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(54) Benævnelse: **SUBSTITUERET PIPERIDINFORBINDELSE SOM OREXIN-TYPE 2-AGONIST TIL BEHANDLING AF NARKOLEPSI**

(56) Fremdragne publikationer:
WO-A1-2014/006402
WO-A2-2012/137982

DESCRIPTION

Description

[Technical Field]

[0001] The present invention relates to a substituted piperidine compound, particularly, a substituted piperidine compound having an orexin type 2 receptor agonist activity.

(Background of the Invention)

[0002] 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 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] 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. 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] 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 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).

[0006] In addition, it is suggested that intraventricular administration of orexin peptide shortens the systemic anesthetic time of rat (non-patent document 8).

[0007] In addition, it is suggested that patients with sleep apnea syndrome show low orexin A concentration levels in plasma (non-patent document 9).

[0008] 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).

[0009] 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).

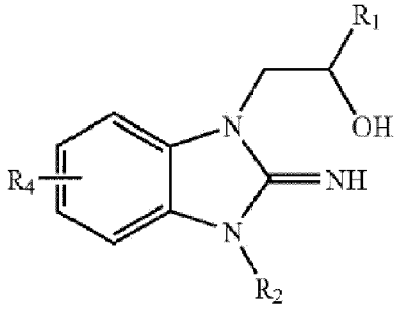
[0010] In addition, it is suggested that the daytime sleepiness of Parkinson's disease patients is caused by orexin nerve fallout (non-patent document 12).

[0011] 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 (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).

[0012] 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, 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's, obesity, insulin resistance syndrome, cardiac failure, diseases related to bone loss, and sepsis; further, it is expected to be useful as an anesthetic antagonist, and a prophylactic or therapeutic drug for side effects and complications due to anesthesia.

[0013] Some of such compounds have been reported (patent document 4, patent document 5, patent document 6, non-patent document 13).

[0014] For example, such compounds include a compound represented by the formula



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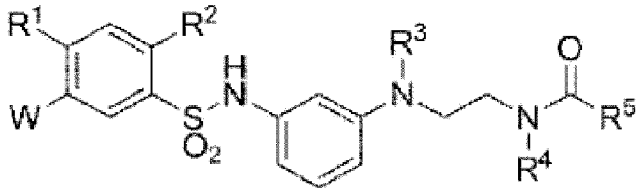
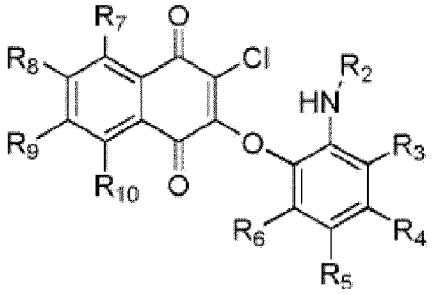
[0015] In addition, for example, such compounds include a compound represented by the formula



[0016] Also, for example, such compounds include a compound represented by the formula



(I)

[0017] 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.

[Document List]

[Patent documents]

[0018]

patent document 1: WO 2015/073707 A1

patent document 2: WO 2015/048091 A1

patent document 3: WO 2015/147240 A1

patent document 4: US 8,258,163 B2

patent document 5: WO 2015/088000 A1

patent document 6: WO 2014/198880 A1

patent document 7: WO 2014/006402

patent document 8: WO 2012/137982

[non-patent documents]

[0019]

non-patent document 1: Cell, Vol.92, 573-585, 1998

non-patent document 2: Cell, Vol.98, 365-376, 1999

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

non-patent document 7: Cell Metabolism, Vol.9, 64-76, 2009

non-patent document 8: Neuroscience, Vol.121, 855-863, 2003

non-patent document 9: Respiration, Vol.71, 575-579, 2004

non-patent document 10: Peptides, Vol.23, 1683-1688, 2002

non-patent document 11: Journal of the American College of Cardiology. Vol. 66, 2015, pages 2522-2533

non-patent document 12: Brain, Vol. 130, 2007, pages 1586-1595

non-patent document 13: Journal of Medicinal Chemistry. Vol. 58, pages 7931-7937

[SUMMARY OF THE INVENTION]

[Problems to be Solved by the Invention]

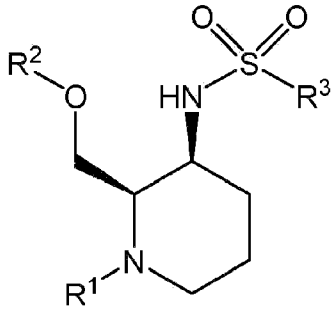
[0020] The present invention aims to provide a substituted piperidine compound having an orexin type 2 receptor agonist activity.

