mg), (3,5-difluorophenyl)boronic acid (26.6 mg), XPhos Pd G3 (2.85 mg), 1M aqueous tripotassium phosphate solution (0.337 mL) and THF (2 mL) was stirred at 70°C for 1 hr. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane), and the obtained solid was crystallized from ethyl acetate/hexane to give the title compound (35.8 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.83-2.14 (4H, m), 2.69-2.80 (1H, m), 2.83 (3H, s), 2.86-2.97 (1H, m), 3.09-3.21 (1H, m, J = 9.5 Hz), 3.34 (1H, brs), 3.61 (2H, q, J = 7.6 Hz), 3.79 (3H, q, J = 8.0 Hz), 4.28 (1H, d, J = 6.4 Hz), 7.15-7.26 (1H, m), 7.29-7.34 (1H, m), 7.34-7.40 (1H, m), 7.44 (2H, dd, J = 9.5, 2.3 Hz), 7.48 (1H, brs), 7.53 (1H, d, J = 7.6 Hz), 7.60 (1H, s).

[0445]

Example 346

N-((2S,3S)-1-((1-cyanocyclobutyl)carbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (30 mg), 1-cyanocyclobutanecarboxylic acid (11.7 mg) and DMF (1 mL) were added HATU (44.5 mg) and DIPEA (30.2 mg) at room
5 temperature. The mixture was stirred overnight at room temperature. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium
10 sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane), and the obtained solid was crystallized from ethyl acetate/hexane to give the title compound (28.7 mg).
¹H NMR (300 MHz, DMSO-d₆) δ 1.58-1.75 (1H, m), 1.94-2.11 (2H, m), 2.14-2.25 (1H, m), 2.37-2.48 (3H, m), 2.52-2.59 (1H, m), 2.71-2.83 (4H, m), 3.01 (1H, dd, J = 13.6, 6.4 Hz), 3.37-3.45 (1H, m), 3.48-3.61 (1H, m), 3.85-4.05 (1H, m), 4.46 (1H, q, J = 6.4 Hz), 7.09-7.23 (1H, m), 7.26-7.38 (2H, m), 7.42-7.56 (4H, m), 7.58-7.67 (2H, m).

20 [0446]

Example 347

N-((2S,3S)-1-(5-azaspiro[2.3]hex-5-ylcarbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride
25 (30.3 mg) and THF (2 mL) were added bis(trichloromethyl) carbonate (18.7 mg) and DIPEA (20.4 mg) at 0°C. The mixture was stirred at 0°C for 20 min, and concentrated under reduced pressure. To the residue were added THF (2 mL), 5-
30 azaspiro[2.3]hexane hydrochloride (37.7 mg) and DIPEA (81 mg), and the mixture was stirred overnight at room temperature. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with
35 saturated brine, dried over anhydrous magnesium sulfate, and

concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane), and the obtained solid was crystallized from ethyl acetate/hexane to give the title compound (27.2 mg).

5 ¹H NMR (300 MHz, DMSO-d₆) δ 0.38-0.52 (4H, m), 1.80-1.97 (1H, m), 2.03-2.20 (1H, m), 2.68-2.79 (1H, m), 2.85 (3H, s), 2.88-2.98 (1H, m), 3.13-3.25 (1H, m), 3.26-3.38 (1H, m), 3.64 (2H, d, J = 8.0 Hz), 3.80 (1H, brs), 3.86 (2H, d, J = 8.0 Hz), 4.23-4.41 (1H, m), 7.11-7.24 (1H, m), 7.25-7.31 (1H, m), 7.32-7.39
10 (1H, m), 7.43-7.55 (5H, m), 7.55-7.60 (1H, m).

[0447]

Example 348

N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide
15

[0448]

A) tert-butyl (2S,3S)-2-((2-bromo-1,3-thiazol-4-yl)methyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate

To a mixture of tert-butyl (2S,3S)-3-amino-2-((2-bromo-1,3-thiazol-4-yl)methyl)pyrrolidine-1-carboxylate (300 mg), TEA (126 mg) and THF (3 mL) was added ethanesulfonyl chloride (128 mg) at room temperature. The mixture was stirred at room temperature for 1 hr, and diluted with ethyl acetate. The insoluble substance was removed by filtration, and the filtrate
20 was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (240 mg).

MS: [M+H]⁺ 454.2.

[0449]

30 B) tert-butyl (2S,3S)-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate

A mixture of tert-butyl (2S,3S)-2-((2-bromo-1,3-thiazol-4-yl)methyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate (240 mg), (3,5-difluorophenyl)boronic acid (125 mg), (A-taPhos)₂PdCl₂ (35.5 mg), potassium carbonate (146 mg), DME (2.4
35

mL) and water (0.8 mL) was stirred under nitrogen atmosphere at 90°C for 30 min. The mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (240 mg).

5 MS: [M+H]⁺ 488.2.

[0450]

C) N-((2S,3S)-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide dihydrochloride

To a mixture of tert-butyl (2S,3S)-2-((2-(3,5-
10 difluorophenyl)-1,3-thiazol-4-yl)methyl)-3-
((ethylsulfonyl)amino)pyrrolidine-1-carboxylate (240 mg) and MeOH (1 mL) was added 4M hydrogen chloride/cyclopentyl methyl ether solution (4 mL) at room temperature. The mixture was stirred at room temperature for 30 min, and the reaction
15 mixture was concentrated to give the title compound (226 mg).
MS: [M+H]⁺ 388.2.

[0451]

D) N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2-(3,5-
difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-
20 yl)ethanesulfonamide

A mixture of N-((2S,3S)-2-((2-(3,5-difluorophenyl)-1,3-
thiazol-4-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide
dihydrochloride (70 mg), DIPEA (79 mg) and THF (5 mL) was added
a solution of bis(trichloromethyl) carbonate (36.1 mg) in THF
25 (5 mL) at 0°C. The mixture was stirred at 0°C for 20 min, and
the reaction solution was concentrated. To the obtained
residue were added THF (5 mL) and azetidine (43.4 mg). The
mixture was stirred at room temperature for 1 hr. The reaction
mixture was concentrated under reduced pressure, and the
30 residue was purified by silica gel column chromatography
(methanol/ethyl acetate) to give the title compound (52 mg).
¹H NMR (300 MHz, DMSO-d₆) δ 1.10-1.22 (3H, m), 1.70-1.89 (1H,
m), 1.93-2.16 (3H, m), 2.83-3.21 (5H, m), 3.23-3.30 (1H, m),
3.56-3.70 (2H, m), 3.76-3.93 (3H, m), 4.27-4.40 (1H, m), 7.33-
35 7.44 (1H, m), 7.47-7.55 (2H, m), 7.57-7.70 (2H, m).

[0452]

Example 349

N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2,2-dimethylpropanoyl)pyrrolidin-3-yl)methanesulfonamide

5 [0453]

A) tert-butyl (2S,3S)-3-amino-2-(3-bromo-2-fluorobenzyl)pyrrolidine-1-carboxylate

A racemate (848 mg) of tert-butyl cis-3-amino-2-(3-bromo-2-fluorobenzyl)pyrrolidine-1-carboxylate was resolved by HPLC
10 (column: CHIRALPAK AD (AK001), 50 mmID×500 mmL, Manufactured by Daicel Chemical Industries, mobile phase: hexane/ethanol=850/150) to give the title compound (352 mg) having a shorter retention time.

MS: [M+H-tBu]⁺ 316.9.

15 [0454]

B) tert-butyl (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate

To a mixture of tert-butyl (2S,3S)-3-amino-2-(3-bromo-2-fluorobenzyl)pyrrolidine-1-carboxylate (349 mg), TEA (189 mg)
20 and THF (3.3 mL) was added methanesulfonyl chloride (129 mg) at room temperature. The mixture was stirred at room temperature for 1 hr, and the reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The organic layer was washed with aqueous sodium hydrogencarbonate solution
25 and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (386 mg).

MS: [M+H-Boc]⁺ 350.9.

30 [0455]

C) tert-butyl (2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate

A mixture of tert-butyl (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((methylsulfonyl)amino)pyrrolidine-1-
35 carboxylate (380 mg), (3-fluorophenyl)boronic acid (236 mg),

XPhos Pd G3 (35.6 mg), 1 M aqueous tripotassium phosphate solution (2.53 mL) and THF (9 mL) was stirred under argon atmosphere at 70°C for 1 hr. The mixture was poured into aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give crystals. The crystals were collected by filtration, and washed with diisopropyl ether-hexane to give the title compound (353 mg).

MS: [M-H]⁻ 465.0.

[0456]

D) N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of tert-butyl ((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate (349 mg) and toluene (3.8 mL) was added TFA (3.8 mL) at room temperature. The mixture was stirred at room temperature for 1 hr, and poured into saturated aqueous sodium hydrogencarbonate solution under ice-cooling. The mixture was basified to pH=8 with potassium carbonate, and extracted with ethyl acetate-THF. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, methanol/ethyl acetate) to give the title compound (283 mg).

MS: [M+H]⁺ 367.2.

[0457]

E) N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2,2-dimethylpropanoyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide (68 mg), TEA (75 mg) and THF (1.6 mL) was added 2,2-dimethylpropanoyl chloride

(67.1 mg) at room temperature. The mixture was stirred at room temperature for 3 hr, added to aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate-THF. The organic layer was washed with water and saturated brine, dried over
5 anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (68.9 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.25 (9H, s), 1.95-2.04 (1H, m),
10 2.28-2.39 (1H, m), 2.53 (3H, s), 2.92-3.08 (2H, m), 3.64-3.71 (2H, m), 3.92-4.05 (1H, m), 4.65-4.75 (2H, m), 7.03-7.11 (1H, m), 7.15-7.26 (2H, m), 7.27-7.32 (2H, m), 7.36-7.45 (1H, m), 7.53 (1H, td, J = 7.1, 1.7 Hz).

[0458]

15 Example 350

N-((2S,3S)-1-(cyclobutylcarbonyl)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide (66 mg), TEA (54.7
20 mg) and THF (1.6 mL) was added cyclobutanecarbonyl chloride (42.7 mg) at room temperature. The mixture was stirred at room temperature for 2 hr, added to aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate-THF. The organic layer was washed with water and saturated brine, dried over
25 anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give crystals. The crystals were collected by filtration, and washed with diisopropyl ether-hexane to give the title compound (49.9 mg).
30 ¹H NMR (300 MHz, CDCl₃) δ 1.67-2.40 (8H, m), 2.57-3.22 (6H, m), 3.27-3.77 (2H, m), 3.94-4.08 (1H, m), 4.26-4.64 (1H, m), 4.75-4.83 (1H, m), 7.03-7.12 (1H, m), 7.14-7.24 (2H, m), 7.27-7.34 (2H, m), 7.36-7.50 (2H, m).

[0459]

35 Example 351

N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-((1-methylcyclopropyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide

To a solution of N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide (66 mg), 1-methylcyclopropanecarboxylic acid (23.4 mg), DIPEA (46.6 mg) and DMF (1 mL) was added HATU (103 mg) at room temperature. The mixture was stirred at room temperature for 3 hr, added to aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate-THF. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (54.5 mg).

¹H NMR (300 MHz, CDCl₃) δ 0.46-0.61 (2H, m), 0.71-0.80 (1H, m), 0.94-1.03 (1H, m), 1.25 (3H, s), 1.88-2.02 (1H, m), 2.27-2.39 (1H, m), 2.70 (3H, s), 2.91-2.99 (1H, m), 3.05 (1H, dd, J = 14.2, 7.4 Hz), 3.58-3.76 (2H, m), 3.94-4.06 (1H, m), 4.66 (1H, q, J = 6.5 Hz), 4.77 (1H, dd, J = 9.3, 4.4 Hz), 7.03-7.11 (1H, m), 7.17 (1H, t, J = 7.8 Hz), 7.20-7.25 (1H, m), 7.27-7.44 (4H, m).

[0460]

Example 352

N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide (68 mg), DIPEA (48.0 mg) and THF (1.6 mL) was added bis(trichloromethyl) carbonate (44.1 mg) at 0°C. The mixture was stirred at 0°C for 20 min, and the reaction mixture was concentrated under reduced pressure. The residue was diluted with THF (1.6 mL), and azetidine (63.6 mg) was added thereto at room temperature. The mixture was stirred at 70°C for 20 min, added to aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate-THF. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated

under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (40.0 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.89-2.01 (1H, m), 2.13-2.26 (3H, m),
5 2.68 (3H, s), 2.90-2.99 (1H, m), 3.02-3.11 (1H, m), 3.24-3.41 (2H, m), 3.80-4.06 (5H, m), 4.53 (1H, q, J = 6.8 Hz), 4.64 (1H, dd, J = 9.1, 3.4 Hz), 7.03-7.11 (1H, m), 7.16-7.25 (2H, m), 7.27-7.33 (2H, m), 7.36-7.44 (2H, m).

[0461]

10 Example 364

N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-(biphenyl-3-ylmethyl)pyrrolidin-3-yl)ethanesulfonamide

[0462]

A) tert-butyl (2S,3S)-2-(3-bromobenzyl)-3-
15 ((ethylsulfonyl)amino)pyrrolidine-1-carboxylate

To a mixture of tert-butyl (2S,3S)-3-amino-2-(3-bromobenzyl)pyrrolidine-1-carboxylate (3.2 g), TEA (1.37 g) and THF (50 mL) was added ethanesulfonyl chloride (1.39 g) at room temperature. The mixture was stirred at room temperature for 1
20 hr. The insoluble substance was removed by filtration, and washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane). The obtained oil was crystallized from ethyl acetate, and diluted with hexane.
25 The precipitate was collected by filtration to give the title compound (3.46 g).

MS: [M+H-Boc]⁺ 347.2.

[0463]

B) tert-butyl (2S,3S)-2-(biphenyl-3-ylmethyl)-3-
30 ((ethylsulfonyl)amino)pyrrolidine-1-carboxylate

A mixture of tert-butyl (2S,3S)-2-(3-bromobenzyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate (1.0 g), phenylboronic acid (0.409 g), XPhos Pd G3 (0.057 g), 1 M aqueous tripotassium phosphate solution (6.71 mL) and THF (20
35 mL) was stirred at 70°C for 1.5 hr. The mixture was

concentrated. The residue was partitioned between ethyl acetate and water, and the mixture was extracted with ethyl acetate. The extract was washed with 1 M aqueous sodium hydroxide solution and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was crystallized from ethyl acetate/hexane, and the precipitate was collected by filtration to give the title compound (714 mg).

MS: [M+H-Boc]⁺ 345.3.

10 [0464]

C) N-((2S,3S)-2-(biphenyl-3-ylmethyl)pyrrolidin-3-yl)ethanesulfonamide hydrochloride

A mixture of tert-butyl (2S,3S)-2-(biphenyl-3-ylmethyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate (714 mg), 4M hydrogen chloride/ethyl acetate solution (5 mL) and ethyl acetate (10 mL) was stirred overnight at room temperature. The mixture was diluted with ethyl acetate, and the precipitate was collected by filtration to give the title compound (576 mg).

MS: [M+H]⁺ 345.3.

20 [0465]

D) N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-(biphenyl-3-ylmethyl)pyrrolidin-3-yl)ethanesulfonamide

A mixture of N-((2S,3S)-2-(biphenyl-3-ylmethyl)pyrrolidin-3-yl)ethanesulfonamide hydrochloride (576 mg), DIPEA (391 mg) and THF (10 mL) was added dropwise to a mixture of bis(trichloromethyl) carbonate (359 mg) and THF (10 mL), and the mixture was stirred at room temperature for 30 min, and concentrated. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was mixed with THF (10 mL), and to the mixture was added azetidine (432 mg) at room temperature. The mixture was stirred at room temperature for 4 hr. Azetidine (432 mg) was

added to the mixture, and the mixture was stirred at room temperature for 15 min, and concentrated. The obtained residue was partitioned between ethyl acetate and 1 M hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic
5 layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained crystals were recrystallized from ethyl acetate/hexane to give the title compound (453 mg).

^1H NMR (300 MHz, CDCl_3) δ 1.18 (3H, t, $J = 7.4$ Hz), 1.75-1.92
10 (1H, m), 2.08-2.24 (3H, m), 2.73-2.97 (3H, m), 3.16-3.42 (3H, m), 3.80-3.97 (3H, m), 4.02 (2H, q, $J = 8.0$ Hz), 4.32 (1H, d, $J = 8.3$ Hz), 4.46-4.55 (1H, m), 7.27-7.49 (6H, m), 7.51 (1H, s), 7.55-7.62 (2H, m).

[0466]

15 Example 366

(2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-N,N-dimethyl-3-((methylsulfonyl)amino)pyrrolidine-1-carboxamide

[0467]

A) tert-butyl (2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-
20 3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate

A mixture of tert-butyl (2S,3S)-2-(3-bromobenzyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate (1.73 g), (3,5-difluorophenyl)boronic acid (0.947 g), potassium carbonate (1.11 g), (A-taPhos) $_2\text{PdCl}_2$ (0.135 g), DME (20 mL) and water (4
25 mL) was stirred at 70°C for 2 hr. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (1.74 g).

MS: $[\text{M}+\text{Na}]^+$ 489.3.

30 [0468]

B) N-((2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride

A mixture of tert-butyl (2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-3-
35 ((methylsulfonyl)amino)pyrrolidine-1-carboxylate (1.74 g), 4M

hydrogen chloride/CPME solution (18.7 mL) and methanol (10 mL) was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure. The obtained solid was washed with ethyl acetate to give the title compound (1.47

5 g).

MS: $[M+H]^+$ 367.2.

[0469]

C) (2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-N,N-dimethyl-3-((methanesulfonyl)amino)pyrrolidine-1-carboxamide

10 To a mixture of N-((2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (1.47 g) and THF (20 mL) were added TEA (1.29 g) and dimethylcarbonyl chloride (0.589 g) at room temperature. The mixture was stirred at room temperature for 1 hr, and to the
15 mixture was added saturated brine, and the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (1.49 g).

^1H NMR (400 MHz, CDCl_3) δ 2.03-2.11 (2H, m), 2.63-2.72 (1H, m),
20 2.73 (3H, s), 2.85 (6H, s), 3.23-3.38 (2H, m), 3.56-3.65 (1H, m), 3.85-3.93 (1H, m), 4.41-4.50 (1H, m), 4.69 (1H, d, $J = 8.6$ Hz), 6.73-6.81 (1H, m), 7.06-7.15 (2H, m), 7.32-7.41 (3H, m), 7.49 (1H, s).

[0470]

25 Example 373

(2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((ethylsulfonyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide
[0471]

A) tert-butyl (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate
30

To a mixture of tert-butyl (2S,3S)-3-amino-2-(3-bromo-2-fluorobenzyl)pyrrolidine-1-carboxylate (1.20 g), TEA (0.651 g), DMAP (0.118 g) and THF (11.5 mL) was added ethanesulfonyl chloride (0.620 g) at room temperature. The mixture was
35 stirred at room temperature for 2 hr, poured into water, and

extracted with ethyl acetate. The organic layer was washed with 10% aqueous citric acid solution, aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced
5 pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.43 g).

MS: [M-H]⁻ 463.1.

[0472]

10 B) tert-butyl (2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate

A mixture of tert-butyl (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate (465 mg), (3-fluorophenyl)boronic acid (280 mg), XPhos Pd G3
15 (42.3 mg), 1 M aqueous tripotassium phosphate solution (3.00 mL) and THF (11 mL) was stirred under argon atmosphere at 70°C for 1 hr. The reaction mixture was poured into aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and
20 saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (449 mg).

MS: [M-H]⁻ 479.2.

25 [0473]

C) N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide

To a mixture of tert-butyl (2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-
30 ((ethylsulfonyl)amino)pyrrolidine-1-carboxylate (444 mg) and toluene (4.8 mL) was added TFA (4.8 mL) at room temperature. The mixture was stirred at room temperature for 1 hr, and the reaction solution was poured into saturated aqueous sodium hydrogencarbonate solution under ice-cooling. The mixture was
35 basified to pH=8 with potassium carbonate, and extracted with

ethyl acetate/THF. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, methanol/ethyl

5 acetate) to give the title compound (341 mg).

MS: $[M+H]^+$ 381.2.

[0474]

D) (2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carbonyl chloride

10 To a mixture of N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide (215 mg), DIPEA (146 mg) and THF (4.8 mL) was added bis(trichloromethyl) carbonate (134 mg) at 0°C. The mixture was stirred at 0°C for 10 min, and then at room temperature for 10 min. The mixture
15 was poured into water, and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane), and the obtained
20 crystals were collected by filtration, and washed with diisopropyl ether/hexane to give the title compound (223 mg).

MS: $[M-H]^-$ 441.1.

[0475]

E) (2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((ethylsulfonyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide

25 To a mixture of (2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carbonyl chloride (110 mg) and THF (1.9 mL) was added 2M dimethylamine/THF solution (0.373 mL) at room temperature. The
30 mixture was stirred at room temperature for 30 min, and then at 70°C for 10 min. The mixture was poured into aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate/THF. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium
35 sulfate, and concentrated under reduced pressure. The residue

was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (97.0 mg).
¹H NMR (300 MHz, CDCl₃) δ 1.27 (3H, t, J = 7.4 Hz), 2.06-2.20 (2H, m), 2.79 (6H, s), 2.81-2.95 (3H, m), 3.00-3.10 (1H, m),
5 3.28 (1H, ddd, J = 10.3, 8.4, 4.4 Hz), 3.62 (1H, dt, J = 10.3, 7.9 Hz), 3.88-3.98 (1H, m), 4.48-4.59 (2H, m), 7.02-7.10 (1H, m), 7.16 (1H, t, J = 7.6 Hz), 7.20-7.25 (1H, m), 7.26-7.31 (2H, m), 7.32-7.43 (2H, m).

[0476]

10 Example 387

N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide (60 mg), 2-
15 hydroxy-2-methylpropanoic acid (22.2 mg), DIPEA (42.3 mg) and DMF (1 mL) was added HATU (93 mg) at room temperature. The mixture was stirred at room temperature for 3 hr, and the reaction mixture was poured into aqueous sodium hydrogencarbonate solution, and the mixture was extracted with
20 ethyl acetate/THF. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (63.8 mg).
25 ¹H NMR (300 MHz, CDCl₃) δ 1.41 (3H, s), 1.43 (3H, s), 1.89-2.01 (1H, m), 2.29-2.41 (1H, m), 2.66 (3H, s), 2.91-3.00 (1H, m), 3.06-3.16 (1H, m), 3.68 (2H, brs), 3.84 (1H, brs), 3.97-4.10 (1H, m), 4.74 (2H, brs), 7.07 (1H, tdd, J = 8.4, 2.6, 1.0 Hz), 7.16-7.25 (2H, m), 7.26-7.33 (2H, m), 7.36-7.45 (2H, m).

30 [0477]

Example 389

N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide

To a mixture of N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide (59 mg), 2-hydroxy-
35

2-methylpropanoic acid (21.0 mg), DIPEA (40.1 mg) and DMF (1 mL) was added HATU (88 mg) at room temperature. The mixture was stirred at room temperature for 3 hr, and the reaction mixture was poured into aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate/THF. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (62.4 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.22 (3H, t, J = 7.4 Hz), 1.40 (3H, s), 1.42 (3H, s), 1.85-1.99 (1H, m), 2.28-2.41 (1H, m), 2.86 (2H, q, J = 7.4 Hz), 2.95 (1H, dd, J = 15.0, 3.9 Hz), 3.08-3.19 (1H, m), 3.67 (2H, brs), 3.83-4.06 (2H, m), 4.56 (1H, brs), 4.73 (1H, brs), 7.07 (1H, tdd, J = 8.4, 2.6, 1.0 Hz), 7.15-7.25 (2H, m), 7.27-7.32 (2H, m), 7.36-7.44 (2H, m).

[0478]

Example 395

N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

[0479]

A) tert-butyl (2S,3S)-3-((methylsulfonyl)amino)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidine-1-carboxylate

A mixture of tert-butyl (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate (450 mg), (3,5-difluorophenyl)boronic acid (315 mg), XPhos Pd G3 (42.2 mg), 1 M aqueous tripotassium phosphate solution (2.99 mL) and THF (11 mL) was stirred under argon atmosphere at 70°C for 1 hr. The reaction mixture was poured into aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl

acetate/hexane) to give the title compound (482 mg).

MS: [M-H]⁻ 483.2.

[0480]

B) N-((2S,3S)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of tert-butyl (2S,3S)-3-((methylsulfonyl)amino)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidine-1-carboxylate (477 mg) and toluene (5.2 mL) was added TFA (5.2 mL) at room temperature. The mixture was stirred at room temperature for 1 hr, and the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution under ice-cooling. The mixture was basified to pH=8 with potassium carbonate, and extracted with ethyl acetate/THF. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, methanol/ethyl acetate) to give the title compound (339 mg).

MS: [M+H]⁺ 385.2.

[0481]

C) N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-((2S,3S)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide (60 mg), 2-hydroxy-2-methylpropanoic acid (21.1 mg), DIPEA (40.3 mg) and DMF (1 mL) was added HATU (89 mg) at room temperature. The mixture was stirred at room temperature for 3 hr, and the reaction mixture was poured into aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate/THF. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (63.1 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.40 (3H, s), 1.42 (3H, s), 1.91-2.03 (1H, m), 2.30-2.42 (1H, m), 2.70 (3H, s), 2.89-2.97 (1H, m), 3.10 (1H, dd, J = 14.0, 8.0 Hz), 3.63-3.84 (3H, m), 3.96-4.07 (1H, m), 4.68-4.84 (2H, m), 6.82 (1H, tt, J = 8.9, 2.3 Hz),
5 7.02-7.10 (2H, m), 7.19 (1H, t, J = 7.6 Hz), 7.26-7.31 (1H, m), 7.44 (1H, t, J = 6.7 Hz).

[0482]

Example 399

(2S,3S)-3-((ethylsulfonyl)amino)-N,N-dimethyl-2-((2,3',5'-
10 trifluorobiphenyl-3-yl)methyl)pyrrolidine-1-carboxamide
[0483]

A) (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((ethylsulfonyl)amino)-
N,N-dimethylpyrrolidine-1-carboxamide

To a mixture of tert-butyl (2S,3S)-2-(3-bromo-2-
15 fluorobenzyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate (340 mg) and MeOH (1 mL) was added 4M hydrogen chloride/CPME solution (3.65 mL) at room temperature. The mixture was stirred for 1 hr, and the reaction solution was concentrated under reduced pressure. The obtained residue was mixed with
20 THF (4 mL). To the mixture were added TEA (739 mg) and dimethylcarbonyl chloride (393 mg) at room temperature. The mixture was stirred at 70°C for 1 hr. To the reaction mixture was added saturated brine, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous sodium
25 sulfate, and concentrated under reduced pressure. The obtained solid was washed with ethyl acetate to give the title compound (327 mg).

MS: [M+H]⁺ 436.2.

[0484]

30 B) (2S,3S)-3-((ethylsulfonyl)amino)-N,N-dimethyl-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidine-1-carboxamide

A mixture of (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-
((ethylsulfonyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide
(70.4 mg), (3,5-difluorophenyl)boronic acid (38.2 mg), XPhos Pd
35 G3 (4.10 mg), 1 M aqueous tripotassium phosphate solution

(0.484 mL) and THF (2 mL) was stirred at 70°C for 1.5 hr. To the mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (62.0 mg).

¹H NMR (400 MHz, DMSO-d₆) δ 1.20 (3H, t, J = 7.3 Hz), 1.82-1.98 (1H, m), 2.02-2.19 (1H, m), 2.58 (6H, s), 2.68 (1H, dd, J = 14.1, 9.2 Hz), 2.91 (1H, dd, J = 13.4, 5.7 Hz), 2.96-3.06 (2H, m), 3.07-3.18 (1H, m), 3.54-3.65 (1H, m), 3.76 (1H, t, J = 6.1 Hz), 4.35-4.47 (1H, m), 7.13-7.21 (1H, m), 7.23-7.32 (3H, m), 7.33-7.41 (2H, m), 7.51 (1H, d, J = 6.8 Hz).

[0485]

Example 402

N-((2S,3S)-1-isobutyryl -2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

To a mixture of N-((2S,3S)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide (60 mg), TEA (47.4 mg) and THF (1.4 mL) was added 2-methylpropanoyl chloride (33.3 mg) at room temperature. The mixture was stirred at room temperature for 1 hr, poured into aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate/THF. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate), and the obtained solid was collected by filtration, and washed with diisopropyl ether/hexane to give the title compound (56.7 mg).

¹H NMR (300 MHz, CDCl₃) δ 0.56-1.12 (6H, m), 1.86-2.05 (1H, m), 2.31-2.43 (1H, m), 2.54-3.21 (6H, m), 3.42-3.79 (2H, m), 3.96-4.10 (1H, m), 4.36-4.68 (1H, m), 4.72-4.80 (1H, m), 6.77-6.86 (1H, m), 6.98-7.53 (5H, m).

[0486]

Example 404

N-((2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide

5 [0487]

A) tert-butyl (2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate

A mixture of tert-butyl (2S,3S)-2-(3-bromobenzyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate (1.00 g), (3,5-
10 difluorophenyl)boronic acid (0.529 g), XPhos Pd G3 (0.057 g), 1 M aqueous tripotassium phosphate solution (6.71 mL) and THF (20 mL) was stirred at 70°C for 2 hr. The reaction mixture was concentrated under reduced pressure, the residue was diluted with saturated aqueous sodium hydrogencarbonate solution, and
15 the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (1.08 g).
20 MS: [M+H-Boc]⁺ 381.3.

[0488]

B) N-((2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide hydrochloride

To a mixture of tert-butyl (2S,3S)-2-((3',5'-
25 difluorobiphenyl-3-yl)methyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate (1.10 g) and ethyl acetate (5 mL) was added 4M hydrogen chloride/ethyl acetate solution (11.2 mL) at room temperature. The mixture was stirred at room temperature for 2 hr, and concentrated
30 under reduced pressure. The obtained solid was collected by filtration with ethyl acetate, and dried to give the title compound (875 mg).

MS: [M+H]⁺ 381.3.

[0489]

35 C) N-((2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-1-(2-

hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide

To a mixture of N-((2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide hydrochloride (100 mg), 2-hydroxy-2-methylpropanoic acid (32.5 mg), DIPEA (62.0 mg) and DMF (1 mL) was added HATU (137 mg) at room temperature. The mixture was stirred at room temperature for 3 hr, to the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate), and recrystallized from ethyl acetate/hexane to give the title compound (60.0 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 0.99-1.33 (9H, m), 1.80-2.24 (2H, m), 2.61-3.21 (4H, m), 3.38-3.93 (3H, m), 4.31-4.52 (1H, m), 4.95-5.37 (1H, m), 7.20 (1H, tt, J = 9.3, 2.3 Hz), 7.30-7.54 (6H, m), 7.65 (1H, s).

[0490]

Example 417

N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide [0491]

A) tert-butyl (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-(((fluoromethyl)sulfonyl)amino)pyrrolidine-1-carboxylate

To a mixture of tert-butyl (2S,3S)-3-amino-2-(3-bromo-2-fluorobenzyl)pyrrolidine-1-carboxylate (1.24 g), DIPEA (0.859 g) and THF (11 mL) was added fluoromethanesulfonyl chloride (0.484 g) at 0°C. The mixture was stirred at room temperature for 1 hr, poured into water, and extracted with ethyl acetate. The organic layer was washed with aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.49 g).

MS: [M-H]⁻ 466.9.

[0492]

B) N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide

5 To a mixture of tert-butyl (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-(((fluoromethyl)sulfonyl)amino)pyrrolidine-1-carboxylate (1.48 g) and toluene (16 mL) was added TFA (16 mL) at room temperature. The mixture was stirred at room temperature for 1 hr, and the reaction solution was poured into
10 saturated aqueous sodium hydrogencarbonate solution under ice-cooling. The mixture was basified to pH=8 with potassium carbonate, and extracted with ethyl acetate/THF(3:1). The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under
15 reduced pressure. The residue was purified by silica gel column chromatography (NH, methanol/ethyl acetate) to give the title compound (1.09 g).

MS: [M+H]⁺ 368.9.

[0493]

20 C) N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide

To a mixture of N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide (556 mg), 2-hydroxy-2-methylpropanoic acid (204 mg), DIPEA (389 mg)
25 and DMF (10 mL) was added HATU (859 mg) at room temperature. The mixture was stirred at room temperature for 3.5 hr, and the reaction mixture was poured into aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate/THF. The organic layer was washed with water and
30 saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained solid was collected by filtration, and washed with diisopropyl ether to give the title compound (627 mg).

MS: [M+H]⁺ 455.0.

35 [0494]

D) N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide

A mixture of N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide (73 mg), (3-fluorophenyl)boronic acid (44.9 mg), XPhos Pd G3 (6.79 mg), 1 M aqueous tripotassium phosphate solution (0.481 mL) and THF (1.6 mL) was stirred under argon atmosphere at 70°C for 1 hr. The reaction mixture was poured into aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (57.0 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.42 (3H, s), 1.43 (3H, s), 1.85-2.02 (1H, m), 2.29-2.40 (1H, m), 2.95-3.04 (1H, m), 3.13 (1H, dd, J = 14.0, 8.0 Hz), 3.62-3.88 (3H, m), 4.03-4.12 (1H, m), 4.59-4.82 (2H, m), 4.85-5.06 (2H, m), 7.04-7.12 (1H, m), 7.17-7.25 (2H, m), 7.27-7.34 (2H, m), 7.36-7.45 (2H, m).

[0495]

Example 421

N-((2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide

[0496]

A) tert-butyl (2S,3S)-2-(3-bromobenzyl)-3-(((fluoromethyl)sulfonyl)amino)pyrrolidine-1-carboxylate

To a mixture of tert-butyl (2S,3S)-3-amino-2-(3-bromobenzyl)pyrrolidine-1-carboxylate (1.22 g), DIPEA (0.888 g) and THF (12 mL) was added fluoromethanesulfonyl chloride (0.501 g) at 0°C. The mixture was stirred at room temperature for 1.5 hr, poured into water, and extracted with ethyl acetate. The organic layer was washed with aqueous sodium hydrogencarbonate

solution and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.46 g).

5 MS: [M+H-Boc]⁺ 350.9.

[0497]

B) N-((2S,3S)-2-(3-bromobenzyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide

To a mixture of tert-butyl (2S,3S)-2-(3-bromobenzyl)-3-
10 (((fluoromethyl)sulfonyl)amino)pyrrolidine-1-carboxylate (1.45 g) and toluene (15.5 mL) was added TFA (15.5 mL) at room temperature. The mixture was stirred at room temperature for 1 hr, and the reaction solution was poured into saturated aqueous sodium hydrogencarbonate solution under ice-cooling. The
15 mixture was basified to pH=8 with potassium carbonate, and extracted with ethyl acetate/THF. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH,
20 methanol/ethyl acetate) to give the title compound (693 mg).
MS: [M+H]⁺ 350.9.

[0498]

C) N-((2S,3S)-2-(3-bromobenzyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide

25 To a mixture of N-((2S,3S)-2-(3-bromobenzyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide (692 mg), 2-hydroxy-2-methylpropanoic acid (267 mg), DIPEA (509 mg) and DMF (13 mL) was added HATU (1.12 g) at room temperature. The mixture was stirred at room temperature for 3.5 hr, and the reaction
30 mixture was poured into aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate/THF. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel
35 column chromatography (ethyl acetate/hexane) to give the title

compound (788 mg).

MS: [M+H]⁺ 437.0.

[0499]

D) N-((2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide

A mixture of N-((2S,3S)-2-(3-bromobenzyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide (71 mg), (3,5-difluorophenyl)boronic acid (51.3 mg), XPhos Pd G3 (6.87 mg), 1 M aqueous tripotassium phosphate solution (0.487 mL) and THF (1.6 mL) was stirred under argon atmosphere at 70°C for 1 hr. The reaction mixture was poured into aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (41.4 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.43 (6H, brs), 1.83-1.99 (1H, m), 2.26-2.39 (1H, m), 2.98-3.19 (2H, m), 3.73 (3H, brs), 4.03-4.13 (1H, m), 4.55-5.04 (4H, m), 6.79 (1H, tt, J = 8.9, 2.3 Hz), 7.05-7.14 (2H, m), 7.31-7.51 (4H, m).

[0500]

Example 423

1-fluoro-N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

A mixture of N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide (73 mg), (3,5-difluorophenyl)boronic acid (50.6 mg), XPhos Pd G3 (6.79 mg), 1 M aqueous tripotassium phosphate solution (0.481 mL) and THF (1.6 mL) was stirred under argon atmosphere at 70°C for 1 hr. The reaction mixture was poured into aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic

layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title

5 compound (44.4 mg).

^1H NMR (300 MHz, CDCl_3) δ 1.41 (3H, s), 1.43 (3H, s), 1.89–2.03 (1H, m), 2.30–2.41 (1H, m), 2.93–3.01 (1H, m), 3.12 (1H, dd, J = 14.0, 7.6 Hz), 3.63–3.83 (3H, m), 4.02–4.13 (1H, m), 4.65–4.86 (2H, m), 4.87–5.08 (2H, m), 6.82 (1H, tt, J = 8.9, 2.5 Hz),
10 7.01–7.10 (2H, m), 7.21 (1H, t, J = 7.6 Hz), 7.27–7.32 (1H, m), 7.41–7.48 (1H, m).

[0501]

Example 424

1,1-difluoro-N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-
15 ((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

[0502]

A) tert-butyl (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-
(((difluoromethyl)sulfonyl)amino)pyrrolidine-1-carboxylate

20 To a mixture of tert-butyl (2S,3S)-3-amino-2-(3-bromo-2-fluorobenzyl)pyrrolidine-1-carboxylate (1.33 g), 2,6-di-tert-butylpyridine (1.50 g) and THF (11 mL) was added

difluoromethanesulfonyl chloride (1.07 g) at -78°C . The mixture was stirred at 0°C for 1 hr, poured into water, and
25 extracted with ethyl acetate. The organic layer was washed with aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title
30 compound (955 mg).

MS: $[\text{M}-\text{H}]^-$ 484.9.

[0503]

B) N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)pyrrolidin-3-yl)-1,1-difluoromethanesulfonamide

35 To a mixture of tert-butyl (2S,3S)-2-(3-bromo-2-

fluorobenzyl)-3-(((difluoromethyl)sulfonyl)amino)pyrrolidine-1-carboxylate (949 mg) and toluene (10.2 mL) was added TFA (10.2 mL) at room temperature. The mixture was stirred at room temperature for 1 hr, and the reaction solution was poured into
5 saturated aqueous sodium hydrogencarbonate solution under ice-cooling. The mixture was basified to pH=8 with potassium carbonate, and extracted with ethyl acetate/THF. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced
10 pressure. The residue was purified by silica gel column chromatography (NH, methanol/ethyl acetate) to give the title compound (643 mg).

MS: [M+H]⁺ 386.9.

[0504]

15 C) N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)-1,1-difluoromethanesulfonamide

To a mixture of N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)pyrrolidin-3-yl)-1,1-difluoromethanesulfonamide (639 mg), 2-hydroxy-2-methylpropanoic acid (223 mg), DIPEA (427
20 mg) and DMF (11 mL) was added HATU (941 mg) at room temperature. The mixture was stirred at room temperature for 3.5 hr, and the reaction mixture was poured into aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate/THF. The organic layer was washed with water and
25 saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (702 mg).

MS: [M+H]⁺ 473.0.

30 [0505]

D) 1,1-difluoro-N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

A mixture of N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)-1-(2-
35 hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)-1,1-

5 difluoromethanesulfonamide (76 mg), (3,5-difluorophenyl)boronic acid (50.7 mg), XPhos Pd G3 (6.80 mg), 1 M aqueous tripotassium phosphate solution (0.482 mL) and THF (1.6 mL) was stirred under argon atmosphere at 70°C for 1 hr. The reaction mixture was poured into aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (63.6 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.42 (3H, s), 1.43 (3H, s), 1.88-2.03 (1H, m), 2.36-2.42 (1H, m), 2.94-3.02 (1H, m), 3.13 (1H, dd, J = 14.0, 7.8 Hz), 3.64-3.80 (3H, m), 4.11-4.22 (1H, m), 4.75 (1H, brs), 5.10 (1H, brs), 6.04 (1H, t, J = 54.0 Hz), 6.83 (1H, tt, J = 8.9, 2.3 Hz), 7.01-7.09 (2H, m), 7.21 (1H, t, J = 7.6 Hz), 7.26-7.32 (1H, m), 7.43 (1H, t, J = 6.4 Hz).

[0506]

Example 428

20 N-((2S,3S)-2-((3'-chloro-2,5'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)methanesulfonamide
[0507]

A) N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride

25 To tert-butyl (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate (5 g) was added 4M hydrogen chloride/ethyl acetate solution (22.2 mL) at room temperature. The mixture was stirred at room temperature for 10 hr, and the reaction solution was concentrated under reduced pressure. The obtained solid was washed with diisopropyl ether to give the title compound (4.11 g).

MS: [M+H]⁺ 351.1.

[0508]

B) N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)methanesulfonamide
35

To a mixture of N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (4.11 g), 2-hydroxy-2-methylpropanoic acid (1.32 g) and DMF (40 mL) were added HATU (4.84 g) and TEA (4.29 g) at room temperature. The mixture was stirred overnight at room temperature, to the reaction mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (3.30 g). MS: [M+H]⁺ 437.2.

[0509]

C) N-((2S,3S)-2-((3'-chloro-2,5'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)methanesulfonamide

A mixture of N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)methanesulfonamide (70 mg), (3-chloro-5-fluorophenyl)boronic acid (41.9 mg), XPhos Pd G3 (4.06 mg), 1 M aqueous tripotassium phosphate solution (0.480 mL) and THF (2 mL) was stirred at 70°C for 1 hr. The reaction mixture was purified by silica gel column chromatography (NH, ethyl acetate/hexane), and then purified by HPLC (C18, mobile phase: water/acetonitrile (containing 0.1% TFA)). To the obtained fraction was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the title compound (19 mg).

¹H NMR (400 MHz, DMSO-d₆) δ 1.01-1.27 (6H, m), 1.96-2.06 (1H, m), 2.08-2.25 (1H, m), 2.55-2.73 (1H, m), 2.91 (3H, s), 2.95-3.12 (1H, m), 3.42-3.98 (3H, m), 4.56-4.71 (1H, m), 4.92-5.39 (1H, m), 7.05-7.20 (1H, m), 7.29-7.53 (6H, m).

[0510]

Example 431

N-((2S,3S)-2-((3'-chloro-2-fluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide

5 [0511]

A) N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)pyrrolidin-3-yl)ethanesulfonamide hydrochloride

To tert-butyl (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate (847 mg) was
10 added 4M hydrogen chloride/ethyl acetate solution (8 mL) at room temperature. The mixture was stirred at room temperature for 1 hr, and the reaction mixture was concentrated under reduced pressure. The obtained solid was washed with ethyl acetate to give the title compound (527 mg).

15 MS: [M+H]⁺ 364.9.

[0512]

B) N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide

To a mixture of N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)pyrrolidin-3-yl)ethanesulfonamide hydrochloride
20 (727 mg), 2-hydroxy-2-methylpropanoic acid (227 mg) and DMF (5 mL) were added HATU (1.03 g) and TEA (549 mg) at room temperature. The mixture was stirred at room temperature for 2 hr, to the reaction mixture was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with
25 ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl
30 acetate/hexane) to give the title compound (569 mg).

MS: [M+H]⁺ 451.0.

[0513]

C) N-((2S,3S)-2-((3'-chloro-2-fluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide

35 A mixture of N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)-1-(2-

hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide (60 mg), (3-chlorophenyl)boronic acid (31.2 mg), XPhos Pd G3 (3.38 mg), 1 M aqueous tripotassium phosphate solution (0.399 mL) and THF (2 mL) was stirred at 70°C for 1 hr. The reaction mixture
5 was purified by silica gel column chromatography (NH, ethyl acetate/hexane), and then purified by HPLC (C18, mobile phase: water/acetonitrile (containing 0.1% TFA)). To the obtained fraction was added saturated aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate.
10 The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give the title compound (38 mg).
¹H NMR (400 MHz, DMSO-d₆) δ 1.03-1.17 (6H, m), 1.18-1.23 (3H, m), 1.99-2.23 (2H, m), 2.54-2.67 (1H, m), 2.95-3.11 (3H, m),
15 3.62-3.83 (2H, m), 3.84-3.98 (1H, m), 4.53-4.73 (1H, m), 4.89-5.04 (1H, m), 7.07-7.17 (1H, m), 7.26-7.39 (2H, m), 7.41-7.52 (4H, m), 7.54-7.62 (1H, m).

[0514]

Example 435

20 N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide
A mixture of N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide (70 mg), (3,5-difluorophenyl)boronic acid (36.7 mg), XPhos Pd G3
25 (3.94 mg), 1 M aqueous tripotassium phosphate solution (0.465 mL) and THF (3 mL) was stirred at 70°C for 1.5 hr. The reaction mixture was partitioned between ethyl acetate and water, and the mixture was extracted with ethyl acetate. The organic layer was washed with aqueous sodium hydrogencarbonate
30 solution and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, methanol/ethyl acetate). The obtained solid was recrystallized from ethyl acetate/hexane/water to give the title compound
35 (65.9 mg).

¹H NMR (400 MHz, CDCl₃) δ 1.24 (3H, t, J = 7.3 Hz), 1.39 (3H, s), 1.41 (3H, s), 1.87-2.01 (1H, m), 2.28-2.43 (1H, m), 2.79-2.98 (3H, m), 3.05-3.18 (1H, m), 3.68 (2H, brs), 3.83 (1H, brs), 3.90-4.05 (1H, m), 4.50-4.63 (1H, m), 4.75 (1H, brs), 6.74-6.90 (1H, m), 6.98-7.11 (2H, m), 7.14-7.22 (1H, m), 7.24-7.32 (1H, m), 7.36-7.47 (1H, m).

[0515]

Example 437

N-((2S,3S)-2-((3'-chloro-2,5'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide

A mixture of N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide (70 mg), (3-chloro-5-fluorophenyl)boronic acid (40.6 mg), XPhos Pd G3 (3.94 mg), 1 M aqueous tripotassium phosphate solution (0.465 mL) and THF (3 mL) was stirred at 70°C for 2.5 hr. The reaction mixture was partitioned between ethyl acetate and water, and the mixture was extracted with ethyl acetate. The organic layer was washed with aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, methanol/ethyl acetate). The obtained solid was recrystallized from ethyl acetate/hexane/water to give the title compound (10 mg).

¹H NMR (400 MHz, CDCl₃) δ 1.24 (3H, t, J = 6.8 Hz), 1.40 (3H, s), 1.41 (3H, brs), 1.82-2.04 (1H, m), 2.25-2.44 (1H, m), 2.77-3.01 (3H, m), 3.05-3.23 (1H, m), 3.68 (2H, brs), 3.81 (1H, brs), 3.90-4.08 (1H, m), 4.39-4.58 (1H, m), 4.75 (1H, brs), 7.04-7.22 (3H, m), 7.23-7.35 (2H, m), 7.37-7.47 (1H, m).

[0516]

Example 439

N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)cyclopropanesulfonamide

[0517]

A) tert-butyl (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-
((cyclopropylsulfonyl)amino)pyrrolidine-1-carboxylate

To a mixture of tert-butyl (2S,3S)-3-amino-2-(3-bromo-2-fluorobenzyl)pyrrolidine-1-carboxylate (1 g), TEA (0.542 g),
5 DMAP (0.327 g) and THF (10 mL) was added cyclopropanesulfonyl chloride (0.753 g) at room temperature. The mixture was stirred at 50°C for 3.5 hr, and to the reaction mixture was added ethyl acetate. The insoluble substance was removed by filtration, and the filtrate was concentrated under reduced
10 pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.2 g).

MS: [M+H-Boc]⁺ 377.1.

[0518]

15 B) N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)pyrrolidin-3-yl)cyclopropanesulfonamide hydrochloride

To tert-butyl (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((cyclopropylsulfonyl)amino)pyrrolidine-1-carboxylate (722 mg) was added 4M hydrogen chloride/ethyl acetate solution (7.56 mL)
20 at room temperature. The mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure. The residue was washed with diisopropyl ether to give the title compound (617 mg).

MS: [M+H]⁺ 377.1.