[Means of Solving the Problems]

[0021] The present inventors have found that a compound represented by the following formula (II) or a salt thereof (sometimes to be referred to as compound (II) in the present specification) has an orexin type 2 receptor agonist activity. As a result of further studies, they have completed the present invention.

[0022] Accordingly, the present invention relates to

1. [1] A medicament comprising a compound represented by the formula:



(II)

wherein

R^1 is(1) a hydrogen atom,

(2) a C_{1-6} alkyl-carbonyl group optionally substituted by 1 to 7 substituents selected from (i) a halogen atom, (ii) a cyano group, (iii) a hydroxy group, (iv) a C_{3-10} cycloalkyl group, (v) a C_{1-6} alkoxy group, (vi) a C_{6-14} aryl group, (vii) a C_{6-14} aryloxy group, (viii) a pyrazolyl group, a thiazolyl group, a pyrimidinyl group or a pyridazinyl group, each of which is optionally substituted by an oxo group, (ix) a pyrazolyloxy group optionally substituted by 1 to 3 C_{1-6} alkyl groups, (x) a C_{1-6} alkyl-carbonyl group, (xi) a C_{1-6} alkoxy-carbonyl group, (xii) a C_{1-6} alkyl-carbonyloxy group, (xiii) a C_{1-6} alkylsulfonyl group, (xiv) a mono- or di-C_{1-6} alkylamino group, (xv) a C_{1-6} alkyl-carbonylamino group and (xvi) a (C_{1-6} alkyl) (C_{1-6} alkyl-carbonyl) amino group,

(3) a C_{3-10} cycloalkyl-carbonyl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a cyano group, a hydroxy group, an oxo group and a C_{1-6} alkyl group,

(4) a C_{1-6} alkoxy-carbonyl group optionally substituted by 1 to 6 substituents selected from deuterium, a halogen atom and a C_{6-14} aryl group,

(5) a C_{3-10} cycloalkyloxy-carbonyl group optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group,

(6) a C_{6-14} aryl-carbonyl group optionally substituted by 1 to 3 substituents selected from a halogen atom and a C_{6-14} aryl group,

(7) a C_{6-14} aryloxy-carbonyl group,

(8) a furylcarbonyl group, a thienylcarbonyl group, a pyrazolylcarbonyl group, an isoxazolylcarbonyl group or a pyridylcarbonyl group, each of which is optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group,

(9) an azetidinylcarbonyl group, an oxetanylcarbonyl group, a pyrrolidinylcarbonyl group, a tetrahydrofuranylcarbonyl group, a tetrahydropyranylcarbonyl group or a morpholinylcarbonyl group, each of which is optionally substituted by 1 to 3 substituents selected from an oxo group, a C_{1-6} alkyl-carbonyl group, a C_{1-6} alkoxy-carbonyl group and a C_{1-6} alkylsulfonyl group,

(10) a mono- or di-C_{1-6} alkyl-carbamoyl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a cyano group, a hydroxy group and a C_{1-6} alkoxy group,

(11) a mono- or di-C_{3-10} cycloalkyl-carbamoyl group,

(12) a mono- or di-C_{6-14} aryl-carbamoyl group,

(13) a C_{1-6} alkylsulfonyl group,

(14) a C_{3-10} cycloalkylsulfonyl group,

(15) a C_{6-14} arylsulfonyl group optionally substituted by 1 to 3 halogen atoms,

(16) a thienylsulfonyl group, a pyrazolylsulfonyl group, an imidazolylsulfonyl group, a pyridylsulfonyl group or a dihydrochromenylsulfonyl group, each of which is optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group,

(17) a mono- or di-C_{1-6} alkyl-sulfamoyl group or

(18) a C_{1-6} alkyl-carbonyl-carbonyl group;

R^2 is a C_{3-6} cycloalkyl group, a pyrrolidinyl group, a piperidinyl group or a dioxanyl group, each of which is optionally substituted by 1 to 3 substituents selected from

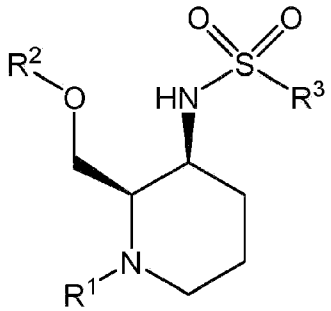
1. (1) deuterium,
2. (2) a halogen atom,
3. (3) a hydroxy group,
4. (4) a C_{1-6} alkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom and a C_{6-14} aryl group,
5. (5) a C_{3-10} cycloalkyl group,

6. (6) a C_{1-6} alkoxy group optionally substituted by a C_{3-10} cycloalkyl group,
7. (7) a C_{6-14} aryl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a cyano group, a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms and a hydroxy group,
8. (8) a C_{6-14} aryloxy group,
9. (9) a tri-C_{1-6} alkylsilyloxy group,
10. (10) a pyrazolyl group, a thiazolyl group, a pyridyl group, a pyrimidinyl group, a quinazolinyl group, a benzothiazolyl group or an isoquinolinyl group, each of which is optionally substituted by 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkyl group and a C_{1-6} alkoxy group, and
11. (11) a C_{6-14} aryl-carbonyl group; and

R^3 is a C_{1-6} alkyl group, or a mono- or di-C_{1-6} alkylamino group,

or a salt thereof.

2. [2] The present invention further relates to a compound represented by the formula:



(II)

wherein

R^1 is

1. (1) a hydrogen atom,
2. (2) a C_{1-6} alkyl-carbonyl group optionally substituted by 1 to 7 substituents selected from
   (i) a halogen atom, (ii) a cyano group, (iii) a hydroxy group, (iv) a C_{3-10} cycloalkyl group, (v) a C_{1-6} alkoxy group, (vi) a C_{6-14} aryl group, (vii) a C_{6-14} aryloxy group, (viii) a pyrazolyl group, a thiazolyl group, a pyrimidinyl group or a pyridazinyl group, each of which is optionally substituted by an oxo group, (ix) a pyrazolyloxy group optionally substituted by 1 to 3 C_{1-6} alkyl groups, (x) a C_{1-6} alkyl-carbonyl group, (xi) a C_{1-6} alkoxy-carbonyl group, (xii) a C_{1-6} alkyl-carbonyloxy group, (xiii) a C_{1-6} alkylsulfonyl group, (xiv) a mono- or di-C_{1-6} alkylamino group, (xv) a C_{1-6} alkyl-carbonylamino group and (xvi) a (C_{1-6} alkyl) (C_{1-6} alkyl-carbonyl) amino group,
3. (3) a C_{3-10} cycloalkyl-carbonyl group optionally substituted by 1 to 3 substituents

selected from a halogen atom, a cyano group, a hydroxy group, an oxo group and a C_{1-6} alkyl group,

4. (4) a C_{1-6} alkoxy-carbonyl group optionally substituted by 1 to 6 substituents selected from deuterium, a halogen atom and a C_{6-14} aryl group,
5. (5) a C_{3-10} cycloalkyloxy-carbonyl group optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group,
6. (6) a C_{6-14} aryl-carbonyl group optionally substituted by 1 to 3 substituents selected from a halogen atom and a C_{6-14} aryl group,
7. (7) a C_{6-14} aryloxy-carbonyl group,
8. (8) a furylcarbonyl group, a thienylcarbonyl group, a pyrazolylcarbonyl group, an isoxazolylcarbonyl group or a pyridylcarbonyl group, each of which is optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group,
9. (9) an azetidinylcarbonyl group, an oxetanylcarbonyl group, a pyrrolidinylcarbonyl group, a tetrahydrofuranylcarbonyl group, a tetrahydropyranylcarbonyl group or a morpholinylcarbonyl group, each of which is optionally substituted by 1 to 3 substituents selected from an oxo group, a C_{1-6} alkyl-carbonyl group, a C_{1-6} alkoxy-carbonyl group and a C_{1-6} alkylsulfonyl group,
10. (10) a mono- or di-C_{1-6} alkyl-carbamoyl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a cyano group, a hydroxy group and a C_{1-6} alkoxy group,
11. (11) a mono- or di-C_{3-10} cycloalkyl-carbamoyl group,
12. (12) a mono- or di-C_{6-14} aryl-carbamoyl group,
13. (13) a C_{1-6} alkylsulfonyl group,
14. (14) a C_{3-10} cycloalkylsulfonyl group,
15. (15) a C_{6-14} arylsulfonyl group optionally substituted by 1 to 3 halogen atoms,
16. (16) a thienylsulfonyl group, a pyrazolylsulfonyl group, an imidazolylsulfonyl group, a pyridylsulfonyl group or a dihydrochromenylsulfonyl group, each of which is optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group,
17. (17) a mono- or di-C_{1-6} alkyl-sulfamoyl group or
18. (18) a C_{1-6} alkyl-carbonyl-carbonyl group;