25 [0519]

C) N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)cyclopropanesulfonamide

To a mixture of N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)pyrrolidin-3-yl)cyclopropanesulfonamide
30 hydrochloride (607 mg), 2-hydroxy-2-methylpropanoic acid (183 mg) and DMF (10 mL) were added HATU (837 mg) and TEA (445 mg) at room temperature. The mixture was stirred at room temperature for 2 hr, to the reaction mixture was added saturated aqueous sodium hydrogencarbonate solution, and the
35 mixture was extracted with ethyl acetate. The organic layer

was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title
5 compound (527 mg).

MS: [M+H]⁺ 463.1.

[0520]

D) N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)cyclopropanesulfonamide
10

A mixture of N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)cyclopropanesulfonamide (73.3 mg), (3,5-difluorophenyl)boronic acid (37.5 mg), XPhos Pd G3 (4.02 mg), 1
15 M aqueous tripotassium phosphate solution (0.475 mL) and THF (3 mL) was stirred at 70°C for 1.5 hr. The reaction mixture was partitioned between ethyl acetate and water, and the mixture was extracted with ethyl acetate. The organic layer was washed with aqueous sodium hydrogencarbonate solution and saturated
20 brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (35.8 mg).

¹H NMR (400 MHz, CDCl₃) δ 0.83-0.98 (2H, m), 1.10 (2H, brs),
25 1.38 (3H, brs), 1.40 (3H, brs), 1.93-2.14 (2H, m), 2.25-2.45 (1H, m), 2.80-2.99 (1H, m), 3.05-3.23 (1H, m), 3.71 (2H, brs), 3.86 (1H, brs), 3.95-4.06 (1H, m), 4.78 (1H, brs), 4.96 (1H, d, J = 7.1 Hz), 6.81 (1H, t, J = 8.4 Hz), 6.99-7.11 (2H, m), 7.12-7.20 (1H, m), 7.22-7.31 (1H, m), 7.40 (1H, brs).

30 [0521]

Example 362

N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((3',5'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide

[0522]

35 A) (2S,3S)-2-((3',5'-difluoro[biphenyl]-3-yl)methyl)-3-

((ethylsulfonyl)amino)pyrrolidine-1-carbonyl chloride

To a mixture of N-((2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide hydrochloride (1.0 g), DIPEA (0.620 g) and THF (30 mL) was added

5 bis(trichloromethyl) carbonate (0.569 g) in THF (5 mL) at 0°C. After being stirred at 0°C for 10 min, the mixture was warmed up to room temperature and stirred for 3 hr. The mixture was concentrated in vacuo. The residue was triturated with ethyl acetate and the insoluble substance was removed by filtration.

10 The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.06 g).

MS: [M-H]⁻ 441.2.

[0523]

15 B) N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((3',5'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide

To a mixture of (2S,3S)-2-((3',5'-difluoro[biphenyl]-3-yl)methyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carbonyl chloride (500 mg), azetidine (129 mg) and THF (10 mL) was added
20 TEA (343 mg) at room temperature. The mixture was stirred at room temperature for 3 hr, then diluted with THF and the insoluble substance was removed by filtration. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) and
25 recrystallized from ethyl acetate/hexane to give the title compound (380 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.18-1.28 (3H, m), 1.75-1.90 (1H, m), 2.08-2.25 (3H, m), 2.81-2.99 (3H, m), 3.16 (1H, dd, J = 14.0, 4.9 Hz), 3.26-3.43 (2H, m), 3.80-4.08 (5H, m), 4.36 (1H, d, J =
30 8.7 Hz), 4.43-4.53 (1H, m), 6.78 (1H, tt, J = 8.9, 2.3 Hz), 7.07-7.17 (2H, m), 7.31-7.43 (3H, m), 7.46-7.50 (1H, m).

[0524]

Example 372

N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide
35

Azetidine (244 mg) was added to a stirred mixture of (2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carbonyl chloride (632 mg) and THF (6 mL) at room temperature. After being stirred for 30 min, the reaction mixture was concentrated in vacuo. The residue was diluted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, filtrated and concentrated in vacuo. The obtained solid was crystallized from ethyl acetate/ethanol to give the title compound (416 mg).

¹H NMR (400 MHz, CDCl₃) δ 1.23 (3H, t, J = 7.4 Hz), 1.82-1.97 (1H, m), 2.08-2.30 (3H, m), 2.78-2.91 (2H, m), 2.92-3.06 (2H, m), 3.22-3.40 (2H, m), 3.74-4.02 (5H, m), 4.46-4.61 (2H, m), 7.03-7.11 (1H, m), 7.14-7.25 (2H, m), 7.26-7.44 (4H, m).

[0525]

Example 377

(2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((dimethylsulfamoyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide

[0526]

A) tert-butyl (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((dimethylsulfamoyl)amino)pyrrolidine-1-carboxylate

Dimethylsulfamoyl chloride (2.31 g) was added to a mixture of tert-butyl (2S,3S)-3-amino-2-(3-bromo-2-fluorobenzyl)pyrrolidine-1-carboxylate (2.5 g), TEA (1.36 g), DMAP (0.982 g) and THF (25 mL) at room temperature. After being stirred at 50°C for 4 hr, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (2.4 g).

MS: [M+H-Boc]⁺ 380.0.

[0527]

B) N'-((2S,3S)-2-(3-bromo-2-fluorobenzyl)pyrrolidin-3-yl)-N,N-dimethylsulfuric diamide hydrochloride

A mixture of tert-butyl (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((dimethylsulfamoyl)amino)pyrrolidine-1-carboxylate (2.4 g) and 4M hydrogen chloride/ethyl acetate solution (12.5 mL) was stirred at room temperature under a dry atmosphere (CaCl₂ tube) overnight. The mixture was concentrated in vacuo. The residue was washed with diisopropyl ether to give the title compound (1.78 g).

MS: [M+H]⁺ 379.9.

[0528]

- 10 C) (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((dimethylsulfamoyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide

To a mixture of N'-((2S,3S)-2-(3-bromo-2-fluorobenzyl)pyrrolidin-3-yl)-N,N-dimethylsulfuric diamide hydrochloride (1.78 g), TEA (4.32 g) and THF (20 mL) was added dimethylcarbamoyl chloride (2.30 g) at room temperature. The mixture was refluxed for 3 hr. The mixture was quenched with saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (1.9 g).

MS: [M+H]⁺ 451.0.

25 [0529]

- D) (2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((dimethylsulfamoyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide

A mixture of (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((dimethylsulfamoyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide (600 mg), (3-fluorophenyl)boronic acid (242 mg), XPhos Pd G3 (16.9 mg), 1M aqueous tripotassium phosphate solution (3.99 mL) and THF (6 mL) was stirred at 70°C for 1 hr. The aqueous phase was removed and the organic layer was concentrated in vacuo. The residue was purified by silica gel

column chromatography (NH, ethyl acetate/hexane) and the resulting solid was crystallized from ethyl acetate/hexane to give the title compound (562 mg).

¹H NMR (400 MHz, CDCl₃) δ 2.03-2.23 (2H, m), 2.73 (6H, s), 2.76
5 (6H, s), 2.85-2.93 (1H, m), 2.94-3.03 (1H, m), 3.20-3.32 (1H, m), 3.53-3.67 (1H, m), 3.81-3.92 (1H, m), 4.48 (1H, d, J = 8.1 Hz), 4.54-4.62 (1H, m), 7.01-7.08 (1H, m), 7.12-7.18 (1H, m), 7.20-7.26 (2H, m), 7.27-7.43 (3H, m).

[0530]

10 Example 407

(2S,3S)-2-(biphenyl-3-ylmethyl)-3-((ethylsulfonyl)amino)-N-methoxy-N-methylpyrrolidine-1-carboxamide

To a stirred mixture of N-((2S,3S)-2-(biphenyl-3-ylmethyl)pyrrolidin-3-yl)ethanesulfonamide hydrochloride (293
15 mg), DIPEA (298 mg) and THF (3 mL) was added methoxy(methyl)carbamoyl chloride (143 mg) at room temperature. After 15 min, the reaction mixture was concentrated in vacuo. The residue was diluted with ethyl acetate, washed with saturated brine, and purified by silica gel column
20 chromatography (ethyl acetate/hexane) and recrystallized from ethyl acetate/hexane to give the title compound (302 mg).

¹H NMR (400 MHz, CDCl₃) δ 1.19 (3H, t, J = 7.4 Hz), 1.83-1.94 (1H, m), 2.06-2.23 (1H, m), 2.72-2.94 (3H, m), 2.98 (3H, s), 3.17-3.27 (1H, m), 3.42-3.52 (1H, m), 3.55 (3H, s), 3.60-3.70
25 (1H, m), 3.86-4.02 (1H, m), 4.40 (1H, d, J = 8.8 Hz), 4.52-4.68 (1H, m), 7.27-7.62 (9H, m).

[0531]

Example 441

N-((2S,3S)-1-(oxetane-2-carbonyl)-2-[(2,3',5'-trifluoro[1,1'-
30 biphenyl]-3-yl)methyl]pyrrolidin-3-yl)methanesulfonamide

[0532]

A) N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)-1-(oxetan-2-ylcarbonyl)pyrrolidin-3-yl)methanesulfonamide

HATU (374 mg) was added to a mixture of N-((2S,3S)-2-(3-
35 bromo-2-fluorobenzyl)pyrrolidin-3-yl)methanesulfonamide

hydrochloride (318 mg), oxetane-2-carboxylic acid (100 mg), TEA (415 mg) and DMF (6 mL) at room temperature. The mixture was stirred at room temperature for 30 min. The mixture was quenched with saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (methanol/ethyl acetate). The solid was crystallized from ethyl acetate/diisopropyl ether/hexane to give the title compound (244 mg)

MS: [M+H]⁺ 435.2.

[0533]

B) N-((2S,3S)-1-(oxetane-2-carbonyl)-2-[(2,3',5'-trifluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl)methanesulfonamide

A mixture of N-((2S,3S)-2-(3-bromo-2-fluorobenzyl)-1-(oxetan-2-ylcarbonyl)pyrrolidin-3-yl)methanesulfonamide (76.5 mg), (3,5-difluorophenyl)boronic acid (41.6 mg), Xphos Pd G3 (4.46 mg), 1M aqueous tripotassium phosphate solution (0.527 mL) and THF (3 mL) was stirred at 70°C for 1.5 hr. The mixture was partitioned between ethyl acetate and water and extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give a solid. The residue was purified by silica gel column chromatography (NH, methanol/ethyl acetate) to give the title compound (42.4 mg).

¹H NMR (400 MHz, CDCl₃) δ 1.82-1.98 (1H, m), 2.25-2.63 (2H, m), 2.69-3.03 (5H, m), 3.06-3.16 (1H, m), 3.25-3.81 (2H, m), 3.93-4.58 (3H, m), 4.62-5.25 (3H, m), 6.76-7.55 (6H, m).

[0534]

Example 450

N-[(2S,3S)-2-[(2,3'-difluoro[1,1'-biphenyl]-3-yl)methyl]-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl]-1-

fluorocyclopropane-1-sulfonamide

[0535]

A) tert-butyl (2S,3S)-3-((cyclopropylsulfonyl)amino)-2-((2,3'-difluoro[biphenyl]-3-yl)methyl)pyrrolidine-1-carboxylate

5 A mixture of tert-butyl (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((cyclopropylsulfonyl)amino)pyrrolidine-1-carboxylate (1.17 g), (3-fluorophenyl)boronic acid (0.514 g), XPhos Pd G3 (0.207 g), 1M aqueous tripotassium phosphate solution (7.35 mL) and THF (10 mL) was stirred at 70°C for 1 hr.
10 The mixture was poured into water at room temperature and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (NH, ethyl acetate/Hexane) to
15 give title compound (1.02 g).

MS: [M+H-Boc]⁺ 393.1.

[0536]

B) tert-butyl (2S,3S)-2-((2,3'-difluoro[biphenyl]-3-yl)methyl)-3-(((1-fluorocyclopropyl)sulfonyl)amino)pyrrolidine-1-
20 carboxylate

To a mixture of tert-butyl (2S,3S)-3-((cyclopropylsulfonyl)amino)-2-((2,3'-difluoro[biphenyl]-3-yl)methyl)pyrrolidine-1-carboxylate (156 mg) and THF (3 mL) was added 2.6M n-butyllithium/hexane solution (0.268 mL) dropwise
25 at -78°C. After being stirred at -78°C for 1 hr, a solution of N-fluoro-N-(phenylsulfonyl)benzenesulfonamide (120 mg) in THF (1 mL) was added dropwise to the reaction mixture. The mixture was stirred at 0°C under nitrogen atmosphere for 1 hr and then at room temperature for 2 hr. The mixture was quenched with
30 saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give
35 title compound (81.9 mg).

MS: [M+H-Boc]⁺ 411.3.

[0537]

C) N-((2S,3S)-2-((2,3'-difluoro[biphenyl]-3-yl)methyl)pyrrolidin-3-yl)-1-fluorocyclopropanesulfonamide
5 hydrochloride

To a mixture of tert-butyl (2S,3S)-2-((2,3'-difluoro[biphenyl]-3-yl)methyl)-3-((1-fluorocyclopropyl)sulfonyl)amino)pyrrolidine-1-carboxylate (81.9 mg) and ethyl acetate (0.5 mL) was added 4M hydrogen
10 chloride/ethyl acetate solution (0.802 mL) at room temperature. The mixture was stirred at room temperature overnight. The mixture was concentrated in vacuo to give the title compound (57.0 mg).

MS: [M+H]⁺ 411.3.

15 [0538]

D) N-[(2S,3S)-2-[(2,3'-difluoro[1,1'-biphenyl]-3-yl)methyl]-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl]-1-fluorocyclopropane-1-sulfonamide

A mixture of N-((2S,3S)-2-((2,3'-difluoro[biphenyl]-3-yl)methyl)pyrrolidin-3-yl)-1-fluorocyclopropanesulfonamide
20 hydrochloride (447 mg), DIPEA (1.29 g) and THF (5 mL) was stirred at room temperature for 30 min. To the suspension was added dropwise 1-chloro-2-methyl-1-oxopropan-2-yl acetate (198 mg) at 0°C, and the mixture was stirred at same temperature for
25 1 hr. To the mixture were added water (2 mL) and 4M aqueous lithium hydroxide solution (2.00 mL) and the mixture was stirred at room temperature overnight. The mixture was diluted with saturated brine and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous magnesium
30 sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) and then preparative HPLC (C18, mobile phase: water/acetonitrile (containing 0.1% TFA)). The desired fraction was neutralized with saturated aqueous sodium hydrogencarbonate solution and
35 extracted with ethyl acetate. The organic layer was separated,

washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The solid was crystallized from ethanol/water to give the title compound (140 mg).

5 ¹H NMR (400 MHz, CDCl₃) δ 1.14-1.52 (10H, m), 1.79-2.03 (1H, m), 2.28-2.42 (1H, m), 2.91-3.04 (1H, m), 3.11-3.26 (1H, m), 3.52-3.95 (3H, m), 4.07-4.24 (1H, m), 4.69-5.06 (2H, m), 7.03-7.10 (1H, m), 7.15-7.25 (2H, m), 7.27-7.44 (4H, m).

[0539]

10 Example 456

N-((2S,3S)-1-(azetidine-1-carbonyl)-2-[(2-fluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl)ethanesulfonamide
[0540]

A) N-((2S,3S)-2-((2-fluoro[biphenyl]-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide hydrochloride
15

A mixture of tert-butyl (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate (0.698 g), phenylboronic acid (0.238 g), XPhos Pd G3 (0.019 g), 2M aqueous tripotassium phosphate solution (2.25 mL) and THF (3
20 mL) was stirred at 70°C for 1 hr. The aqueous phase was removed and the organic layer was concentrated in vacuo. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give a solid. 4M hydrogen chloride/ethyl acetate solution (7.50 mL) was added to a stirred mixture of
25 the solid (694 mg) and ethyl acetate (2 mL) at room temperature. After 18 hr, the reaction mixture was concentrated in vacuo, and the resulting solid was collected by filtration to give the title compound (568 mg).

MS: [M+H]⁺ 363.3.

30 [0541]

B) N-((2S,3S)-1-(azetidine-1-carbonyl)-2-[(2-fluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl)ethanesulfonamide

To a stirred mixture of N-((2S,3S)-2-((2-fluoro[biphenyl]-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide
35 hydrochloride (568 mg), bis(trichloromethyl) carbonate (254 mg)

and THF (6 mL) was added DIPEA (368 mg) at 0°C. After being stirred at room temperature for 30 min, the reaction mixture was concentrated in vacuo. The residue was diluted with ethyl acetate, washed with saturated brine, and purified by silica gel column chromatography (ethyl acetate/hexane) to give an oil. Azetidine (243 mg) was added to a stirred mixture of the oil (603 mg) and THF (7 mL) at room temperature. After being stirred for 30 min, the reaction mixture was concentrated in vacuo. The residue was diluted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, filtrated and concentrated in vacuo. The obtained solid was crystallized from hexane/ethanol to give the title compound (516 mg).
¹H NMR (400 MHz, CDCl₃) δ 1.21 (3H, t, J = 7.4 Hz), 1.82-1.96 (1H, m), 2.06-2.28 (3H, m), 2.76-2.90 (2H, m), 2.93-3.08 (2H, m), 3.20-3.40 (2H, m), 3.82 (2H, q, J = 7.8 Hz), 3.88-4.06 (3H, m), 4.52 (1H, q, J = 6.6 Hz), 4.58-4.65 (1H, m), 7.13-7.20 (1H, m), 7.27-7.33 (1H, m), 7.33-7.39 (2H, m), 7.41-7.48 (2H, m), 7.49-7.56 (2H, m).

[0542]

20 Example 457

N-((2S,3S)-1-(3-hydroxy-2,2-dimethylpropanoyl)-2-[(2,3',5'-trifluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl)methanesulfonamide

[0543]

25 A) N-((2S,3S)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride

A mixture of tert-butyl (2S,3S)-3-((methylsulfonyl)amino)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidine-1-carboxylate

30 (1.67 g), 4M hydrogen chloride/ethyl acetate solution (20 mL) and ethyl acetate (20 mL) was stirred at room temperature overnight. The mixture was diluted with ethyl acetate and the precipitate was collected by filtration to give the title compound (1.37 g).

35 MS: [M+H]⁺ 385.2.

[0544]

B) N-((2S,3S)-1-(3-hydroxy-2,2-dimethylpropanoyl)-2-((2,3',5'-trifluoro[1,1'-biphenyl]-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

5 HATU (67.8 mg) was added to a mixture of N-((2S,3S)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (50 mg), 3-hydroxy-2,2-dimethylpropanoic acid (18.2 mg), DIPEA (77 mg) and DMF (1 mL) at room temperature. After being stirred at room temperature
10 for 7 hr, the reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogencarbonate solution, water and saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel
15 column chromatography (ethyl acetate) to give an oil. The oil was crystallized from ethyl acetate/hexane to give the title compound (24.7 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.18 (3H, s), 1.19 (3H, s), 1.86-2.11 (1H, m), 2.31-2.47 (1H, m), 2.31-2.47 (1H, m), 2.72 (3H, s),
20 2.86 (1H, dd, J = 13.8, 5.5 Hz), 3.06 (1H, dd, J = 13.4, 7.4 Hz), 3.15-3.25 (1H, m), 3.28-3.39 (1H, m), 3.53 (1H, dd, J = 10.8, 6.2 Hz), 3.64-3.73 (2H, m), 3.89-4.08 (1H, m), 4.56-4.68 (1H, m), 4.75-4.84 (1H, m), 6.77-6.87 (1H, m), 7.01-7.13 (2H, m), 7.15-7.26 (2H, m), 7.38-7.47 (1H, m).

25 [0545]

Example 459

N-((2S,3S)-1-(azetidine-1-carbonyl)-2-((3'-fluoro[1,1'-biphenyl]-3-yl)methyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide

30 [0546]

A) benzyl ((2S,3S)-2-(3-bromobenzyl)pyrrolidin-3-yl)carbamate hydrochloride

To a mixture of tert-butyl (2S,3S)-3-amino-2-(3-bromobenzyl)pyrrolidine-1-carboxylate (10.7 g), 2M aqueous
35 sodium hydroxide solution (19 mL) and THF (100 mL) was added

benzyl carbonochloridate (5.98 g) at 0°C. The mixture was stirred at room temperature for 30 min. To the mixture was added saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous sodium sulfate and concentrated in vacuo. To a mixture of obtained residue and ethyl acetate (20 mL) was added 4M hydrogen chloride/ethyl acetate solution (75 mL) at room temperature. The mixture was stirred at room temperature overnight. The mixture was concentrated in vacuo. The residue was triturated with ethyl acetate and the precipitate was collected by filtration to give the title compound (12.8 g). MS: [M+H]⁺ 389.0.

[0547]

15 B) benzyl ((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-(3-bromobenzyl)pyrrolidin-3-yl)carbamate

To a mixture of benzyl ((2S,3S)-2-(3-bromobenzyl)pyrrolidin-3-yl)carbamate hydrochloride (5 g) and THF (100 mL) were added bis(trichloromethyl) carbonate (2.79 g) and DIPEA (3.04 g) at 0°C. After being stirred at 0°C for 20 min, the mixture was concentrated in vacuo. To the residue were added THF (100 mL) and azetidine (5.36 g). The mixture was stirred at room temperature overnight. The mixture was quenched with saturated aqueous sodium hydrogencarbonate solution at room temperature and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The solid was crystallized from ethyl acetate/diisopropyl ether to give the title compound (4.74 g).

30 MS: [M+H]⁺ 472.1.

[0548]

C) benzyl ((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((3'-fluoro[biphenyl]-3-yl)methyl)pyrrolidin-3-yl)carbamate

A mixture of benzyl ((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-(3-bromobenzyl)pyrrolidin-3-yl)carbamate (1.4 g), (3-

fluorophenyl)boronic acid (0.539 g), XPhos Pd G3 (0.038 g), 1M aqueous tripotassium phosphate solution (8.89 mL) and THF (20 mL) was stirred at 70°C for 5 hr. After cooling, the insoluble substance was removed by filtration, and the filtrate was concentrated in vacuo. The residue was extracted with ethyl acetate/THF. The organic layer was separated, washed with saturated brine, passed through NH silica gel and concentrated in vacuo. The obtained solid was washed with ethyl acetate and diisopropyl ether to give the title compound (1.25 g).

10 MS: [M+H]⁺ 488.2.

[0549]

D) ((2S,3S)-3-amino-2-((3'-fluoro[biphenyl]-3-yl)methyl)pyrrolidin-1-yl)(azetidin-1-yl)methanone

A mixture of benzyl ((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((3'-fluoro[biphenyl]-3-yl)methyl)pyrrolidin-3-yl)carbamate (1.25 g), 10% palladium on carbon (0.12 g), EtOH (20 mL) and THF (20 mL) was hydrogenated under balloon pressure at room temperature for 1 hr. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (NH, methanol/ethyl acetate) to give the title compound (900 mg).

20 MS: [M+H]⁺ 354.0.

[0550]

E) N-((2S,3S)-1-(azetidine-1-carbonyl)-2-((3'-fluoro[1,1'-biphenyl]-3-yl)methyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide

25

To a mixture of ((2S,3S)-3-amino-2-((3'-fluoro[biphenyl]-3-yl)methyl)pyrrolidin-1-yl)(azetidin-1-yl)methanone (100 mg) and THF (2 mL) were added DIPEA (47.5 mg) and fluoromethanesulfonyl chloride (41.3 mg) at room temperature. After being stirred for 30 min, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane). The solid was crystallized from ethyl acetate/hexane to give the title compound (58 mg).

30

35

¹H NMR (400 MHz, DMSO-d₆) δ 1.86-2.00 (3H, m), 2.02-2.16 (1H, m), 2.70-2.82 (1H, m), 2.85-2.95 (1H, m), 3.10-3.21 (1H, m), 3.32-3.38 (1H, m), 3.52-3.64 (2H, m), 3.72-3.88 (3H, m), 4.20-4.31 (1H, m), 5.17-5.50 (2H, m), 7.14-7.22 (1H, m), 7.26-7.30 (1H, m), 7.33-7.39 (1H, m), 7.46-7.58 (5H, m), 8.22 (1H, brs).

[0551]

Example 460

N-((2S,3S)-1-(azetidine-1-carbonyl)-2-([1,1'-biphenyl]-3-yl)methyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide

10 [0552]

A) benzyl ((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-([biphenyl]-3-ylmethyl)pyrrolidin-3-yl)carbamate

A mixture of benzyl ((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-(3-bromobenzyl)pyrrolidin-3-yl)carbamate (1.4 g), phenylboronic acid (0.470 g), XPhos Pd G3 (0.038 g), 1M aqueous tripotassium phosphate solution (8.89 mL) and THF (20 mL) was stirred at 70°C for 5 hr. After cooling, the insoluble substance was removed by filtration, and the filtrate was concentrated in vacuo. The residue was extracted with ethyl acetate/THF. The organic layer was separated, washed with saturated brine, passed through NH silica gel and concentrated in vacuo. The obtained solid was washed with ethyl acetate and diisopropyl ether to give the title compound (1.08 g).

MS: [M+H]⁺ 470.2.

25 [0553]

B) ((2S,3S)-3-amino-2-([biphenyl]-3-ylmethyl)pyrrolidin-1-yl)(azetidin-1-yl)methanone

A mixture of benzyl ((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-([biphenyl]-3-ylmethyl)pyrrolidin-3-yl)carbamate (1.08 g), 10% palladium on carbon (0.10 g), EtOH (20 mL) and THF (20 mL) was hydrogenated under balloon pressure at room temperature for 1 hr. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (NH, methanol/ethyl acetate) to give the title compound (700 mg).

MS: [M+H]⁺ 336.1.

[0554]

C) N-{(2S,3S)-1-(azetidine-1-carbonyl)-2-([1,1'-biphenyl]-3-yl)methyl}pyrrolidin-3-yl}-1-fluoromethanesulfonamide

5 To a mixture of ((2S,3S)-3-amino-2-([biphenyl]-3-ylmethyl)pyrrolidin-1-yl)(azetidin-1-yl)methanone (100 mg) in THF (2 mL) were added DIPEA (50.1 mg) and fluoromethanesulfonyl chloride (43.5 mg) at 0°C. After being stirred for 30 min, the mixture was concentrated in vacuo. The residue was purified by
10 silica gel column chromatography (ethyl acetate/hexane). The solid was crystallized from ethyl acetate/hexane to give the title compound (98 mg).

¹H NMR (400 MHz, DMSO-d₆) δ 1.85-1.99 (3H, m), 2.03-2.14 (1H, m), 2.69-2.79 (1H, m), 2.85-2.95 (1H, m), 3.12-3.20 (1H, m),
15 3.31-3.39 (1H, m), 3.52-3.67 (2H, m), 3.71-3.87 (3H, m), 4.19-4.29 (1H, m), 5.18-5.46 (2H, m), 7.21-7.29 (1H, m), 7.31-7.38 (2H, m), 7.42-7.50 (3H, m), 7.51-7.55 (1H, m), 7.64-7.72 (2H, m), 8.22 (1H, brs).

[0555]

20 Example 462

N-{(2S,3S)-1-(azetidine-1-carbonyl)-2-((3'-fluoro[1,1'-biphenyl]-3-yl)methyl)pyrrolidin-3-yl}cyclopropanesulfonamide

To a mixture of ((2S,3S)-3-amino-2-((3'-fluoro[biphenyl]-3-yl)methyl)pyrrolidin-1-yl)(azetidin-1-yl)methanone (200 mg)
25 and THF (4 mL) were added DIPEA (95 mg), DMAP (69.1 mg) and cyclopropanesulfonyl chloride (88 mg) at room temperature. After being stirred for 10 hr, the mixture was quenched with saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic layer was separated,
30 dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (methanol/ethyl acetate). The solid was crystallized from ethyl acetate/diisopropyl ether to give the title compound (221 mg).

¹H NMR (400 MHz, DMSO-d₆) δ 0.77-1.00 (4H, m), 1.88-2.03 (3H, m),
35 2.03-2.16 (1H, m), 2.37-2.48 (1H, m), 2.70-2.81 (1H, m),

2.88-2.97 (1H, m), 3.13-3.23 (1H, m), 3.33-3.39 (1H, m), 3.53-3.65 (2H, m), 3.72-3.86 (3H, m), 4.21-4.30 (1H, m), 7.13-7.23 (1H, m), 7.26-7.39 (2H, m), 7.45-7.61 (6H, m).

[0556]

5 Example 463

N-((2S,3S)-1-(azetidine-1-carbonyl)-2-([1,1'-biphenyl]-3-yl)methyl)pyrrolidin-3-yl)cyclopropanesulfonamide

To a mixture of ((2S,3S)-3-amino-2-([biphenyl]-3-ylmethyl)pyrrolidin-1-yl)(azetidin-1-yl)methanone (200 mg) and
10 THF (4 mL) were added DIPEA (100 mg), DMAP (14.6 mg) and cyclopropanesulfonyl chloride (92 mg) at room temperature. After being stirred overnight, the mixture was quenched with saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic layer was separated,
15 dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (methanol/ethyl acetate). The solid was crystallized from ethyl acetate/diisopropyl ether to give the title compound (228 mg).
¹H NMR (400 MHz, DMSO-d₆) δ 0.79-0.99 (4H, m), 1.87-2.01 (3H, m),
20 2.02-2.15 (1H, m), 2.38-2.47 (1H, m), 2.69-2.79 (1H, m), 2.87-2.98 (1H, m), 3.12-3.22 (1H, m), 3.32-3.39 (1H, m), 3.51-3.67 (2H, m), 3.72-3.84 (3H, m), 4.20-4.30 (1H, m), 7.22-7.29 (1H, m), 7.30-7.39 (2H, m), 7.41-7.49 (3H, m), 7.50-7.57 (2H, m), 7.62-7.71 (2H, m).

25 [0557]

Example 466

N-((2S,3S)-1-(azetidine-1-carbonyl)-2-((2-fluoro[1,1'-biphenyl]-3-yl)methyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide

30 [0558]

A) tert-butyl (2S,3S)-3-(((benzyloxy)carbonyl)amino)-2-(3-bromo-2-fluorobenzyl)pyrrolidine-1-carboxylate

To a mixture of tert-butyl (2S,3S)-3-amino-2-(3-bromo-2-fluorobenzyl)pyrrolidine-1-carboxylate (1.43 g), 2M aqueous
35 sodium hydroxide solution (2.30 mL) and THF (20 mL) was added

benzyl carbonochloridate (0.719 g) at 0°C. The mixture was stirred at room temperature for 30 min. To the mixture was added saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous sodium sulfate and concentrated in vacuo to give the title compound (2.03 g).

MS: [M+H-Boc]⁺ 407.0.

[0559]

10 B) benzyl ((2S,3S)-2-(3-bromo-2-fluorobenzyl)pyrrolidin-3-yl)carbamate hydrochloride

A mixture of tert-butyl (2S,3S)-3-(((benzyloxy)carbonyl)amino)-2-(3-bromo-2-fluorobenzyl)pyrrolidine-1-carboxylate (1.94 g) and 4M hydrogen chloride/ethyl acetate solution (9.58 mL) was stirred at room temperature overnight. The mixture was concentrated in vacuo. The residue was triturated with ethyl acetate and the precipitate was collected by filtration to give the title compound (1.54 g).

20 MS: [M+H]⁺ 407.0.

[0560]

C) benzyl ((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-(3-bromo-2-fluorobenzyl)pyrrolidin-3-yl)carbamate

To a mixture of benzyl ((2S,3S)-2-(3-bromo-2-fluorobenzyl)pyrrolidin-3-yl)carbamate hydrochloride (1.54 g) and THF (30 mL) were added bis(trichloromethyl) carbonate (0.824 g) and DIPEA (0.897 g) at 0°C. After being stirred at 0°C for 20 min, the mixture was concentrated in vacuo. To the residue were added THF (30 mL) and azetidine (0.991 g). The mixture was stirred at room temperature overnight. The mixture was quenched with saturated aqueous sodium hydrogencarbonate solution at room temperature and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The solid was crystallized from ethyl

acetate/diisopropyl ether to give the title compound (1.64 g).

MS: [M+H]⁺ 490.1.

[0561]

D) benzyl ((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2-fluoro[biphenyl]-3-yl)methyl)pyrrolidin-3-yl)carbamate

A mixture of benzyl ((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((3-bromo-2-fluorobenzyl)pyrrolidin-3-yl)carbamate (600 mg), phenylboronic acid (194 mg), XPhos Pd G3 (15.5 mg), 1M aqueous tripotassium phosphate solution (3.67 mL) and THF (20 mL) was stirred at 70°C for 5 hr. After cooling, the insoluble substance was removed by filtration, and the filtrate was concentrated in vacuo. The residue was extracted with ethyl acetate/THF. The organic layer was separated, washed with saturated brine, passed through NH silica gel and concentrated in vacuo. The obtained solid was washed with ethyl acetate and diisopropyl ether to give the title compound (500 mg).

MS: [M+H]⁺ 488.2.

[0562]

E) ((2S,3S)-3-amino-2-((2-fluoro[biphenyl]-3-yl)methyl)pyrrolidin-1-yl)(azetidin-1-yl)methanone

A mixture of benzyl ((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2-fluoro[biphenyl]-3-yl)methyl)pyrrolidin-3-yl)carbamate (500 mg), 10% palladium on carbon (50 mg), EtOH (20 mL) and THF (20 mL) was hydrogenated under balloon pressure at room temperature for 1 hr. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (NH, methanol/ethyl acetate) to give the title compound (360 mg).

MS: [M+H]⁺ 354.0.

[0563]

F) N-((2S,3S)-1-(azetidine-1-carbonyl)-2-((2-fluoro[1,1'-biphenyl]-3-yl)methyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide

To a mixture of ((2S,3S)-3-amino-2-((2-fluoro[biphenyl]-3-yl)methyl)pyrrolidin-1-yl)(azetidin-1-yl)methanone (100 mg)

and THF (2 mL) were added DIPEA (47.5 mg) and fluoromethanesulfonyl chloride (41.3 mg) at 0°C. After being stirred for 30 min, the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane). The solid was crystallized from ethyl acetate/hexane to give the title compound (98 mg).

¹H NMR (400 MHz, DMSO-d₆) δ 1.90-2.19 (4H, m), 2.60-2.71 (1H, m), 2.86-2.97 (1H, m), 3.09-3.20 (1H, m), 3.32-3.39 (1H, m), 3.43-3.53 (2H, m), 3.66-3.77 (2H, m), 3.80-3.89 (1H, m), 4.34-4.46 (1H, m), 5.22-5.55 (2H, m), 7.13-7.20 (1H, m), 7.25-7.34 (2H, m), 7.35-7.42 (1H, m), 7.44-7.51 (2H, m), 7.52-7.57 (2H, m), 8.15-8.34 (1H, m).

[0564]

Example 467

N-((2S,3S)-1-(azetidine-1-carbonyl)-2-((2,3'-difluoro[1,1'-biphenyl]-3-yl)methyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide

[0565]

A) benzyl ((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3'-difluoro[biphenyl]-3-yl)methyl)pyrrolidin-3-yl)carbamate

A mixture of benzyl ((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-(3-bromo-2-fluorobenzyl)pyrrolidin-3-yl)carbamate (600 mg), (3-fluorophenyl)boronic acid (223 mg), XPhos Pd G3 (15.5 mg), 1M aqueous tripotassium phosphate solution (3.67 mL) and THF (20 mL) was stirred at 70°C for 5 hr. After cooling, the insoluble substance was removed by filtration, and the filtrate was concentrated in vacuo. The residue was extracted with ethyl acetate/THF. The organic layer was separated, washed with saturated brine, passed through NH silica gel and concentrated in vacuo. The obtained solid was washed with ethyl acetate and diisopropyl ether to give the title compound (475 mg).

MS: [M+H]⁺ 506.2.

[0566]

B) ((2S,3S)-3-amino-2-((2,3'-difluoro[biphenyl]-3-yl)methyl)pyrrolidin-1-yl)(azetidin-1-yl)methanone

A mixture of benzyl ((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-
((2,3'-difluoro[biphenyl]-3-yl)methyl)pyrrolidin-3-yl)carbamate
(475 mg), 10% palladium on carbon (0.47 g), EtOH (20 mL) and
THF (20 mL) was hydrogenated under balloon pressure at room
5 temperature for 1 hr. The catalyst was removed by filtration
and the filtrate was concentrated in vacuo. The residue was
purified by silica gel column chromatography (NH,
methanol/ethyl acetate) to give the title compound (330 mg).
MS: [M+H]⁺ 372.1.

10 [0567]

C) N-((2S,3S)-1-(azetidine-1-carbonyl)-2-[(2,3'-difluoro[1,1'-
biphenyl]-3-yl)methyl]pyrrolidin-3-yl)-1-
fluoromethanesulfonamide

To a mixture of ((2S,3S)-3-amino-2-((2,3'-
15 difluoro[biphenyl]-3-yl)methyl)pyrrolidin-1-yl)(azetidin-1-
yl)methanone (100 mg) and THF (2 mL) were added DIPEA (45.2 mg)
and fluoromethanesulfonyl chloride (39.3 mg) at 0°C. After
being stirred for 30 min, the mixture was concentrated in vacuo.
The residue was purified by silica gel column chromatography
20 (ethyl acetate/hexane). The solid was crystallized from ethyl
acetate/hexane to give the title compound (80 mg).

¹H NMR (400 MHz, DMSO-d₆) δ 1.85-2.21 (4H, m), 2.60-2.70 (1H,
m), 2.88-2.99 (1H, m), 3.08-3.18 (1H, m), 3.32-3.39 (1H, m),
3.42-3.52 (2H, m), 3.65-3.76 (2H, m), 3.78-3.91 (1H, m), 4.34-
25 4.45 (1H, m), 5.22-5.56 (2H, m), 7.15-7.28 (2H, m), 7.29-7.42
(4H, m), 7.48-7.57 (1H, m), 8.15-8.36 (1H, m).

[0568]

Example 471

N-((2S,3S)-2-([(1,1'-biphenyl]-3-yl)methyl]-1-
30 (cyclobutanecarbonyl)pyrrolidin-3-yl)ethanesulfonamide

To a mixture of N-((2S,3S)-2-(biphenyl-3-
ylmethyl)pyrrolidin-3-yl)ethanesulfonamide hydrochloride (100
mg), cyclobutanecarboxylic acid (31.5 mg), HATU (120 mg) and
DMF (1 mL) was added TEA (80 mg) at 0°C. The mixture was
35 stirred at room temperature for 30 min. To the mixture was

added saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was
5 purified by silica gel column chromatography (methanol/ethyl acetate). The residue was crystallized from ethyl acetate/diisopropyl ether to give the title compound (75 mg).
¹H NMR (400 MHz, DMSO-d₆) δ 0.91-1.30 (5H, m), 1.38-2.36 (8H, m), 2.63-3.31 (5H, m), 3.38-3.88 (2H, m), 3.99-4.39 (1H, m),
10 7.12-7.68 (9H, m).

[0569]

Example 474

(2S,3S)-3-[(ethanesulfonyl)amino]-2-[(3'-fluoro[1,1'-biphenyl]-3-yl)methyl]-N-methoxy-N-methylpyrrolidine-1-carboxamide

15 [0570]

A) tert-butyl (2S,3S)-3-((ethylsulfonyl)amino)-2-((3'-fluoro[biphenyl]-3-yl)methyl)pyrrolidine-1-carboxylate

A mixture of tert-butyl (2S,3S)-2-(3-bromobenzyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate (671 mg), (3-
20 fluorophenyl)boronic acid (273 mg), XPhos Pd G3 (38.1 mg), 1M aqueous tripotassium phosphate solution (4.50 mL) and THF (7.5 mL) was stirred at 70°C for 1 hr. The mixture was concentrated in vacuo to remove THF, and the residue was extracted with ethyl acetate. The organic layer was concentrated in vacuo. The
25 residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (690 mg).

MS: [M-H]⁻ 461.3.

[0571]

B) N-((2S,3S)-2-((3'-fluoro[biphenyl]-3-yl)methyl)pyrrolidin-3-
30 yl)ethanesulfonamide hydrochloride

4M Hydrogen chloride/ethyl acetate solution (7.46 mL) was added to a stirred mixture of tert-butyl (2S,3S)-3-((ethylsulfonyl)amino)-2-((3'-fluoro[biphenyl]-3-yl)methyl)pyrrolidine-1-carboxylate (0.690 g) and ethyl acetate
35 (3 mL) at room temperature. After 1 hr, the resulting solid was

collected by filtration to give the title compound (508 mg).

MS: [M+H]⁺ 363.2.

[0572]

C) (2S,3S)-3-((ethylsulfonyl)amino)-2-((3'-fluoro[biphenyl]-3-yl)methyl)pyrrolidine-1-carbonyl chloride

To a mixture of N-((2S,3S)-2-((3'-fluoro[biphenyl]-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide hydrochloride (508 mg), bis(trichloromethyl) carbonate (302 mg) and THF (6 mL) was added DIPEA (329 mg) at 0°C. After being stirred at room temperature for 30 min, the reaction mixture was concentrated in vacuo. The residue was diluted with ethyl acetate, washed with saturated brine, and purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (542 mg).

MS: [M-H]⁻ 423.2.

[0573]

D) (2S,3S)-3-[(ethanesulfonyl)amino]-2-[(3'-fluoro[1,1'-biphenyl]-3-yl)methyl]-N-methoxy-N-methylpyrrolidine-1-carboxamide

DIPEA (330 mg) was added to a stirred mixture of (2S,3S)-3-((ethylsulfonyl)amino)-2-((3'-fluoro[biphenyl]-3-yl)methyl)pyrrolidine-1-carbonyl chloride (271 mg), N-methoxymethanamine hydrochloride (124 mg) and THF (3 mL) at room temperature. After being stirred at 60°C for 2 hr, the reaction mixture was cooled down to room temperature, quenched with saturated brine and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give a solid. The solid was crystallized from ethyl acetate/hexane to give the title compound (248 mg).

¹H NMR (400 MHz, CDCl₃) δ 1.23 (3H, t, J = 7.4 Hz), 1.80-1.92 (1H, m), 2.09-2.23 (1H, m), 2.86 (2H, q, J = 7.3 Hz), 2.90-2.97 (1H, m), 2.98 (3H, s), 3.14-3.22 (1H, m), 3.42-3.52 (1H, m), 3.56 (3H, s), 3.60-3.70 (1H, m), 3.89-4.01 (1H, m), 4.35 (1H, d, J = 8.8 Hz), 4.53-4.66 (1H, m), 6.98-7.07 (1H, m), 7.27-7.45 (6H, m), 7.50 (1H, s).

[0574]

Example 475

(2S,3S)-3-[(dimethylsulfamoyl)amino]-2-[(2-fluoro[1,1'-biphenyl]-3-yl)methyl]-N,N-dimethylpyrrolidine-1-carboxamide

5 A mixture of (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((dimethylsulfamoyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide (650 mg), phenylboronic acid (228 mg), XPhos Pd G3 (18.3 mg), 1M aqueous tripotassium phosphate solution (4.32 mL) and THF (3.6 mL) was stirred at 70°C for 1 hr. The mixture was
10 diluted with saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography (NH, ethyl
15 acetate/hexane). The solid was crystallized from ethyl acetate/hexane to give the title compound (560 mg).

¹H NMR (400 MHz, CDCl₃) δ 2.05-2.22 (2H, m), 2.71 (6H, s), 2.77 (6H, s), 2.84-2.92 (1H, m), 2.96-3.07 (1H, m), 3.20-3.30 (1H, m), 3.55-3.66 (1H, m), 3.82-3.91 (1H, m), 4.31-4.42 (1H, m),
20 4.54-4.63 (1H, m), 7.11-7.19 (1H, m), 7.26-7.39 (3H, m), 7.40-7.47 (2H, m), 7.48-7.56 (2H, m).

[0575]

Example 476

(2S,3S)-3-[(dimethylsulfamoyl)amino]-N,N-dimethyl-2-[(2,3',5'-trifluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidine-1-carboxamide

25 A mixture of (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((dimethylsulfamoyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide (650 mg), (3,5-difluorophenyl)boronic acid (296 mg), XPhos Pd G3 (18.3 mg), 1M aqueous tripotassium phosphate
30 solution (4.32 mL) and THF (3.6 mL) was stirred at 70°C for 1 hr. The mixture was diluted with saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated in
35 vacuo. The residue was purified by silica gel column

chromatography (NH, ethyl acetate/hexane). The solid was crystallized from ethyl acetate/hexane to give the title compound (600 mg).

¹H NMR (400 MHz, CDCl₃) δ 2.03-2.21 (2H, m), 2.75 (6H, s), 2.77
5 (6H, s), 2.83-2.93 (1H, m), 2.94-3.04 (1H, m), 3.20-3.32 (1H, m), 3.54-3.65 (1H, m), 3.81-3.92 (1H, m), 4.30-4.40 (1H, m), 4.52-4.63 (1H, m), 6.76-6.84 (1H, m), 7.02-7.10 (2H, m), 7.13-7.20 (1H, m), 7.21-7.25 (1H, m), 7.34-7.41 (1H, m).

[0576]

10 Example 477

(2S,3S)-2-[(3',5'-difluoro[1,1'-biphenyl]-3-yl)methyl]-3-
[(ethanesulfonyl)amino]-N-methoxy-N-methylpyrrolidine-1-
carboxamide

To a mixture of N-((2S,3S)-2-((3',5'-difluorobiphenyl-3-
15 yl)methyl)pyrrolidin-3-yl)ethanesulfonamide hydrochloride (500 mg), TEA (607 mg) and THF (10 mL) was added N-methoxy-N-methylcarbamoyl chloride (310 mg) at room temperature. The mixture was refluxed for 15 min. The mixture was diluted with THF and the precipitate was removed by filtration. The filtrate
20 was concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) and recrystallized from ethyl acetate/hexane to give the title compound (467 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.27 (3H, t, J = 7.4 Hz), 1.78-1.93
25 (1H, m), 2.11-2.27 (1H, m), 2.85-3.00 (6H, m), 3.07-3.18 (1H, m), 3.41-3.53 (1H, m), 3.57 (3H, s), 3.59-3.72 (1H, m), 3.90-4.03 (1H, m), 4.39 (1H, d, J = 9.1 Hz), 4.55-4.65 (1H, m), 6.77 (1H, tt, J = 8.9, 2.3 Hz), 7.07-7.18 (2H, m), 7.31-7.43 (3H, m), 7.45-7.52 (1H, m).

30 [0577]

Example 479

1-fluoro-N-[(2S,3S)-2-[(2-fluoro[1,1'-biphenyl]-3-yl)methyl]-1-
(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl]cyclopropane-1-
sulfonamide

35 [0578]

A) tert-butyl (2S,3S)-3-((cyclopropylsulfonyl)amino)-2-((2-fluoro[biphenyl]-3-yl)methyl)pyrrolidine-1-carboxylate

A mixture of tert-butyl (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((cyclopropylsulfonyl)amino)pyrrolidine-1-carboxylate (500 mg), phenylboronic acid (153 mg), XPhos Pd G3 (8.87 mg), 1M aqueous tripotassium phosphate solution (3.14 mL) and THF (2 mL) was stirred at 70°C for 1 hr. The mixture was poured into water at room temperature and extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (490 mg).

MS: [M+H-Boc]⁺ 375.1.

[0579]

B) 1-fluoro-N-[(2S,3S)-2-[(2-fluoro[1,1'-biphenyl]-3-yl)methyl]-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl]cyclopropane-1-sulfonamide

To a mixture of tert-butyl (2S,3S)-3-((cyclopropylsulfonyl)amino)-2-((2-fluoro[biphenyl]-3-yl)methyl)pyrrolidine-1-carboxylate (490 mg) and THF (4 mL) was added 2.6M n-butyllithium/hexane solution (1.39 mL) dropwise at -78°C. After being stirred at -78°C for 30 min, a mixture of N-fluoro-N-(phenylsulfonyl)benzenesulfonamide (488 mg) and THF (4 mL) was added dropwise to the reaction mixture. The mixture was stirred at 0°C under nitrogen atmosphere for 1 hr. The mixture was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane). The mixture of the residue (280 mg) and 4M hydrogen chloride/ethyl acetate solution (2.84 mL) was stirred at room temperature under a dry atmosphere (CaCl₂) overnight. The mixture was concentrated in vacuo. A mixture of the residue

(244 mg), DIPEA (737 mg) and THF (5 mL) was stirred at room temperature for 30 min. To the suspension was added dropwise 1-chloro-2-methyl-1-oxopropan-2-yl acetate (113 mg) at 0°C and the mixture was stirred at same temperature for 1 h. To the mixture was added 4M aqueous lithium hydroxide solution (1.14 mL) and the mixture was stirred at room temperature overnight. The mixture was diluted with saturated brine and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by preparative HPLC (C18, mobile phase: water/acetonitrile (containing 0.1% TFA)). The desired fraction was neutralized with saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous magnesium sulfate and concentrated in vacuo to give the title compound (20 mg).
¹H NMR (400 MHz, DMSO-d₆) δ 0.97-1.27 (6H, m), 1.35-1.64 (4H, m), 2.03-2.29 (2H, m), 2.57-2.70 (1H, m), 2.98-3.09 (1H, m), 3.66-3.96 (2H, m), 3.98-4.09 (1H, m), 4.58-4.76 (1H, m), 4.90-5.06 (1H, m), 7.03-7.18 (1H, m), 7.21-7.33 (2H, m), 7.34-7.41 (1H, m), 7.42-7.48 (2H, m), 7.49-7.57 (2H, m), 8.35 (1H, brs).
[0580]

Example 480

1-fluoro-N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-[(2,3',5'-trifluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl)cyclopropane-1-sulfonamide
[0581]

A) tert-butyl (2S,3S)-3-((cyclopropylsulfonyl)amino)-2-((2,3',5'-trifluoro[biphenyl]-3-yl)methyl)pyrrolidine-1-carboxylate

A mixture of tert-butyl (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((cyclopropylsulfonyl)amino)pyrrolidine-1-carboxylate (500 mg), (3,5-difluorophenyl)boronic acid (248 mg), XPhos Pd G3 (44.3 mg), 1M aqueous tripotassium phosphate solution (3.14 mL) and THF (2 mL) was stirred at 70°C for 2 hr. The mixture was poured into water at room temperature and

extracted with ethyl acetate. The organic layer was separated, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to
5 give the title compound (488 mg).

MS: [M-H]⁻ 509.2.

[0582]

B) 1-fluoro-N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-
[(2,3',5'-trifluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-
10 yl)cyclopropane-1-sulfonamide

To a mixture of tert-butyl (2S,3S)-3-
((cyclopropylsulfonyl)amino)-2-((2,3',5'-trifluoro[biphenyl]-3-
yl)methyl)pyrrolidine-1-carboxylate (453 mg) and THF (6 mL) was
added 2.6M n-butyllithium/hexane solution (1.19 mL) dropwise at
15 -78°C. After being stirred at -78°C for 30 min, a mixture of N-
fluoro-N-(phenylsulfonyl)benzenesulfonamide (699 mg) and THF
(12 mL) was added dropwise to the reaction mixture. The mixture
was slowly warmed up to room temperature and stirred under
nitrogen atmosphere overnight. The mixture was quenched with
20 saturated aqueous ammonium chloride solution and extracted with
ethyl acetate. The organic layer was separated, washed with
water and saturated brine, dried over anhydrous magnesium
sulfate and concentrated in vacuo. The residue was purified by
silica gel column chromatography (ethyl acetate/hexane). A
25 mixture of the residue and 4M hydrogen chloride/CPME solution
(5 mL) was stirred at room temperature overnight. The mixture
was concentrated in vacuo. The residue was triturated with
ethyl acetate and the resulting solid was collected by
filtration to give a solid. To a mixture of the residue, DIPEA
30 (143 mg) and THF (5 mL) was added dropwise 1-chloro-2-methyl-1-
oxopropan-2-yl acetate (43.8 mg) at room temperature and the
mixture was stirred at same temperature for 1 hr. To the
mixture were added water (2 mL) and 4M aqueous lithium
hydroxide solution (0.443 mL) and the mixture was stirred at
35 room temperature overnight. The mixture was diluted with

saturated brine and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by preparative HPLC (C18, mobile phase: water (containing 10mM

5 NH_4HCO_3)/acetonitrile). The desired fraction was concentrated in vacuo to give the title compound (8.1 mg).

^1H NMR (300 MHz, CDCl_3) δ 1.30-1.54 (10H, m), 1.85-2.12 (1H, m), 2.29-2.48 (1H, m), 2.84-3.03 (1H, m), 3.08-3.30 (1H, m), 3.59-3.94 (3H, m), 4.14 (1H, dt, $J = 11.7, 7.2$ Hz), 4.79 (1H, brs),
10 6.82 (1H, tt, $J = 9.0, 2.4$ Hz), 6.99-7.10 (2H, m), 7.11-7.22 (2H, m), 7.22-7.31 (1H, m), 7.38 (1H, t, $J = 6.2$ Hz).

[0583]

Example 482

N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-
15 2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide

[0584]

A) N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide hydrochloride

To a mixture of tert-butyl (2S,3S)-2-((2,3'-
20 difluorobiphenyl-3-yl)methyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate (5.69 g) and MeOH (10 mL) was added 4M hydrogen chloride/ethyl acetate solution (35.5 mL) at room temperature. The mixture was stirred at room temperature overnight. The solvent was removed in vacuo
25 and the resulting solid was triturated with diisopropyl ether. The precipitate was collected by filtration, washed with diisopropyl ether and dried to give the title compound (4.87 g).
MS: $[\text{M}+\text{H}]^+$ 381.3.

[0585]

30 B) N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide

A mixture of N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide hydrochloride (4.87 g), DIPEA (7.55 g) and THF (50 mL) was stirred at room
35 temperature for 30 min. To the suspension was added dropwise 1-

chloro-2-methyl-1-oxopropan-2-yl acetate (2.31 g) at 0°C and the mixture was stirred at same temperature for 1 hr. To the mixture were added water (30 mL), 2-propanol (10 mL) and 4M aqueous lithium hydroxide solution (14.6 mL) and the mixture
5 was stirred at room temperature overnight. 4M aqueous lithium hydroxide solution (4.38 mL) was added to the mixture. The mixture was stirred at room temperature for 2 hr. The mixture was diluted with saturated brine and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous
10 magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane). The residue was crystallized from ethanol/water to give the title compound (4.75 g) as its hydrate.

15 ¹H NMR (400 MHz, CDCl₃) δ 1.22 (3H, t, J = 7.2 Hz), 1.33-1.47 (6H, m), 1.80-2.03 (1H, m), 2.27-2.42 (1H, m), 2.78-2.92 (2H, m), 2.96 (1H, dd, J = 14.4, 5.5 Hz), 3.13 (1H, dd, J = 14.4, 7.6 Hz), 3.66 (2H, brs), 3.90 (1H, brs), 3.94-4.06 (1H, m), 4.55 (1H, brs), 4.73 (1H, brs), 7.04-7.11 (1H, m), 7.16-7.21
20 (1H, m), 7.21-7.25 (1H, m), 7.27-7.33 (2H, m), 7.35-7.44 (2H, m).

Anal. Calcd for C₂₃H₂₈F₂N₂O₄S·0.3H₂O: C, 58.53; H, 6.11; N, 5.94. Found: C, 58.42; H, 6.35; N, 6.00.

[0586]

25 Example 483

N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

A mixture of N-((2S,3S)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (8.5
30 g), DIPEA (13.1 g) and THF (81 mL) was stirred at room temperature for 30 min. To the suspension was added dropwise 1-chloro-2-methyl-1-oxopropan-2-yl acetate (3.99 g) at 0°C and stirred at same temperature for overnight. To the mixture were
35 added water (53.9 mL) and 4M aqueous lithium hydroxide solution

(25.2 mL) and the mixture was stirred at room temperature overnight. The mixture was quenched with saturated aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate. The extract was washed with saturated brine and passed
5 through a silica gel pad. The solution was purified by silica gel column chromatography (NH, ethyl acetate/hexane). The obtained product was crystallized from ethanol/water to give the title compound (5.27 g) as its hydrate.

¹H NMR (400 MHz, DMSO-d₆) δ 1.04-1.19 (6H, m), 1.90-2.07 (1H,
10 m), 2.11-2.23 (1H, m), 2.59-2.70 (1H, m), 2.85-2.95 (3H, m), 2.95-3.10 (1H, m), 3.69-3.99 (3H, m), 4.50-4.68 (1H, m), 5.00 (1H, s), 7.08-7.18 (1H, m), 7.21-7.51 (6H, m).

Anal. Calcd for C₂₄H₂₇F₃N₂O₅S·1.5H₂O: C, 53.11; H, 5.67; N, 5.63. Found: C, 53.19; H, 5.65; N, 5.61.

15 [0587]

Example 484

N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide
[0588]

20 A) N-((2S,3S)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide hydrochloride

To a mixture of tert-butyl (2S,3S)-2-(3-bromo-2-fluorobenzyl)-3-((ethylsulfonyl)amino)pyrrolidine-1-carboxylate (10 g), (3,5-difluorophenyl)boronic acid (5.09 g), tripotassium
25 phosphate (13.7 g), THF (50 mL) and water (30 mL) was added XPhos Pd G3 (0.273 g) at room temperature. The mixture was stirred at 70°C for 1 hr. After concentration in vacuo, the residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give an oil. 4M Hydrogen
30 chloride/ethyl acetate solution (53.7 mL) was added to a stirred mixture of the oil and ethyl acetate (10 mL) at room temperature. After 18 hr, the reaction mixture was concentrated in vacuo, and the resulting solid was collected by filtration to give the title compound (8.81 g).

35 MS: [M+H]⁺ 399.3.

[0589]

B) N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide

A mixture of N-((2S,3S)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide hydrochloride (8.81 g), DIPEA (7.85 g) and THF (100 mL) was stirred at room temperature for 30 min. To the suspension was added dropwise 1-chloro-2-methyl-1-oxopropan-2-yl acetate (4.00 g) at 0°C. After being stirred for 1 hr at room temperature, water (10 mL) and 4M aqueous lithium hydroxide solution (25.3 mL) were added to the reaction mixture. After 48 hr, the mixture was quenched with saturated aqueous sodium hydrogencarbonate solution, diluted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, filtrated and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate) and crystallized from ethyl acetate/hexane to give the title compound (8.71 g).

¹H NMR (400 MHz, CDCl₃) δ 1.24 (3H, t, J = 7.3 Hz), 1.39 (3H, s), 1.41 (3H, s), 1.83-2.03 (1H, m), 2.23-2.43 (1H, m), 2.83-2.97 (3H, m), 3.12 (1H, dd, J = 14.0, 7.5 Hz), 3.58-3.76 (2H, m), 3.84 (1H, brs), 3.91-4.07 (1H, m), 4.45-4.63 (1H, m), 4.67-4.89 (1H, m), 6.77-6.87 (1H, m), 6.99-7.10 (2H, m), 7.16-7.22 (1H, m), 7.26-7.30 (1H, m), 7.37-7.46 (1H, m).

N-((2S,3S)-1-(2-Hydroxy-2-methylpropanoyl)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide (550 mg) was crystallized from ethyl acetate/hexane to give the title compound (400 mg).

mp 139°C

[0590]

30 Example 485

N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide

[0591]

A) N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride

To a mixture of tert-butyl (2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-

((methylsulfonyl)amino)pyrrolidine-1-carboxylate (1.77 g) and ethyl acetate (20 ml) was added 4M hydrogen chloride/ethyl

5 acetate solution (28.5 mL) at room temperature. The mixture was stirred at room temperature for 2 hr and then at 60°C for 1 hr. After evaporation, the solid was collected by filtration with diisopropyl ether to give the title compound (1.44 g).

MS: [M+H]⁺ 367.0.

10 [0592]

B) (2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carbonyl chloride

To a mixture of N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide hydrochloride (492
15 mg), bis(trichloromethyl) carbonate (217 mg) and THF (6 mL) was added DIPEA (316 mg) at 0°C. After being stirred at room temperature for 30 min, the reaction mixture was concentrated in vacuo. The residue was diluted with ethyl acetate, washed with saturated brine, and purified by silica gel column
20 chromatography (ethyl acetate/hexane) to give the title compound (548 mg).

MS: [M-H]⁻ 427.2.

[0593]

C) N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide
25

Azetidine (209 mg) was added to a stirred mixture of (2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carbonyl chloride (524 mg) and THF (6 mL) at room temperature. After being stirred for 30
30 min, the reaction mixture was concentrated in vacuo. The residue was diluted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, filtrated and concentrated in vacuo. The obtained solid was crystallized from ethyl acetate/EtOH to give the title compound (404 mg).

35 ¹H NMR (400 MHz, CDCl₃) δ 1.87-2.00 (1H, m), 2.09-2.32 (3H, m),

2.69 (3H, s), 2.91-2.99 (1H, m), 3.01-3.10 (1H, m), 3.24-3.41 (2H, m), 3.84 (2H, q, J = 7.8 Hz), 3.90-4.07 (3H, m), 4.53 (1H, q, J = 6.5 Hz), 4.68 (1H, d, J = 6.6 Hz), 7.01-7.11 (1H, m), 7.14-7.25 (2H, m), 7.27-7.33 (2H, m), 7.35-7.46 (2H, m).

5 [0594]

Example 486

(2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-
((ethylsulfonyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide
(2S,3S)-2-((2,3'-Difluorobiphenyl-3-yl)methyl)-3-

10 ((ethylsulfonyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide
(200 mg) was recrystallized from ethyl acetate/hexane to give
the title compound (152 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.26 (3H, t, J = 7.4 Hz), 1.99-2.26
(2H, m), 2.80 (6H, s), 2.81-2.96 (3H, m), 2.99-3.12 (1H, m),
15 3.28 (1H, ddd, J = 10.4, 8.3, 4.4 Hz), 3.61 (1H, dt, J = 10.4,
7.7 Hz), 3.87-3.98 (1H, m), 4.44 (1H, d, J = 8.3 Hz), 4.50-4.60
(1H, m), 7.01-7.10 (1H, m), 7.12-7.19 (1H, m), 7.20-7.31 (3H,
m), 7.32-7.44 (2H, m).

[0595]

20 Example 487

(2S,3S)-3-((ethylsulfonyl)amino)-N,N-dimethyl-2-((2,3',5'-
trifluorobiphenyl-3-yl)methyl)pyrrolidine-1-carboxamide
(2S,3S)-3-((Ethylsulfonyl)amino)-N,N-dimethyl-2-

25 ((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidine-1-
carboxamide (137 mg) was crystallized from ethyl acetate/hexane
to give the title compound (115 mg).

¹H NMR (400 MHz, CDCl₃) δ 1.29 (3H, t, J = 7.4 Hz), 1.99-2.10
(1H, m), 2.11-2.24 (1H, m), 2.79 (6H, s), 2.83-3.10 (4H, m),
3.23-3.34 (1H, m), 3.56-3.66 (1H, m), 3.89-3.98 (1H, m), 4.43
30 (1H, d, J = 8.6 Hz), 4.50-4.59 (1H, m), 6.76-6.85 (1H, m),
7.00-7.09 (2H, m), 7.12-7.21 (1H, m), 7.22-7.25 (1H, m), 7.35-
7.43 (1H, m).

[0596]

Example 488

35 N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-

2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide

A mixture of N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide (1.00 g) and diisopropyl ether (15 ml) was
5 stirred at room temperature for 6 days. The precipitate was collected by filtration and dried to give the title compound (0.973 g).

¹H NMR (400 MHz, CDCl₃) δ 1.22 (3H, t, J = 7.2 Hz), 1.36-1.46 (6H, m), 1.80-2.03 (1H, m), 2.28-2.43 (1H, m), 2.76-2.91 (2H,
10 m), 2.96 (1H, dd, J = 14.5, 4.6 Hz), 3.13 (1H, dd, J = 14.4, 7.2 Hz), 3.66 (2H, brs), 3.89 (1H, brs), 3.94-4.05 (1H, m), 4.54 (1H, brs), 4.73 (1H, brs), 7.04-7.11 (1H, m), 7.16-7.21 (1H, m), 7.21-7.25 (1H, m), 7.27-7.33 (2H, m), 7.35-7.45 (2H, m).

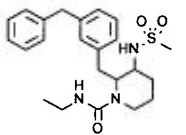
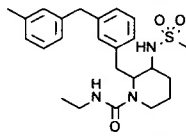
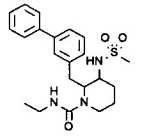
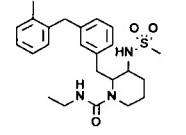
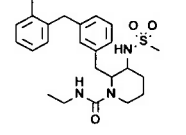
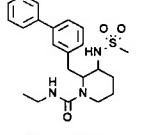
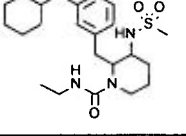
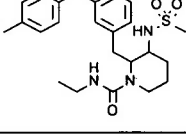
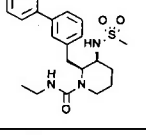
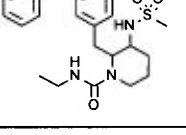
15 mp 89°C

[0597]

The compounds of Examples are shown in the following tables. MS in the tables means actual measured value. The compounds of Examples 2 to 18, 20 to 23, 25, 26, 28 to 63, 65
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25 396 to 398, 400, 401, 403, 405, 406, 408 to 416, 418 to 420, 422, 425 to 427, 429, 430, 432 to 434, 436, 438, 440, 442 to 449, 451 to 455, 458, 461, 464, 465, 468-470, 472, 473, 478 and 481 in the following tables were produced according to the methods described in the above-mentioned Examples, or methods
30 analogous thereto.

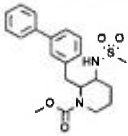
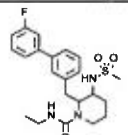
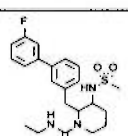
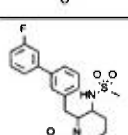
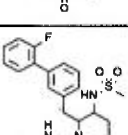
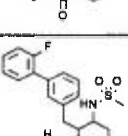
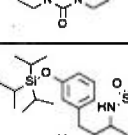
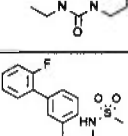
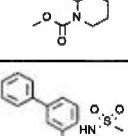
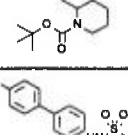
[0598]

Table 1-1

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
1	cis-2-(3-benzylbenzyl)-N-ethyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide			430.3
2	cis-N-ethyl-2-(3-(3-methylbenzyl)benzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide			444.2
3	cis-2-(biphenyl-3-ylmethyl)-N-ethyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide			416.1
4	cis-N-ethyl-2-(3-(2-methylbenzyl)benzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide			444.2
5	trans-N-ethyl-2-(3-(2-methylbenzyl)benzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide			442.2
6	trans-2-(biphenyl-3-ylmethyl)-N-ethyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide			416.1
7	cis-2-(3-(cyclohexyloxy)benzyl)-N-ethyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide			438.1
8	cis-N-ethyl-2-(3-(4-methylbenzyl)benzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide			444.2
9	(2S,3S)-2-(biphenyl-3-ylmethyl)-N-ethyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide			416.1
10	cis-N-ethyl-3-((methylsulfonyl)amino)-2-(3-phenoxybenzyl)piperidine-1-carboxamide			430.1

[0599]

Table 1-2

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
11	methyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			403.1
12	trans-N-ethyl-2-((3'-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide			434.1
13	cis-N-ethyl-2-((3'-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide			434.1
14	methyl cis-2-((3'-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			421.1
15	cis-N-ethyl-2-((2'-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide			434.1
16	trans-N-ethyl-2-((2'-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide			434.1
17	cis-N-ethyl-3-((methylsulfonyl)amino)-2-(3-((triisopropylsilyl)oxy)benzyl)piperidine-1-carboxamide			512.3
18	methyl cis-2-((2'-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			421.1
19	tert-butyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			443.1
20	methyl cis-2-((4'-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			421.1

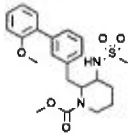
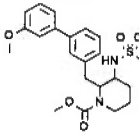
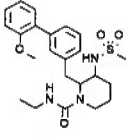
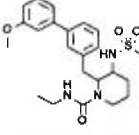
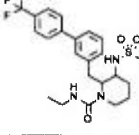
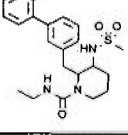
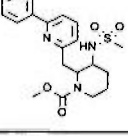
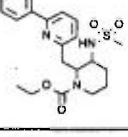
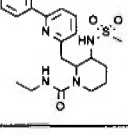
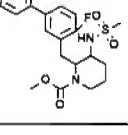
[0600]

Table 1-3

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
21	methyl cis-2-((2'-methylbiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			417.1
22	N-(cis-1-acetyl-2-(biphenyl-3-ylmethyl)piperidin-3-yl)methanesulfonamide			387.1
23	methyl cis-2-((3'-methylbiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			417.1
24	methyl cis-2-(3-iodobenzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			452.8
25	methyl cis-3-((methylsulfonyl)amino)-2-(3-(pyridin-3-yl)benzyl)piperidine-1-carboxylate			404.0
26	methyl cis-2-((4'-methoxybiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			433.0
27	methyl cis-3-((methylsulfonyl)amino)-2-(3-(pyrrolidin-1-yl)benzyl)piperidine-1-carboxylate			396.2
28	methyl cis-3-((methylsulfonyl)amino)-2-(3-(pyridin-2-yl)benzyl)piperidine-1-carboxylate			404.1
29	ethyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			417.1
30	cis-N-ethyl-2-((4'-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide			434.1

[0601]

Table 1-4

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
31	methyl cis-2-((2'-methoxybiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			433.0
32	methyl cis-2-((3'-methoxybiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			433.0
33	cis-N-ethyl-2-((2'-methoxybiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide			446.1
34	cis-N-ethyl-2-((3'-methoxybiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide			446.1
35	cis-N-ethyl-3-((methylsulfonyl)amino)-2-((4-(trifluoromethyl)biphenyl-3-yl)methyl)piperidine-1-carboxamide			484.0
36	cis-N-ethyl-2-((2'-methylbiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide			430.1
37	methyl cis-3-((methylsulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate			404.1
38	ethyl cis-3-((methylsulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate			418.1
39	cis-N-ethyl-3-((methylsulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxamide			417.1
40	methyl cis-2-((4-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			421.1

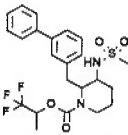
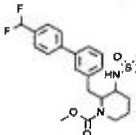
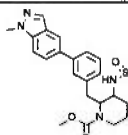
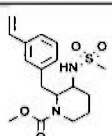
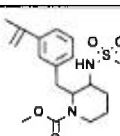
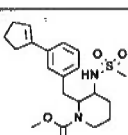
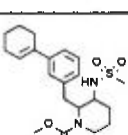
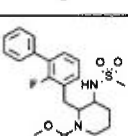
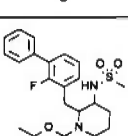
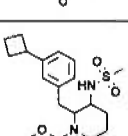
[0602]

Table 1-5

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
41	methyl cis-2-((6-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			421.1
42	ethyl cis-2-((6-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			435.1
43	N-(cis-2-(biphenyl-2-ylmethyl)piperidin-3-yl)methanesulfonamide		HCl	345.0
44	methyl cis-3-((methylsulfonyl)amino)-2-(3-(trifluoromethyl)benzyl)piperidine-1-carboxylate			395.1
45	propyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			431.1
46	butyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			445.1
47	2-methoxyethyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			447.0
48	2,2-difluoroethyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			451.1
49	2,2,2-trifluoroethyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			469.0
50	isopropyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			431.1

[0603]

Table 1-6

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
51	1,1,1-trifluoropropan-2-yl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			483.0
52	methyl cis-2-((4'-(difluoromethyl)biphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			453.0
53	methyl cis-2-(3-(1-methyl-1H-indazol-5-yl)benzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			457.1
54	methyl cis-3-((methylsulfonyl)amino)-2-(3-vinylbenzyl)piperidine-1-carboxylate			353.0
55	methyl cis-3-((methylsulfonyl)amino)-2-(3-(prop-1-en-2-yl)benzyl)piperidine-1-carboxylate			367.1
56	methyl cis-2-(3-(cyclopent-1-en-1-yl)benzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			393.1
57	methyl cis-2-(3-(cyclohex-1-en-1-yl)benzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			407.1
58	methyl cis-2-((2-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			421.0
59	ethyl cis-2-((2-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			435.1
60	methyl cis-2-(3-cyclobutylbenzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			381.1

[0604]

Table 1-7

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
61	methyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			389.1
62	cis-N-ethyl-3-((methylsulfonyl)amino)-2-(2-phenoxybenzyl)piperidine-1-carboxamide			432.1
63	cis-N-ethyl-3-((methylsulfonyl)amino)-2-(4-phenoxybenzyl)piperidine-1-carboxamide			432.0
64	isopropyl cis-3-((methylsulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate			432.1
65	ethyl cis-3-((methylsulfonyl)amino)-2-((5-phenylpyridin-3-yl)methyl)piperidine-1-carboxylate			418.1
66	isopropyl cis-3-((methylsulfonyl)amino)-2-((5-phenylpyridin-3-yl)methyl)piperidine-1-carboxylate			432.1
67	ethyl cis-2-(3-chloro-2-fluorobenzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			393.0
68	methyl cis-2-((6-methylbiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			417.2
69	methyl cis-2-((5-methylbiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			417.2
70	ethyl cis-3-((methylsulfonyl)amino)-2-((2-phenylpyridin-4-yl)methyl)piperidine-1-carboxylate			418.1

[0605]

Table 1-8

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
71	isopropyl cis-3-((methylsulfonyl)amino)-2-((2-phenylpyridin-4-yl)methyl)piperidine-1-carboxylate			432.1
72	cis-N-ethyl-3-((methylsulfonyl)amino)-2-((2-phenylpyridin-4-yl)methyl)piperidine-1-carboxamide			417.2
73	isopropyl cis-3-((methylsulfonyl)amino)-2-(2-phenoxybenzyl)piperidine-1-carboxylate			445.2
74	isopropyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			417.1
75	ethyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			403.1
76	isopropyl cis-3-((methylsulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate (optical isomer)			432.1
77	methyl cis-2-(3-cyclopropylbenzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			367.1
78	isopropyl cis-2-(dibenzo[b,d]furan-4-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			443.2
79	propyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			417.2
80	trans-2-(biphenyl-3-ylmethyl)-N-ethyl-3-((methylsulfonyl)amino)pyrrolidine-1-carboxamide			402.0

[0606]

Table 1-9

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
81	N-(cis-2-(biphenyl-3-ylmethyl)pyrrolidin-3-yl)methanesulfonamide			331.0
82	isopropyl cis-3-((methylsulfonyl)amino)-2-((6-(prop-1-en-2-yl)pyridin-2-yl)methyl)piperidine-1-carboxylate			396.2
83	isopropyl cis-2-((6-isopropylpyridin-2-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			398.1
84	isopropyl cis-3-((methylsulfonyl)amino)-2-((4-phenyl-1H-pyrazol-1-yl)methyl)piperidine-1-carboxylate			421.1
85	methyl cis-2-(dibenzo[b,d]furan-4-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			417.0
86	methyl cis-3-((methylsulfonyl)amino)-2-(1-naphthylmethyl)piperidine-1-carboxylate			377.0
87	isopropyl cis-2-(3-isopropylbenzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			395.1
88	tert-butyl cis-3-((methylsulfonyl)amino)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)piperidine-1-carboxylate			452.0
89	isopropyl cis-3-((methylsulfonyl)amino)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)piperidine-1-carboxylate			438.1
90	ethyl cis-3-((methylsulfonyl)amino)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)piperidine-1-carboxylate			424.0

[0607]

Table 1-10

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
91	methyl cis-2-((4-methylbiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			417.0
92	N-(cis-2-(biphenyl-3-ylmethyl)-1-propionylpiperidin-3-yl)methanesulfonamide			401.1
93	N-(cis-2-(biphenyl-3-ylmethyl)-1-(cyclopropylcarbonyl)piperidin-3-yl)methanesulfonamide			413.2
94	N-(cis-2-(biphenyl-3-ylmethyl)-1-(2,2-difluoropropanoyl)piperidin-3-yl)methanesulfonamide			437.1
95	N-(cis-2-(biphenyl-3-ylmethyl)-1-isobutyrylpiperidin-3-yl)methanesulfonamide			415.1
96	isopropyl cis-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			450.1
97	isopropyl cis-2-((6-(2-fluorophenyl)pyridin-2-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			450.1
98	isopropyl cis-2-((6-(2,3-difluorophenyl)pyridin-2-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			468.1
99	isopropyl cis-2-((6-(3,5-difluorophenyl)pyridin-2-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			468.2
100	isopropyl cis-2-((6-(2,5-difluorophenyl)pyridin-2-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			468.2

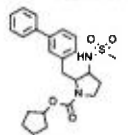
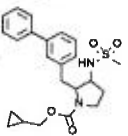
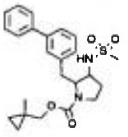
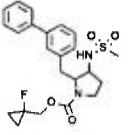
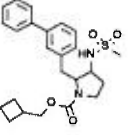
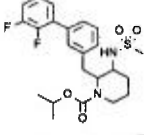
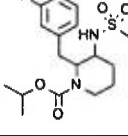
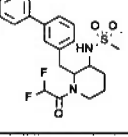
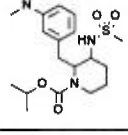
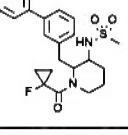
[0608]

Table 1-11

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
101	ethyl (2S,3S)-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate (optical isomer)			403.1
102	butyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			431.0
103	2-methoxyethyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			433.0
104	2,2-difluoroethyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			437.0
105	2,2,2-trifluoroethyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			455.0
106	sec-butyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			429.1
107	isobutyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			431.0
108	cyclopropyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			415.0
109	cyclobutyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			429.0
110	3,3-difluorocyclobutyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			465.0

[0609]

Table 1-12

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
111	cyclopentyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			441.0
112	cyclopropylmethyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			429.0
113	(1-methylcyclopropyl)methyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			441.0
114	(1-fluorocyclopropyl)methyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			445.2
115	cyclobutylmethyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			441.0
116	isopropyl cis-2-((2',3'-difluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			467.2
117	isopropyl cis-2-(3-iodobenzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			478.9
118	N-(cis-2-(biphenyl-3-ylmethyl)-1-(difluoroacetyl)piperidin-3-yl)methanesulfonamide			423.1
119	isopropyl cis-2-(3-(dimethylamino)benzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			398.1
120	N-(cis-2-(biphenyl-3-ylmethyl)-1-((1-fluorocyclopropyl)carbonyl)piperidin-3-yl)methanesulfonamide			431.1

[0610]

Table 1-13

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
121	isopropyl cis-3-((methylsulfonyl)amino)-2-(2-naphthylmethyl)piperidine-1-carboxylate			403.1
122	isopropyl cis-3-((methylsulfonyl)amino)-2-((3-phenyl-1H-pyrazol-1-yl)methyl)piperidine-1-carboxylate			421.1
123	sec-butyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			443.1
124	3-methylbutan-2-yl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			457.1
125	isobutyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			445.0
126	cyclopropyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			429.1
127	cyclobutyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			443.0
128	3,3-difluorocyclobutyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			477.0
129	cyclopentyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			455.0
130	cyclohexyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			469.0

[0611]

Table 1-14

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
131	1-methylcyclopropyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			441.0
132	oxetan-3-yl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			445.0
133	tetrahydrofuran-3-yl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			459.0
134	tetrahydro-2H-pyran-4-yl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			471.0
135	tetrahydro-2H-pyran-3-yl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			473.0
136	cyclopropylmethyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			443.0
137	(1-methylcyclopropyl)methyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			457.0
138	(1-fluorocyclopropyl)methyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			459.0
139	(2,2-difluorocyclopropyl)methyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			477.0
140	cyclobutylmethyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			455.0

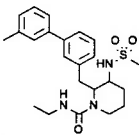
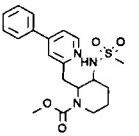
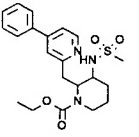
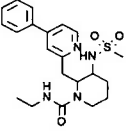
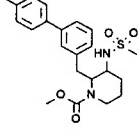
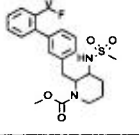
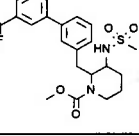
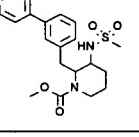
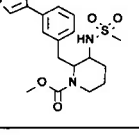
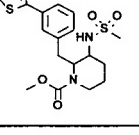
[0612]

Table 1-15

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
141	cyclopentylmethyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			469.0
142	oxetan-2-ylmethyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			458.9
143	oxetan-3-ylmethyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			459.0
144	tetrahydrofuran-2-ylmethyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			473.0
145	phenyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			465.0
146	benzyl cis-2-(biphenyl-3-ylmethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			477.0
147	ethyl cis-2-((4-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			435.1
148	ethyl cis-2-(3-bromo-4-fluorobenzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			436.9
149	methyl cis-2-((5-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			421.1
150	N-(cis-2-((6-fluorobiphenyl-3-yl)methyl)piperidin-3-yl)methanesulfonamide hydrochloride		HCl	363.0

[0613]

Table 1-16

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
151	cis-N-ethyl-2-((3'-methylbiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide			430.1
152	methyl cis-3-((methylsulfonyl)amino)-2-((4-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate			404.1
153	ethyl cis-3-((methylsulfonyl)amino)-2-((4-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate			418.1
154	cis-N-ethyl-3-((methylsulfonyl)amino)-2-((4-phenylpyridin-2-yl)methyl)piperidine-1-carboxamide			417.1
155	methyl cis-2-((4'-methylbiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			417.1
156	methyl cis-3-((methylsulfonyl)amino)-2-((2'-trifluoromethyl)biphenyl-3-yl)methyl)piperidine-1-carboxylate			471.0
157	methyl cis-3-((methylsulfonyl)amino)-2-((3'-trifluoromethyl)biphenyl-3-yl)methyl)piperidine-1-carboxylate			470.9
158	methyl cis-3-((methylsulfonyl)amino)-2-(3-(pyridin-4-yl)benzyl)piperidine-1-carboxylate			404.0
159	methyl cis-3-((methylsulfonyl)amino)-2-(3-(3-thienyl)benzyl)piperidine-1-carboxylate			407.0
160	methyl cis-3-((methylsulfonyl)amino)-2-(3-(2-thienyl)benzyl)piperidine-1-carboxylate			409.1

[0614]

Table 1-17

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
161	methyl cis-2-(3-(1-methyl-1H-pyrazol-3-yl)benzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			407.0
162	methyl cis-2-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			407.1
163	methyl cis-2-(3-(1-methyl-1H-pyrazol-5-yl)benzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			407.1
164	methyl cis-2-(3-methylbenzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			340.9
165	methyl cis-2-((3',4'-difluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			437.1
166	methyl cis-2-((2',4'-difluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			439.0
167	methyl cis-2-((2',3'-difluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			439.1
168	methyl cis-2-((2',6'-difluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			439.0
169	methyl cis-2-((3',5'-difluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			439.1
170	methyl cis-2-((2',5'-difluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			439.1

[0615]

Table 1-18

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
171	methyl cis-2-((3'-(difluoromethyl)biphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			453.0
172	isopropyl cis-3-((ethylsulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate			446.2
173	isopropyl cis-2-((6-phenylpyridin-2-yl)methyl)-3-((propylsulfonyl)amino)piperidine-1-carboxylate			460.0
174	isopropyl cis-3-((butylsulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate			474.0
175	isopropyl cis-3-((isobutylsulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate			474.0
176	isopropyl cis-2-((6-phenylpyridin-2-yl)methyl)-3-((vinylsulfonyl)amino)piperidine-1-carboxylate			444.2
177	isopropyl cis-3-((allylsulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate			458.0
178	isopropyl cis-3-((cyclopropylsulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate			458.1
179	isopropyl cis-3-((oxetan-3-ylsulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate			474.1
180	isopropyl cis-2-((6-phenylpyridin-2-yl)methyl)-3-(((2,2,2-trifluoroethyl)sulfonyl)amino)piperidine-1-carboxylate			500.1

[0616]

Table 1-19

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
181	isopropyl cis-3-(((chloromethyl)sulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate			466.1
182	isopropyl cis-3-(((2-hydroxyethyl)sulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate trifluoroacetic acid salt		CF3COOH	461.9
183	isopropyl cis-3-(((2-methoxyethyl)sulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate			476.1
184	isopropyl cis-3-(((cyanomethyl)sulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate			457.0
185	isopropyl cis-3-((dimethylsulfamoyl)amino)-2-((6-phenylpyridin-2-yl)methyl)piperidine-1-carboxylate			461.2
186	isopropyl cis-3-((ethylsulfonyl)amino)-2-((6-(prop-1-en-2-yl)pyridin-2-yl)methyl)piperidine-1-carboxylate			410.0
187	isopropyl cis-2-((6-(prop-1-en-2-yl)pyridin-2-yl)methyl)-3-((propylsulfonyl)amino)piperidine-1-carboxylate			424.1
188	isopropyl cis-3-((butylsulfonyl)amino)-2-((6-(prop-1-en-2-yl)pyridin-2-yl)methyl)piperidine-1-carboxylate			438.0
189	isopropyl cis-2-((6-(prop-1-en-2-yl)pyridin-2-yl)methyl)-3-((vinylsulfonyl)amino)piperidine-1-carboxylate			408.0
190	isopropyl cis-3-((allylsulfonyl)amino)-2-((6-(prop-1-en-2-yl)pyridin-2-yl)methyl)piperidine-1-carboxylate			422.0

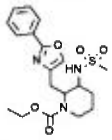
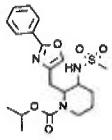
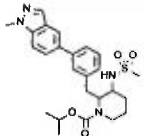
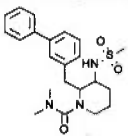
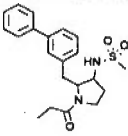
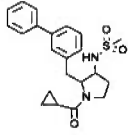
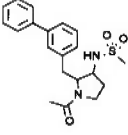
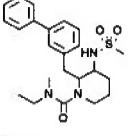
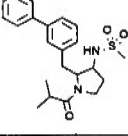
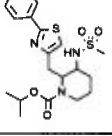
[0617]

Table 1-20

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
191	isopropyl cis-3-((cyclopropylsulfonyl)amino)-2-((6-(prop-1-en-2-yl)pyridin-2-yl)methyl)piperidine-1-carboxylate			422.0
192	isopropyl cis-3-((oxetan-3-ylsulfonyl)amino)-2-((6-(prop-1-en-2-yl)pyridin-2-yl)methyl)piperidine-1-carboxylate			438.0
193	isopropyl cis-2-((6-(prop-1-en-2-yl)pyridin-2-yl)methyl)-3-(((2,2,2-trifluoroethyl)sulfonyl)amino)piperidine-1-carboxylate			464.0
194	isopropyl cis-3-(((chloromethyl)sulfonyl)amino)-2-((6-(prop-1-en-2-yl)pyridin-2-yl)methyl)piperidine-1-carboxylate			430.0
195	isopropyl cis-3-(((2-methoxyethyl)sulfonyl)amino)-2-((6-(prop-1-en-2-yl)pyridin-2-yl)methyl)piperidine-1-carboxylate			440.0
196	isopropyl cis-3-(((cyanomethyl)sulfonyl)amino)-2-((6-(prop-1-en-2-yl)pyridin-2-yl)methyl)piperidine-1-carboxylate			421.0
197	isopropyl cis-3-((dimethylsulfamoyl)amino)-2-((6-(prop-1-en-2-yl)pyridin-2-yl)methyl)piperidine-1-carboxylate			425.1
198	isopropyl 3-((methylsulfonyl)amino)-2-((1-phenylpyrrolidin-3-yl)methyl)piperidine-1-carboxylate			424.1
199	methyl cis-2-(biphenyl-3-ylmethyl)-3-((cyclopropylsulfonyl)amino)piperidine-1-carboxylate			429.1
200	methyl cis-2-(biphenyl-3-ylmethyl)-3-((dimethylsulfamoyl)amino)piperidine-1-carboxylate			432.1

[0618]

Table 1-21

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
201	ethyl cis-3-((methylsulfonyl)amino)-2-((2-phenyl-1,3-oxazol-4-yl)methyl)piperidine-1-carboxylate			408.1
202	isopropyl cis-3-((methylsulfonyl)amino)-2-((2-phenyl-1,3-oxazol-4-yl)methyl)piperidine-1-carboxylate			422.1
203	isopropyl cis-2-(3-(1-methyl-1H-indazol-5-yl)benzyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			485.2
204	cis-2-(biphenyl-3-ylmethyl)-N,N-dimethyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide			416.1
205	N-(cis-2-(biphenyl-3-ylmethyl)-1-propionylpyrrolidin-3-yl)methanesulfonamide			387.1
206	N-(cis-2-(biphenyl-3-ylmethyl)-1-(cyclopropylcarbonyl)pyrrolidin-3-yl)methanesulfonamide			399.1
207	N-(cis-1-acetyl-2-(biphenyl-3-ylmethyl)pyrrolidin-3-yl)methanesulfonamide			373.1
208	cis-2-(biphenyl-3-ylmethyl)-N-ethyl-N-methyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide			430.1
209	N-(cis-2-(biphenyl-3-ylmethyl)-1-isobutyrylpyrrolidin-3-yl)methanesulfonamide			401.1
210	isopropyl cis-3-((methylsulfonyl)amino)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)piperidine-1-carboxylate (optical isomer)			438.1

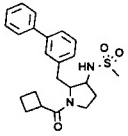
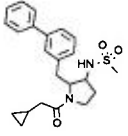
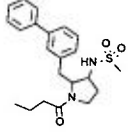
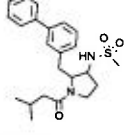
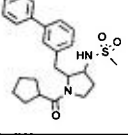
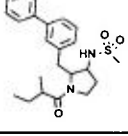
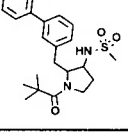
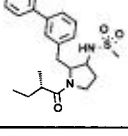
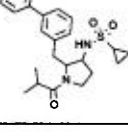
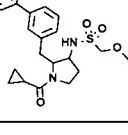
[0619]

Table 1-22

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
211	ethyl cis-3-((methylsulfonyl)amino)-2-((4-phenyl-1,3-thiazol-2-yl)methyl)piperidine-1-carboxylate			424.0
212	isopropyl cis-3-((methylsulfonyl)amino)-2-((4-phenyl-1,3-thiazol-2-yl)methyl)piperidine-1-carboxylate			438.1
213	isopropyl cis-3-((methylsulfonyl)amino)-2-(pyridin-3-ylmethyl)piperidine-1-carboxylate			356.0
214	isopropyl cis-3-((methylsulfonyl)amino)-2-((1-phenylpiperidin-3-yl)methyl)piperidine-1-carboxylate			438.1
215	isopropyl cis-3-((methylsulfonyl)amino)-2-(3-(pyrimidin-2-yl)benzyl)piperidine-1-carboxylate			433.2
216	isopropyl cis-3-((methylsulfonyl)amino)-2-((1-phenyl-1H-pyrazol-3-yl)methyl)piperidine-1-carboxylate			421.2
217	methyl cis-3-((methylsulfonyl)amino)-2-((1-phenylpiperidin-3-yl)methyl)piperidine-1-carboxylate			410.3
218	isopropyl cis-3-((methylsulfonyl)amino)-2-((1-(pyrimidin-2-yl)piperidin-3-yl)methyl)piperidine-1-carboxylate			440.2
219	isopropyl cis-3-((methylsulfonyl)amino)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidine-1-carboxylate			424.0
220	N-(cis-2-((2-(2,3-difluorophenyl)-1,3-thiazol-4-yl)methyl)-1-isobutylpyrrolidin-3-yl)methanesulfonamide			444.1

[0620]

Table 1-23

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
221	N-(cis-2-(biphenyl-3-ylmethyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)methanesulfonamide			413.2
222	N-(cis-2-(biphenyl-3-ylmethyl)-1-(cyclopropylacetyl)pyrrolidin-3-yl)methanesulfonamide			413.2
223	N-(cis-2-(biphenyl-3-ylmethyl)-1-butylpyrrolidin-3-yl)methanesulfonamide			401.1
224	N-(cis-2-(biphenyl-3-ylmethyl)-1-(3-methylbutanoyl)pyrrolidin-3-yl)methanesulfonamide			415.1
225	N-(cis-2-(biphenyl-3-ylmethyl)-1-(cyclopentylcarbonyl)pyrrolidin-3-yl)methanesulfonamide			427.1
226	N-(cis-2-(biphenyl-3-ylmethyl)-1-(2-methylbutanoyl)pyrrolidin-3-yl)methanesulfonamide			415.1
227	N-(cis-2-(biphenyl-3-ylmethyl)-1-(2,2-dimethylpropanoyl)pyrrolidin-3-yl)methanesulfonamide			415.2
228	N-(cis-2-(biphenyl-3-ylmethyl)-1-((2S)-2-methylbutanoyl)pyrrolidin-3-yl)methanesulfonamide			415.1
229	N-(cis-2-(biphenyl-3-ylmethyl)-1-isobutyrylpyrrolidin-3-yl)cyclopropanesulfonamide			427.3
230	N-(cis-2-(biphenyl-3-ylmethyl)-1-(cyclopropylcarbonyl)pyrrolidin-3-yl)-1-methoxymethanesulfonamide			429.1

[0621]

Table 1-24

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
231	N-(cis-2-(biphenyl-3-ylmethyl)-1-isobutyrylpyrrolidin-3-yl)-1-chloromethanesulfonamide			435.1
232	N-(cis-2-(biphenyl-3-ylmethyl)-1-isobutyrylpyrrolidin-3-yl)-1-fluoromethanesulfonamide			419.1
233	N-(cis-2-(biphenyl-3-ylmethyl)-1-isobutyrylpyrrolidin-3-yl)-1,1-difluoromethanesulfonamide			437.1
234	N-(cis-2-((3',5'-difluorobiphenyl-3-yl)methyl)-1-isobutyrylpyrrolidin-3-yl)methanesulfonamide			437.1
235	N-(cis-2-((2',5'-difluorobiphenyl-3-yl)methyl)-1-isobutyrylpyrrolidin-3-yl)methanesulfonamide			437.1
236	N-(cis-1-isobutyryl-2-((2'-(trifluoromethyl)biphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			469.0
237	N-(cis-2-((2'-chlorobiphenyl-3-yl)methyl)-1-isobutyrylpyrrolidin-3-yl)methanesulfonamide			435.1
238	N-(cis-2-((2',3'-difluorobiphenyl-3-yl)methyl)-1-isobutyrylpyrrolidin-3-yl)methanesulfonamide			437.1
239	N-(cis-2-((2',6'-difluorobiphenyl-3-yl)methyl)-1-isobutyrylpyrrolidin-3-yl)methanesulfonamide			437.1
240	N-(cis-2-((2'-fluorobiphenyl-3-yl)methyl)-1-isobutyrylpyrrolidin-3-yl)methanesulfonamide			419.1

[0622]

Table 1-25

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
241	N-(cis-2-((3'-fluorobiphenyl-3-yl)methyl)-1-isobutyrylpyrrolidin-3-yl)methanesulfonamide			419.1
242	N-(cis-1-isobutyryl-2-((2',3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			455.1
243	N-(cis-1-isobutyryl-2-((2',3',5',6'-tetrafluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			473.1
244	N-(cis-1-isobutyryl-2-(3-(pyrrolidin-1-yl)benzyl)pyrrolidin-3-yl)methanesulfonamide			394.2
245	N-(cis-2-(3-(2,3-dihydro-1H-indol-1-yl)benzyl)-1-isobutyrylpyrrolidin-3-yl)methanesulfonamide			442.0
246	N-(cis-1-isobutyryl-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			408.1
247	N-(cis-1-(cyclopropylcarbonyl)-2-((6-phenylpyridin-2-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			400.1
248	ethyl cis-3-((methylsulfonyl)amino)-2-((6-phenylpyridin-2-yl)methyl)pyrrolidine-1-carboxylate			404.0
249	methyl cis-2-(biphenyl-3-ylmethyl)-3-((ethylsulfonyl)amino)piperidine-1-carboxylate			417.0
250	methyl cis-2-(biphenyl-3-ylmethyl)-3-((isopropylsulfonyl)amino)piperidine-1-carboxylate			431.0

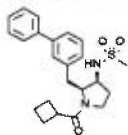
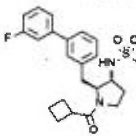
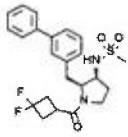
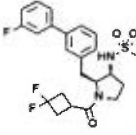
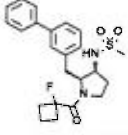
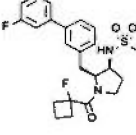
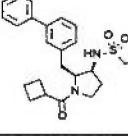
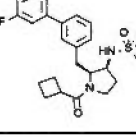
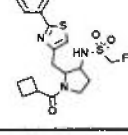
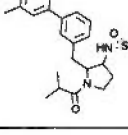
[0623]

Table 1-26

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
251	cis-2-(biphenyl-3-ylmethyl)-N-ethyl-3-((methylsulfonyl)amino)azetidine-1-carboxamide			388.0
252	N-(cis-1-(2,2-dimethylpropanoyl)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			422.2
253	1-fluoro-N-(cis-1-isobutyryl-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			426.2
254	N-(cis-1-(cyclobutylcarbonyl)-2-((2-(3-fluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			438.1
255	N-(cis-1-(cyclobutylcarbonyl)-2-((2-(2-fluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			438.2
256	N-(cis-1-(cyclobutylcarbonyl)-2-((2-(2,3-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			456.1
257	N-(cis-1-(cyclobutylcarbonyl)-2-((2-(4-fluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			438.1
258	N-(cis-1-(cyclobutylcarbonyl)-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			456.1
259	N-(cis-1-(cyclobutylcarbonyl)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)cyclopropanesulfonamide			446.2
260	N-(cis-1-isobutyryl-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)cyclopropanesulfonamide			434.2

[0624]

Table 1-27

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
261	N-((2S,3S)-2-(biphenyl-3-ylmethyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)methanesulfonamide			413.3
262	N-((2S,3S)-1-(cyclobutylcarbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			431.2
263	N-((2S,3S)-2-(biphenyl-3-ylmethyl)-1-((3,3-difluorocyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			447.1
264	N-((2S,3S)-1-((3,3-difluorocyclobutyl)carbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			465.0
265	N-((2S,3S)-2-(biphenyl-3-ylmethyl)-1-((1-fluorocyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			431.2
266	N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-1-((1-fluorocyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			447.1
267	N-((2S,3S)-2-(biphenyl-3-ylmethyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide			431.2
268	N-((2S,3S)-1-(cyclobutylcarbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide			449.1
269	N-(cis-1-(cyclobutylcarbonyl)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide			438.0
270	N-(cis-1-isobutyryl-2-((3'-methylbiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			415.2

[0625]

Table 1-28

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
271	N-(cis-2-((3'-chlorobiphenyl-3-yl)methyl)-1-isobutyrylpyrrolidin-3-yl)methanesulfonamide			435.2
272	N-(cis-1-isobutyryl-2-((3'-methoxybiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			431.0
273	N-(cis-2-((3'-(difluoromethyl)biphenyl-3-yl)methyl)-1-isobutyrylpyrrolidin-3-yl)methanesulfonamide			451.2
274	N-(cis-2-(biphenyl-3-ylmethyl)-1-((1-methylcyclopropyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			413.3
275	N-(cis-2-(biphenyl-3-ylmethyl)-1-((2,2-dimethylcyclopropyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			427.0
276	N-(cis-1-(bicyclo[1.1.1]pent-1-ylcarbonyl)-2-(biphenyl-3-ylmethyl)pyrrolidin-3-yl)methanesulfonamide			425.0
277	N-(cis-2-(biphenyl-3-ylmethyl)-1-(2,2-difluoropropanoyl)pyrrolidin-3-yl)methanesulfonamide			423.0
278	N-(cis-2-(biphenyl-3-ylmethyl)-1-(2-fluoro-2-methylpropanoyl)pyrrolidin-3-yl)methanesulfonamide			417.2
279	N-(cis-2-(biphenyl-3-ylmethyl)-1-(3,3,3-trifluoro-2-methylpropanoyl)pyrrolidin-3-yl)methanesulfonamide			454.9
280	N-(cis-2-(biphenyl-3-ylmethyl)-1-((1-fluorocyclopropyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			417.0

[0626]

Table 1-29

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
281	N-(cis-2-(biphenyl-3-ylmethyl)-1-((trans-2-fluorocyclopropyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			417.0
282	N-(cis-2-(biphenyl-3-ylmethyl)-1-((cis-2-fluorocyclopropyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			417.0
283	N-(cis-2-(biphenyl-3-ylmethyl)-1-((2,2-difluorocyclopropyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			435.0
284	N-(cis-2-(biphenyl-3-ylmethyl)-1-(oxetan-3-ylcarbonyl)pyrrolidin-3-yl)methanesulfonamide			415.0
285	N-(cis-1-(cyclopropylcarbonyl)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			406.0
286	ethyl cis-3-((methylsulfonyl)amino)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidine-1-carboxylate			410.1
287	isopropyl cis-2-(biphenyl-3-yl(difluoro)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			465.1
288	N-(cis-2-(biphenyl-3-yl(difluoro)methyl)-1-(cyclopropylcarbonyl)piperidin-3-yl)methanesulfonamide			449.2
289	N-(cis-1-acetyl-2-(biphenyl-3-yl(difluoro)methyl)piperidin-3-yl)methanesulfonamide			423.0
290	ethyl cis-2-(biphenyl-3-yl(difluoro)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate			451.0

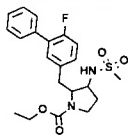
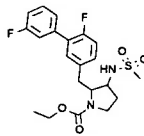
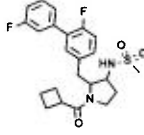
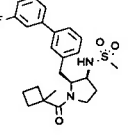
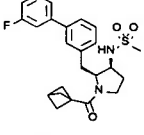
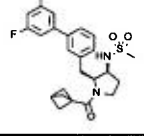
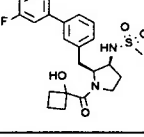
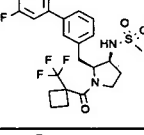
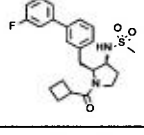
[0627]

Table 1-30

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
291	ethyl cis-2-((2-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			421.0
292	ethyl cis-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			439.2
293	N-(cis-2-((2-fluorobiphenyl-3-yl)methyl)-1-isobutyrylpyrrolidin-3-yl)methanesulfonamide			419.2
294	N-(cis-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-isobutyrylpyrrolidin-3-yl)methanesulfonamide			437.2
295	ethyl cis-2-((5-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			421.0
296	ethyl cis-2-((3',5-difluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			438.9
297	N-(cis-2-((5-fluorobiphenyl-3-yl)methyl)-1-isobutyrylpyrrolidin-3-yl)methanesulfonamide			419.2
298	N-(cis-2-((3',5-difluorobiphenyl-3-yl)methyl)-1-isobutyrylpyrrolidin-3-yl)methanesulfonamide			437.2
299	N-(cis-1-(cyclobutylcarbonyl)-2-((5-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			431.2
300	N-(cis-1-(cyclobutylcarbonyl)-2-((3',5-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			449.2

[0628]

Table 1-31

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
301	ethyl cis-2-((6-fluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			421.0
302	ethyl cis-2-((3',6-difluorobiphenyl-3-yl)methyl)-3-((methylsulfonyl)amino)pyrrolidine-1-carboxylate			439.0
303	N-(cis-1-(cyclobutylcarbonyl)-2-((6-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			431.2
304	N-(cis-1-(cyclobutylcarbonyl)-2-((3',6-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			449.2
305	N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-1-((1-methylcyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			445.3
306	N-((2S,3S)-1-(bicyclo[1.1.1]pent-1-ylcarbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			443.3
307	N-((2S,3S)-1-(bicyclo[1.1.1]pent-1-ylcarbonyl)-2-((3',5'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			460.9
308	N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-1-(1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			447.0
309	N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-1-(1-(trifluoromethyl)cyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			498.9
310	N-((2S,3S)-1-(cyclobutylcarbonyl)-2-((3',5'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			448.9

[0629]

Table 1-32

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
311	N-((2S,3S)-1-(cyclobutylcarbonyl)-2-((3'-methylbiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			427.0
312	N-((2S,3S)-1-(cyclobutylcarbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)-1-methoxymethanesulfonamide			461.0
313	N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			432.2
314	N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-1-((1-methoxycyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			461.1
315	N-(cis-1-(cyclobutylcarbonyl)-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide			470.1
316	N-(cis-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)-1-((1-methylcyclobutyl)carbonyl)pyrrolidin-3-yl)ethanesulfonamide			484.1
317	N-(cis-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)-1-((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-yl)ethanesulfonamide			486.1
318	N-(cis-1-(bicyclo[1.1.1]pent-1-ylcarbonyl)-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide			482.1
319	N-(cis-1-(cyclobutylcarbonyl)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			420.2
320	N-((2S,3S)-1-(cyclobutylcarbonyl)-2-((2-(3-fluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			438.2

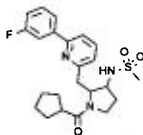
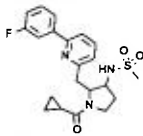
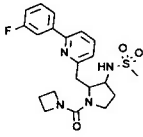
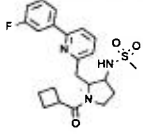
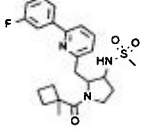
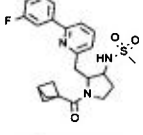
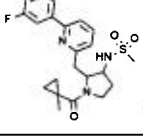
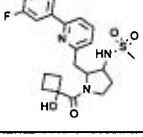
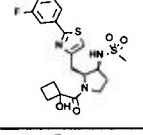
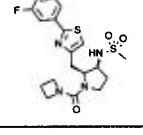
[0630]

Table 1-33

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
321	N-((2S,3S)-1-(cyclobutylcarbonyl)-2-((2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)cyclopropanesulfonamide (optical isomer)			446.1
322	N-(cis-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)-1-((1-methylcyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			468.0
323	N-(cis-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)-1-((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			469.9
324	N-((2S,3S)-2-(biphenyl-3-ylmethyl)-1-(cyclobutylcarbonyl)pyrrolidin-3-yl)-1-methoxymethanesulfonamide			443.1
325	N-(cis-1-(cyclobutylcarbonyl)-2-((5-methyl-2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			434.1
326	N-(cis-1-((1-hydroxycyclobutyl)carbonyl)-2-((5-methyl-2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			450.1
327	N-(cis-1-(azetidin-1-ylcarbonyl)-2-((5-methyl-2-phenyl-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			435.2
328	N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-1-(oxetan-2-ylcarbonyl)pyrrolidin-3-yl)methanesulfonamide			433.1
329	N-(cis-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)-1-isobutyrylpyrrolidin-3-yl)methanesulfonamide			420.2
330	N-(cis-1-(2,2-dimethylpropanoyl)-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			434.2

[0631]

Table 1-34

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
331	N-(cis-1-(cyclopentylcarbonyl)-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			446.2
332	N-(cis-1-(cyclopropylcarbonyl)-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			418.2
333	N-(cis-1-(azetidin-1-ylcarbonyl)-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			433.2
334	N-(cis-1-(cyclobutylcarbonyl)-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			432.2
335	N-(cis-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)-1-((1-methylcyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			446.2
336	N-(cis-1-(bicyclo[1.1.1]pent-1-ylcarbonyl)-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			444.2
337	N-(cis-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)-1-((1-methylcyclopropyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			432.2
338	N-(cis-2-((6-(3-fluorophenyl)pyridin-2-yl)methyl)-1-((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			448.2
339	N-((2S,3S)-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)-1-((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			469.9
340	N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			454.9

[0632]

Table 1-35

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
341	N-((2S,3S)-1-((3-fluoroazetidin-1-yl)carbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			450.2
342	N-((2S,3S)-1-((3,3-difluoroazetidin-1-yl)carbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			468.1
343	N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-1-((2-methylazetidin-1-yl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			446.2
344	N-((2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-1-((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			465.1
345	N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((3',5'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			450.2
346	N-((2S,3S)-1-((1-cyanocyclobutyl)carbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			456.3
347	N-((2S,3S)-1-(5-azaspiro[2.3]hex-5-ylcarbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			458.3
348	N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2-(3,5-difluorophenyl)-1,3-thiazol-4-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			471.2
349	N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2,2-dimethylpropanoyl)pyrrolidin-3-yl)methanesulfonamide			451.1
350	N-((2S,3S)-1-(cyclobutylcarbonyl)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			449.1

[0633]

Table 1-36

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
351	N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-((1-methylcyclopropyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			449.1
352	N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			450.1

[0634]

Table 1-37

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
353	N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-(biphenyl-3-ylmethyl)pyrrolidin-3-yl)methanesulfonamide			414.2
354	(2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-N,N-dimethyl-3-((methylsulfonyl)amino)pyrrolidine-1-carboxamide			420.2
355	N-((2S,3S)-1-(cyclobutylcarbonyl)-2-((2,3,5-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			467.2
356	N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3,5-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			468.2
357	N-((2S,3S)-1-(cyclobutylcarbonyl)-2-((2,3,5-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide			481.2
358	N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3,5-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide			482.2
359	N'-((2S,3S)-1-(cyclobutylcarbonyl)-2-((2,3,5-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)-N,N-dimethylsulfuric diamide			496.2
360	N'-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3,5-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)-N,N-dimethylsulfuric diamide			497.1
361	(2S,3S)-N-ethyl-2-((3'-fluorobiphenyl-3-yl)methyl)-N-methyl-3-((methylsulfonyl)amino)pyrrolidine-1-carboxamide			434.2
362	N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((3',5'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide			464.2

[0635]

Table 1-38

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
363	N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((3'-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide			446.2
364	N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-(biphenyl-3-ylmethyl)pyrrolidin-3-yl)ethanesulfonamide			428.3
365	(2S,3S)-3-((ethylsulfonyl)amino)-2-((3'-fluorobiphenyl-3-yl)methyl)-N,N-dimethylpyrrolidine-1-carboxamide			434.2
366	(2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-N,N-dimethyl-3-((methylsulfonyl)amino)pyrrolidine-1-carboxamide			438.2
367	(2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-3-((ethylsulfonyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide			452.1
368	(2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-N-isopropyl-N-methyl-3-((methylsulfonyl)amino)pyrrolidine-1-carboxamide			448.2
369	(2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-N-ethyl-3-((ethylsulfonyl)amino)-N-methylpyrrolidine-1-carboxamide			466.2
370	(2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-N,N-dimethyl-3-((methylsulfonyl)amino)pyrrolidine-1-carboxamide			438.2
371	(2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-N-ethyl-N-methyl-3-((methylsulfonyl)amino)pyrrolidine-1-carboxamide			452.2
372	N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide			464.2

[0636]

Table 1-39

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
373	(2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((ethylsulfonyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide			452.2
374	N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)cyclopropanesulfonamide			476.1
375	(2S,3S)-3-((cyclopropylsulfonyl)amino)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-N,N-dimethylpyrrolidine-1-carboxamide			464.2
376	N'-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)-N,N-dimethylsulfuric diamide			479.2
377	(2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((dimethylsulfonyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide			467.2
378	N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			468.2
379	(2S,3S)-N,N-dimethyl-3-((methylsulfonyl)amino)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidine-1-carboxamide			456.2
380	N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((3'-chloro-2-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			466.1
381	(2S,3S)-2-((3'-chloro-2-fluorobiphenyl-3-yl)methyl)-N,N-dimethyl-3-((methylsulfonyl)amino)pyrrolidine-1-carboxamide			454.1
382	(2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-N-methoxy-N-methyl-3-((methylsulfonyl)amino)pyrrolidine-1-carboxamide			454.2

[0637]

Table 1-40

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
383	(2S,3S)-2-((2-fluorobiphenyl-3-yl)methyl)-N,N-dimethyl-3-((methylsulfonyl)amino)pyrrolidine-1-carboxamide			420.2
384	N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2-fluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			432.1
385	(2S,3S)-2-(biphenyl-3-ylmethyl)-3-((ethylsulfonyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide			416.2
386	N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			465.2
387	N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)methanesulfonamide			453.2
388	N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-yl)ethanesulfonamide			479.2
389	N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide			465.1
390	N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-yl)cyclopropanesulfonamide			491.2
391	N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)cyclopropanesulfonamide			477.2
392	N'-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-yl)-N,N-dimethylsulfuric diamide			494.2

[0638]

Table 1-41

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
393	N'-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)-N,N-dimethylsulfuric diamide			482.2
394	N-((2S,3S)-1-((1-hydroxycyclobutyl)carbonyl)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			481.1
395	N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			469.1
396	N-((2S,3S)-2-((3'-chloro-2-fluorobiphenyl-3-yl)methyl)-1-((1-hydroxycyclobutyl)carbonyl)pyrrolidin-3-yl)methanesulfonamide			481.1
397	N-((2S,3S)-2-((3'-chloro-2-fluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)methanesulfonamide			469.2
398	(2S,3S)-3-((ethylsulfonyl)amino)-2-((2-fluorobiphenyl-3-yl)methyl)-N,N-dimethylpyrrolidine-1-carboxamide			434.2
399	(2S,3S)-3-((ethylsulfonyl)amino)-N,N-dimethyl-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidine-1-carboxamide			470.2
400	(2S,3S)-2-(biphenyl-3-ylmethyl)-N,N-dimethyl-3-((methylsulfonyl)amino)pyrrolidine-1-carboxamide			402.2
401	(2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((ethylsulfonyl)amino)-N-methoxy-N-methylpyrrolidine-1-carboxamide			468.1
402	N-((2S,3S)-1-isobutyryl-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			455.2

[0639]

Table 1-42

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
403	(2S,3S)-N-methoxy-N-methyl-3-((methylsulfonyl)amino)-2-((2,3,5'-trifluorobiphenyl-3-yl)methyl)pyrrolidine-1-carboxamide			472.2
404	N-((2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide			465.1
405	N-((2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-1-(oxetan-2-ylcarbonyl)pyrrolidin-3-yl)ethanesulfonamide			463.1
406	(2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-N-methoxy-N-methyl-3-((methylsulfonyl)amino)pyrrolidine-1-carboxamide			436.2
407	(2S,3S)-2-(biphenyl-3-ylmethyl)-3-((ethanesulfonyl)amino)-N-methoxy-N-methylpyrrolidine-1-carboxamide			432.2
408	(2S,3S)-2-((2-fluorobiphenyl-3-yl)methyl)-N-methoxy-N-methyl-3-((methylsulfonyl)amino)pyrrolidine-1-carboxamide			436.2
409	(2S,3S)-2-(biphenyl-3-ylmethyl)-N-methoxy-N-methyl-3-((methylsulfonyl)amino)pyrrolidine-1-carboxamide			418.2
410	N-((2S,3S)-2-((2-fluoro-3'-methylbiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)methanesulfonamide			449.2
411	N-((2S,3S)-2-((2,3'-difluoro-5'-methylbiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)methanesulfonamide			467.2
412	N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-1-(2-methoxy-2-methylpropanoyl)pyrrolidin-3-yl)methanesulfonamide			449.2

[0640]

Table 1-43

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
413	N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,2',3'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			471.2
414	N-((2S,3S)-2-((2,2'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)methanesulfonamide			453.2
415	1-fluoro-N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)methanesulfonamide			451.0
416	1,1-difluoro-N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)methanesulfonamide			468.9
417	N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide			469.1
418	N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)-1,1-difluoromethanesulfonamide			487.0
419	N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)-1-methoxymethanesulfonamide			483.2
420	N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)-1-methoxymethanesulfonamide			499.1
421	N-((2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)-1-fluoromethanesulfonamide			469.1
422	N-((2S,3S)-2-((3',5'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)-1,1-difluoromethanesulfonamide			487.0

[0641]

Table 1-44

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
423	1-fluoro-N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3,5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			487.1
424	1,1-difluoro-N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3,5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			505.1
425	N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide			467.2
426	N-((2S,3S)-2-((3'-chlorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide			465.2
427	N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,2',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			471.2
428	N-((2S,3S)-2-((3'-chloro-2,5'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)methanesulfonamide			484.9
429	N-((2S,3S)-2-((3'-fluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide			447.0
430	N-((2S,3S)-2-((2-fluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide			449.2
431	N-((2S,3S)-2-((3'-chloro-2-fluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide			483.1
432	N-((2S,3S)-2-((2-fluoro-3'-methylbiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide			463.2

[0642]

Table 1-45

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
433	N-((2S,3S)-2-((2-fluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)methanesulfonamide			435.2
434	N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,2',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide			485.2
435	N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,2',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide			483.1
436	N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,2',3'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide			485.2
437	N-((2S,3S)-2-((3'-chloro-2,5'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide			499.0
438	N-((2S,3S)-2-((2,3'-difluoro-5'-methylbiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide			481.2
439	N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)cyclopropanesulfonamide			495.1
440	N-((2S,3S)-2-((2-fluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)cyclopropanesulfonamide			461.2

[0643]

Table 1-46

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
441	N-[(2S,3S)-1-(oxetane-2-carbonyl)-2-[(2,3',5'-trifluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl)methanesulfonamide			469.1
442	N-[(2S,3S)-2-[(2-fluoro[1,1'-biphenyl]-3-yl)methyl]-1-(oxetane-2-carbonyl)pyrrolidin-3-yl)methanesulfonamide			433.2
443	N-[(2S,3S)-1-(azetidine-1-carbonyl)-2-[(3-benzylphenyl)methyl]pyrrolidin-3-yl)ethanesulfonamide			442.3
444	N-[cis-1-(azetidine-1-carbonyl)-2-[[dibenzo[b,d]furan-2-yl)methyl]pyrrolidin-3-yl)methanesulfonamide			428.3
445	N-[cis-1-(azetidine-1-carbonyl)-2-[(3-phenoxyphenyl)methyl]pyrrolidin-3-yl)ethanesulfonamide			444.2
446	N-[cis-1-(cyclobutanecarbonyl)-2-[(3-phenoxyphenyl)methyl]pyrrolidin-3-yl)ethanesulfonamide			443.2
447	N-[cis-1-(azetidine-1-carbonyl)-2-[(3-(propan-2-yl)-1-benzofuran-5-yl)methyl]pyrrolidin-3-yl)methanesulfonamide			420.2
448	N-[cis-1-(azetidine-1-carbonyl)-2-[(4-phenoxyphenyl)methyl]pyrrolidin-3-yl)methanesulfonamide			430.2
449	1,1,1-trifluoro-N-[(2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-[(2,3',5'-trifluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl)methanesulfonamide			523.0
450	N-[(2S,3S)-2-[(2,3'-difluoro[1,1'-biphenyl]-3-yl)methyl]-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl]-1-fluorocyclopropane-1-sulfonamide			497.2

[0644]

Table 1-47

451	(2S,3S)-N-ethyl-2-[(3'-fluoro[1,1'-biphenyl]-3-yl)methyl]-3-[(methanesulfonyl)amino]pyrrolidine-1-carboxamide		420.1
452	N-[(2S,3S)-2-[(2,3'-difluoro[1,1'-biphenyl]-3-yl)methyl]-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl]-1-fluoroethane-1-sulfonamide		485.2
453	N'-[(2S,3S)-1-(azetidine-1-carbonyl)-2-[(3-bromo-2-fluorophenyl)methyl]pyrrolidin-3-yl]-N,N-dimethylsulfuric diamide		463.1
454	N-[(2S,3S)-2-[(3',5'-difluoro[1,1'-biphenyl]-3-yl)methyl]-1-(1-methyl-1H-pyrazole-3-carbonyl)pyrrolidin-3-yl]ethanesulfonamide		489.2
455	N-[(2S,3S)-2-[(3',5'-difluoro[1,1'-biphenyl]-3-yl)methyl]-1-(furan-2-carbonyl)pyrrolidin-3-yl]ethanesulfonamide		475.2
456	N-[(2S,3S)-1-(azetidine-1-carbonyl)-2-[(2-fluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl]ethanesulfonamide		446.0
457	N-[(2S,3S)-1-(3-hydroxy-2,2-dimethylpropanoyl)-2-[(2,3',5'-trifluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl]methanesulfonamide		484.9
458	N-[(2S,3S)-2-[(3',5'-difluoro[1,1'-biphenyl]-3-yl)methyl]-1-(1H-imidazol-2-yl)pyrrolidin-3-yl]ethanesulfonamide		447.2
459	N-[(2S,3S)-1-(azetidine-1-carbonyl)-2-[(3'-fluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl]-1-fluoromethanesulfonamide		450.2
460	N-[(2S,3S)-1-(azetidine-1-carbonyl)-2-[(1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl]-1-fluoromethanesulfonamide		432.2

[0645]

Table 1-48

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
461	N-[(2S,3S)-2-[(3',5'-difluoro[1,1'-biphenyl]-3-yl)methyl]-1-(1-methyl-1H-imidazol-2-yl)pyrrolidin-3-yl]ethanesulfonamide			461.2
462	N-[(2S,3S)-1-(azetidine-1-carbonyl)-2-[(3'-fluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl]cyclopropanesulfonamide			458.2
463	N-[(2S,3S)-1-(azetidine-1-carbonyl)-2-[(1,1'-biphenyl)-3-yl)methyl]pyrrolidin-3-yl]cyclopropanesulfonamide			440.2
464	N-[(2S,3S)-1-[1-(hydroxymethyl)cyclopropane-1-carbonyl]-2-[(2,3,5'-trifluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl]methanesulfonamide			483.1
465	N-[(2S,3S)-1-(1H-imidazol-2-yl)-2-[(2,3,5'-trifluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl]ethanesulfonamide			465.2
466	N-[(2S,3S)-1-(azetidine-1-carbonyl)-2-[(2-fluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl]-1-fluoromethanesulfonamide			450.2
467	N-[(2S,3S)-1-(azetidine-1-carbonyl)-2-[(2,3'-difluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl]-1-fluoromethanesulfonamide			468.2
468	N-[(2S,3S)-2-[(3',5'-difluoro[1,1'-biphenyl]-3-yl)methyl]-1-(1-ethyl-1H-imidazol-2-yl)pyrrolidin-3-yl]ethanesulfonamide			475.3
469	N-[(2S,3S)-1-[1-(hydroxymethyl)cyclobutane-1-carbonyl]-2-[(2,3,5'-trifluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl]methanesulfonamide			497.2
470	N-[(2S,3S)-1-(6-chloropyridazin-3-yl)-2-[(3',5'-difluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl]ethanesulfonamide			493.1

[0646]

Table 1-49

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
471	N-[(2S,3S)-2-[(1,1'-biphenyl]-3-yl)methyl]-1-(cyclobutanecarbonyl)pyrrolidin-3-yl]ethanesulfonamide			427.3
472	N-[(2S,3S)-2-[(3',5'-difluoro[1,1'-biphenyl]-3-yl)methyl]-1-(6-methylpyridazin-3-yl)pyrrolidin-3-yl]ethanesulfonamide			473.2
473	N-[(2S,3S)-2-[(3',5'-difluoro[1,1'-biphenyl]-3-yl)methyl]-1-(pyridazin-3-yl)pyrrolidin-3-yl]ethanesulfonamide			459.1
474	(2S,3S)-3-[(ethanesulfonyl)amino]-2-[(3'-fluoro[1,1'-biphenyl]-3-yl)methyl]-N-methoxy-N-methylpyrrolidine-1-carboxamide			450.2
475	(2S,3S)-3-[(dimethylsulfonyl)amino]-2-[(2-fluoro[1,1'-biphenyl]-3-yl)methyl]-N,N-dimethylpyrrolidine-1-carboxamide			449.2
476	(2S,3S)-3-[(dimethylsulfonyl)amino]-N,N-dimethyl-2-[(2,3',5'-trifluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidine-1-carboxamide			485.2
477	(2S,3S)-2-[(3',5'-difluoro[1,1'-biphenyl]-3-yl)methyl]-3-[(ethanesulfonyl)amino]-N-methoxy-N-methylpyrrolidine-1-carboxamide			468.1
478	N-[(2S,3S)-2-[(3',5'-difluoro[1,1'-biphenyl]-3-yl)methyl]-1-(1,2-oxazolidine-2-carbonyl)pyrrolidin-3-yl]ethanesulfonamide			480.2
479	1-fluoro-N-[(2S,3S)-2-[(2-fluoro[1,1'-biphenyl]-3-yl)methyl]-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl]cyclopropane-1-sulfonamide			479.2
480	1-fluoro-N-[(2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-[(2,3',5'-trifluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl]cyclopropane-1-sulfonamide			515.1

[0647]

Table 1-50

EXAMPLE	IUPACNAME	Structure	ADDITIVE	MS
481	N-((2S,3S)-2-[(3',5'-difluoro[1,1'-biphenyl]-3-yl)methyl]-1-(trimethylhydrazinecarbonyl)pyrrolidin-3-yl)ethanesulfonamide			481.2
482	N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide			467.1
483	N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			469.1
484	N-((2S,3S)-1-(2-hydroxy-2-methylpropanoyl)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide			485.2
485	N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3'-difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide			450.1
486	(2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-((ethylsulfonyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide			452.1
487	(2S,3S)-3-((ethylsulfonyl)amino)-N,N-dimethyl-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidine-1-carboxamide			470.2
488	N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide			467.2

5 [0648]

Experimental Example 1: Obtainment of cell stably expressing human orexin type 2 receptor (hOX2R)

To obtain a cell clone stably expressing human orexin type 2 receptor, human orexin type 2 receptor cDNA was inserted
 10 into pcDNA3.1(+) plasmid vector (Invitrogen), and a plasmid DNA for expression of human orexin type 2 receptor (pcDNA3.1(+)/hOX2R) was cloned. The plasmid DNA was introduced into CHO-dhfr cell by an electroporation method, and human

orexin type 2 receptor expressing clone cells were obtained by limiting dilution method by using G418 drug resistance as a selection marker.

[0649]

5 Experimental Example 2: Measurement of orexin type 2 receptor agonist activity

CHO cells forcibly expressing human OX2 receptor were seeded in each well of 384 well black transparent bottom plate (BD Falcon) at 7,500 cells/well, and cultured for one day in a
10 5% CO₂ incubator at 37°C. After removal of the medium in the cell plate, assay buffer A containing a calcium indicator (HBSS (Thermo Fisher Scientific), 20 mM HEPES (Thermo Fisher Scientific), 0.1% BSA (Wako Pure Chemical Industries, Ltd. or Sigma-Aldrich), 2.5 µg/mL Fluo-4 AM (DOJINDO Chemical), 0.08%
15 Pluronic F127 (DOJINDO Chemical), 1.25 mM probenecid (DOJINDO Chemical)) was added at 30 µL/well. The plate was stood for 30 min in a 5% CO₂ incubator at 37°C, and further stood at room temperature for 30 min. A test compound prepared by diluting with assay buffer B (HBSS, 20 mM HEPES, 0.1 % BSA) was added at
20 10 µL/well, and the fluorescence value was measured by FDSSpCELL (Hamamatsu Photonics K.K.) every one sec for 1 min, and thereafter every two sec for 1 min 40 sec. The activity (%) of the test compound was calculated assuming that variation in the fluorescence value when DMSO was added instead of the
25 test compound was 0%, and variation in the fluorescence value when orexin A (human) (PEPTIDE INSTITUTE, INC.) was added at the final concentration of 10 nM was 100%. The activity of each compound at the concentration of 3 µM was shown in Table 2. As is clear from the results, the compound of the present
30 invention was shown to have an agonist activity on human orexin type 2 receptor.

[0650]

Table 2-1

Example No.	OX2R agonist activity (3 μ M, %)
1	81
2	90
3	101
7	62
10	91
11	80
14	82
17	29
22	60
27	66
29	98
35	41
38	75
41	67
50	97
53	72
55	84
60	26
61	74
62	93
63	24
64	96
74	104
76	106
78	35
89	96
93	101
95	97
100	107
101	96
108	69
116	106
122	82
126	90
145	24
159	65
173	68
178	99
181	100
185	99

[0651]

Table 2-2

Example No.	OX2R agonist activity (3 μ M, %)
191	79
204	95
206	94
209	106
210	102
214	70
227	99
254	101
255	101
256	97
258	95
259	95
261	97
262	101
266	107
269	111
293	102
294	104
299	100
300	99
303	95
304	94
305	105
306	100
307	102
308	107
309	101
310	102
311	103
312	103
313	100
314	107
315	105
316	104
317	103
318	102
319	101
320	103
321	104
322	104

[0652]

Table 2-3

Example No.	OX2R agonist activity (3 μ M, %)
323	109
324	103
328	104
333	101
338	103
339	102
340	103
341	98
342	109
343	107
344	99
345	93
346	107
347	87
348	109
349	99
350	99
351	106
352	102

[0653]

Table 2-4

Example No.	OX2R agonist activity (3 μ M, %)
364	104
366	100
373	96
387	106
389	102
395	104
399	107
402	107
404	100
417	110
421	106
423	109
424	101
428	102
431	101
435	107
437	99
439	98

[0654]

Table 2-5

Example No.	OX2R agonist activity (3 μ M, %)
362	103
372	98
377	103
407	107
441	99
450	107
456	104
457	103
459	93
460	92
462	112
463	105
466	108
467	101
471	116
474	109
475	104
476	103
477	106
479	103
480	113
482	110
483	103
484	112
485	104
486	102
487	104
488	101

[0655]

Experimental Example 3: Evaluation of microsome stability in human

Human liver microsomes were purchased from Xenotech, LLC
5 (Lenexa, KS). An incubation mixture consisted of microsomes in
50 mmol/L KH_2PO_4 - K_2HPO_4 phosphate buffer (pH 7.4) and 1 $\mu\text{mol/L}$
test compound. The concentration of microsomal protein was 0.2
mg/mL. An NADPH-generating system (5 mmol/L MgCl_2 , 5 mmol/L
glucose-6-phosphate, 0.5 mmol/L beta-NADP+ and 1.5 unit/mL
10 glucose-6-phosphate dehydrogenase) was added to the incubation
mixture with a half volume of the reaction mixture to initiate
the enzyme reaction. The reaction was terminated 15 and 30
minutes after the initiation of the reaction by mixing the
reaction mixture with acetonitrile, followed by centrifugation
15 at 2500 rpm for 10 min. The supernatant was subjected to
LC/MS/MS analysis. The metabolic velocity was calculated as the
slope of the concentration-time plot. The in vitro intrinsic
metabolic clearance was calculated by dividing initial
metabolic velocity by the test compound concentration in the
20 incubation mixture. The results were shown in Table 3.

[0656]

Table 3

Test compound	Clearance ($\mu\text{L}/\text{min}/\text{mg}$)
Example 450	78
Example 482	26
Example 483	6
Example 484	23

[0657]

25 As is clear from the results, in vitro intrinsic
metabolic clearance of the test compounds of the present
invention was low. That is, these compounds were shown to have
good metabolic stabilities.

[0658]

Experimental Example 4: Evaluation of wake-promoting effects in cynomolgus monkeys

The wake-promoting effects were evaluated by measuring the electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG) in cynomolgus monkeys. Under isoflurane anesthesia (1-5%, Pfizer Japan Inc., Tokyo, Japan), male cynomolgus monkeys (3-5 years old, Hamri Co., Ltd., Ibaraki, Japan) were surgically implanted with radio-telemetry transmitters (TL10M3-D70-EEE, Data Sciences International Inc., MN, USA). EEG leads were stereotaxically positioned at the parietal area and secured to the cranium with stainless-steel screws in contact with the dura. Unilateral EOG leads were positioned at superior orbital margin of one eye and secured with stainless-steel screws. Bilateral EMG leads were implanted into the back cervical muscles. After the surgery, each monkey was given penicillin (100,000 units/head, i.m., Meiji Seika Pharma Co., Ltd., Tokyo, Japan), buprenorphine (0.02 mg/kg, i.m., Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) and prednisolone (1 mg/kg, s.c., Kyoritsu Seiyaku Co., Ltd., Tokyo, Japan) daily for one week. After at least a 1-month recovery period in home cages, the monkeys were habituated to the recording chamber (an acrylic cage 60W x 55D x 75H (cm)) located in a soundproof, electrically shielded room. After we confirmed that monkeys slept sufficiently in the experimental room, cortical EEG, EMG and EOG signals were recorded using Dataquest ART software (Data Sciences International Inc., MN, USA). The signals were semi automatically scored in 20 sec epochs by a sleep scoring system (SleepSign, Kissei Comtec Co., Ltd., Nagano, Japan). This preliminary scoring was visually inspected and corrected if necessary. Test compound (10 mg/kg, Table 4-1) suspended in 0.5% methylcellulose aqueous solution, or vehicle (i.e., 0.5% methylcellulose aqueous solution) was administered orally (p.o.) to monkeys at zeitgeber time 12 (ZT12) in a volume of 5 mL/kg body weight in a cross-over design. EEG, EMG and EOG recordings were performed for 4 h

after the compound administration/treatments. The time spent in wakefulness for 4 h after administration (% of vehicle treatment) was calculated by using SleepSign. Test compound (1 mg/kg, Table 4-2) dissolved in a mixed solution comprising 5% DMSO, 5% Cremophor EL, 20% PEG400 and 70% soluplus (1%(w/v)), or vehicle (i.e., a mixed solution comprising 5% DMSO, 5% Cremophor EL, 20% PEG400 and 70% soluplus (1%(w/v))) was administered subcutaneously (s.c.) to monkeys at ZT12 in a volume of 0.5 mL/kg body weight in a pre-post design. EEG, EMG and EOG recordings were performed for 4 h after the compound administration/treatments. The time spent in wakefulness for 4 h after administration (% of vehicle treatment) was calculated by using SleepSign. The results were shown in Table 4.

[0659]

Table 4-1

Test compound (10 mg/kg, p.o.)	Wakefulness time (% of vehicle treatment) (Mean, n=4-8)
Example 482	280.82
Example 483	359.35
Example 484	492.32

[0660]

Table 4-2

Test compound (1 mg/kg, s.c.)	Wakefulness time (% of vehicle treatment) (Mean, n=1-2)
Example 362	270.87
Example 364	375.40
Example 372	327.78
Example 377	343.49
Example 407	391.30
Example 450	242.72
Example 456	445.67
Example 474	329.00
Example 475	410.04
Example 476	392.22
Example 477	382.61
Example 485	449.21
Example 486	328.47
Example 487	354.86

[0661]

5 As is clear from the results, the test compounds of the present invention increased the wakefulness time as compared with the vehicle treatment group in cynomolgus monkeys. That is, these compounds were shown to be effective for the treatment of narcolepsy.

10 [0662]

Formulation Example 1 (production of capsule)

1) compound of Example 1	30 mg
2) crystalline cellulose	10 mg
3) lactose	19 mg
15 4) magnesium stearate	1 mg
total	60 mg

1), 2), 3) and 4) are mixed and filled in a gelatin capsule.

[0663]

Formulation Example 2 (production of tablet)

1) compound of Example 1	30 g
2) lactose	50 g
5 3) cornstarch	15 g
4) calcium carboxymethylcellulose	44 g
5) magnesium stearate	1 g
1000 tablets	140 g in total

The total amount of 1), 2), 3) and 30 g of 4) are kneaded
10 with water, vacuum dried and sieved. The sieved powder is
mixed with 14 g of 4) and 1 g of 5), and the mixture is punched
by a tableting machine. In this way, 1000 tablets containing
30 mg of the compound of Example 1 per tablet are obtained.

Industrial Applicability

15 [0664]

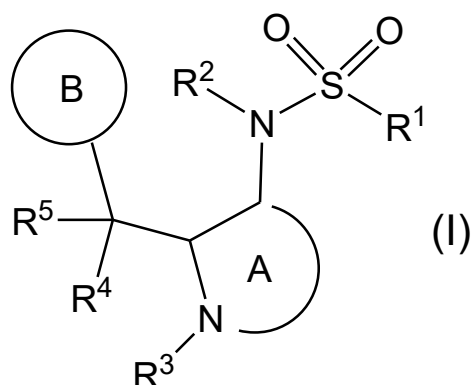
The compound of the present invention has an orexin type
2 receptor agonist activity, and is useful as an agent for the
prophylaxis or treatment of narcolepsy.

[0665]

20 This application is based on patent applications No.
2017-150685 filed on August 3, 2017 and No. 2017-248495 filed
on December 25, 2017 in Japan, the contents of which are
encompassed in full herein.

CLAIMS

1. A compound represented by the formula:



5 wherein

R^1 is

(1) a C_{1-6} alkyl group optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom, and

10 (b) a C_{1-6} alkoxy group,

(2) a C_{3-6} cycloalkyl group optionally substituted by 1 to 3 halogen atoms, or

(3) a mono- or di- C_{1-6} alkylamino group;

R^2 is a hydrogen atom;

15 R^3 is

(1) a C_{1-6} alkoxy-carbonyl group,

(2) a C_{1-6} alkyl-carbonyl group optionally substituted by 1 to 3 hydroxy groups,

(3) a mono- or di- C_{1-6} alkyl-carbamoyl group,

20 (4) a N- C_{1-6} alkyl-N- C_{1-6} alkoxy-carbamoyl group,

(5) a C_{3-6} cycloalkyl-carbonyl group (the C_{3-6} cycloalkyl in the C_{3-6} cycloalkyl-carbonyl group may be a bridged ring group)

optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom,

25 (b) a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms,

(c) a hydroxy group,

(d) a C_{1-6} alkoxy group, and

(e) a cyano group,
(6) an oxetanylcarbonyl group,
(7) an azetidinylcarbonyl group optionally substituted by 1 to 3 substituents selected from
5 (a) a halogen atom, and
(b) a C₁₋₆ alkyl group, or
(8) a 5-azaspiro[2.3]hexylcarbonyl group;
R⁴ and R⁵ are both hydrogen atoms;
Ring A is
10 (1) a pyrrolidine ring, or
(2) a piperidine ring; and
Ring B is
(1) a benzene ring
further substituted by one phenyl group optionally substituted
15 by 1 to 3 substituents selected from
(i) a halogen atom, and
(ii) a C₁₋₆ alkyl group, and
optionally further substituted by one halogen atom,
(2) a pyridine ring further substituted by one phenyl group
20 optionally substituted by 1 to 3 halogen atoms,
(3) a thiazole ring further substituted by one phenyl group
optionally substituted by 1 to 3 halogen atoms, or
(4) a piperidine ring further substituted by one phenyl group.

25 2. The compound or salt according to claim 1, wherein
R¹ is
(1) a C₁₋₆ alkyl group,
(2) a C₃₋₆ cycloalkyl group optionally substituted by 1 to 3
halogen atoms, or
30 (3) a mono- or di-C₁₋₆ alkylamino group;
R² is a hydrogen atom;
R³ is
(1) a C₁₋₆ alkyl-carbonyl group optionally substituted by 1 to 3
hydroxy groups,
35 (2) a mono- or di-C₁₋₆ alkyl-carbamoyl group,

- (3) a N-C₁₋₆ alkyl-N-C₁₋₆ alkoxy-carbamoyl group, or
 (4) an azetidinyldicarbonyl group;
 R⁴ and R⁵ are both hydrogen atoms;
 Ring A is a pyrrolidine ring; and
 5 Ring B is a benzene ring
 further substituted by one phenyl group optionally substituted
 by 1 to 3 halogen atoms, and
 optionally further substituted by one halogen atom.
- 10 3. A compound which is N-((2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl)ethanesulfonamide or a salt thereof.
4. A compound which is N-((2S,3S)-1-(2-hydroxy-2-
 15 methylpropanoyl)-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide or a salt thereof.
5. A compound which is N-((2S,3S)-1-(2-hydroxy-2-
 methylpropanoyl)-2-((2,3',5'-trifluorobiphenyl-3-
 20 yl)methyl)pyrrolidin-3-yl)ethanesulfonamide or a salt thereof.
6. A compound selected from
 (1) N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3'-
 difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)methanesulfonamide,
 25 (2) N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((3',5'-
 difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide,
 (3) N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-(biphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide,
 (4) N-((2S,3S)-1-(azetidin-1-ylcarbonyl)-2-((2,3'-
 30 difluorobiphenyl-3-yl)methyl)pyrrolidin-3-yl)ethanesulfonamide,
 (5) (2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-
 ((ethylsulfonyl)amino)-N,N-dimethylpyrrolidine-1-carboxamide,
 (6) (2S,3S)-2-((2,3'-difluorobiphenyl-3-yl)methyl)-3-
 ((dimethylsulfamoyl)amino)-N,N-dimethylpyrrolidine-1-
 35 carboxamide,

- (7) (2S,3S)-3-((ethylsulfonyl)amino)-N,N-dimethyl-2-((2,3',5'-trifluorobiphenyl-3-yl)methyl)pyrrolidine-1-carboxamide,
(8) (2S,3S)-2-(biphenyl-3-ylmethyl)-3-((ethylsulfonyl)amino)-N-methoxy-N-methylpyrrolidine-1-carboxamide,
5 (9) N-[(2S,3S)-2-[(2,3'-difluoro[1,1'-biphenyl]-3-yl)methyl]-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl]-1-fluorocyclopropane-1-sulfonamide,
(10) N-{(2S,3S)-1-(azetidine-1-carbonyl)-2-[(2-fluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidin-3-yl}ethanesulfonamide,
10 (11) (2S,3S)-3-[(ethanesulfonyl)amino]-2-[(3'-fluoro[1,1'-biphenyl]-3-yl)methyl]-N-methoxy-N-methylpyrrolidine-1-carboxamide,
(12) (2S,3S)-3-[(dimethylsulfamoyl)amino]-2-[(2-fluoro[1,1'-biphenyl]-3-yl)methyl]-N,N-dimethylpyrrolidine-1-carboxamide,
15 (13) (2S,3S)-3-[(dimethylsulfamoyl)amino]-N,N-dimethyl-2-[(2,3',5'-trifluoro[1,1'-biphenyl]-3-yl)methyl]pyrrolidine-1-carboxamide, and
(14) (2S,3S)-2-[(3',5'-difluoro[1,1'-biphenyl]-3-yl)methyl]-3-[(ethanesulfonyl)amino]-N-methoxy-N-methylpyrrolidine-1-
20 carboxamide
or a salt thereof.

7. A medicament comprising the compound or salt according to any one of claims 1 to 6.

25

8. The medicament according to claim 7, for use in therapy, wherein the therapy comprises treatment of a disease or disorder associated with an orexin type 2 receptor agonist.

30 9. The medicament according to claim 8, wherein the disease or disorder is selected from the group consisting of narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome accompanied by narcolepsy-like symptoms, hypersomnia syndrome accompanied by daytime hypersomnia,
35 Alzheimer's, obesity, insulin resistance syndrome, cardiac

failure, diseases related to bone loss, sepsis, disturbance of consciousness such as coma and the like, and side effects and complications due to anesthesia, or the medicament is for use as an anesthetic antagonist.

5

10. The medicament of claim 9, wherein the disease or disorder is selected from the group consisting of narcolepsy, idiopathic hypersomnia, hypersomnia, or sleep apnea syndrome.

10 11. The medicament of claim 9, wherein the disease or disorder is narcolepsy.

12. The compound or salt according to any one of claims 1 to 6 for use in therapy, wherein the therapy comprises treatment of
15 a disease or disorder associated with an orexin type 2 receptor.

13. The compound of claim 12, or a salt thereof, wherein the disease or disorder is selected from the group consisting of narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea
20 syndrome, narcolepsy syndrome accompanied by narcolepsy-like symptoms, hypersomnia syndrome accompanied by daytime hypersomnia, Alzheimer, obesity, insulin resistance syndrome, cardiac failure, diseases related to bone loss, sepsis, disturbance of consciousness such as coma and the like, side
25 effects and complications due to anesthesia, or the compound or salt is for use as an anesthetic antagonist.

14. The compound of claim 12, or a salt thereof, wherein the disease or disorder is selected from the group consisting of
30 narcolepsy, idiopathic hypersomnia, hypersomnia, or sleep apnea syndrome.

15. The compound of claim 12, or a salt thereof, wherein the disease or disorder is narcolepsy.

35

16. Use of the compound or salt according to any one of claims 1 to 6 for the manufacture of a medicament for use in therapy, wherein the therapy comprises treatment of a disease or disorder associated with an orexin type 2 receptor.

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17. The use according to claim 16, wherein the disease or disorder is selected from the group consisting of narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome accompanied by narcolepsy-like symptoms,
10 hypersomnia syndrome accompanied by daytime hypersomnia, Alzheimer, obesity, insulin resistance syndrome, cardiac failure, diseases related to bone loss, sepsis, disturbance of consciousness such as coma and the like, side effects and complications due to anesthesia, or the medicament is for use
15 as an anesthetic antagonist.

18. The use of claim 16, wherein the disease or disorder is selected from the group consisting of narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, or side effects
20 and complications due to anesthesia.

19. The use of claim 16, wherein the disease or disorder is narcolepsy.