R^2 is a C_{3-6} cycloalkyl group, a pyrrolidinyl group, a piperidinyl group or a dioxanyl group, each of which is optionally substituted by 1 to 3 substituents selected from

1. (1) deuterium,
2. (2) a halogen atom,
3. (3) a hydroxy group,
4. (4) a C_{1-6} alkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom and a C_{6-14} aryl group,
5. (5) a C_{3-10} cycloalkyl group,
6. (6) a C_{1-6} alkoxy group optionally substituted by a C_{3-10} cycloalkyl group,

7. (7) a C_{6-14} aryl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a cyano group, a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms and a hydroxy group,
8. (8) a C_{6-14} aryloxy group,
9. (9) a tri-C_{1-6} alkylsilyloxy group,
10. (10) a pyrazolyl group, a thiazolyl group, a pyridyl group, a pyrimidinyl group, a quinazolinyl group, a benzothiazolyl group or an isoquinolinyl group, each of which is optionally substituted by 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkyl group and a C_{1-6} alkoxy group, and
11. (11) a C_{6-14} aryl-carbonyl group; and

R^3 is a C_{1-6} alkyl group, or a mono- or di-C_{1-6} alkylamino group,

or a salt thereof;

for use in therapy.

[Effect of the Invention]

[0023] The compound of the present invention has an orexin type 2 receptor agonist activity, and is useful as a prophylactic or therapeutic agent for narcolepsy.

[Brief Description of the Drawings]

[0024] Fig.1 is a powder X-ray diffraction chart of the crystals obtained in Example 5A.

(Detailed Description of the Invention)

[0025] 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.

[0026] In the present specification, examples of the "halogen atom" include fluorine, chlorine, bromine and iodine.

[0027] In the present specification, examples of the "C_{1-6} alkyl group" include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl and 2-ethylbutyl.

[0028] In the present specification, examples of the "C_{2-6} alkenyl group" include ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl and 5-hexenyl.

[0029] In the present specification, examples of the "C_{3-10} cycloalkyl group" include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl and adamantyl.

[0030] In the present specification, examples of the "C_{6-14} aryl group" include phenyl, 1-naphthyl, 2-naphthyl, 1-anthryl, 2-anthryl and 9-anthryl.

[0031] In the present specification, examples of the "C_{1-6} alkoxy group" include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy and hexyloxy.

[0032] In the present specification, examples of the "C_{3-10} cycloalkyloxy group" include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and cyclooctyloxy.

[0033] In the present specification, examples of the "C_{1-6} alkyl-carbonyl group" include acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 3-methylbutanoyl, 2-methylbutanoyl, 2,2-dimethylpropanoyl, hexanoyl and heptanoyl.

[0034] In the present specification, examples of the "C_{1-6} alkoxy-carbonyl group" include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl and hexyloxycarbonyl.

[0035] In the present specification, examples of the "C_{6-14} aryl-carbonyl group" include benzoyl, 1-naphthoyl and 2-naphthoyl.

[0036] In the present specification, examples of the "mono- or di-C_{1-6} alkyl-carbamoyl group" include methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl and N-ethyl-N-methylcarbamoyl.

[0037] In the present specification, examples of the "C_{1-6} alkylsulfonyl group" include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, sec-butylsulfonyl and tert-butylsulfonyl.

[0038] In the present specification, examples of the "C_{6-14} arylsulfonyl group" include phenylsulfonyl, 1-naphthylsulfonyl and 2-naphthylsulfonyl.

[0039] In the present specification, examples of the "C_{3-6} cycloalkyl group" include the above-mentioned "C_{3-10} cycloalkyl group" wherein the carbon number is 3 to 6.

[0040] In the present specification, examples of the "mono- or di-C_{1-6} alkylamino group" include an amino group mono- or disubstituted by the above-mentioned "C_{1-6} alkyl group". When it is a di-C_{1-6} alkylamino group, two C_{1-6} alkyl groups may be the same or different (e.g., N-ethyl-N-methylamino).

[0041] The definition of each symbol in the formula (II) is described in detail below.

[0042] R^1 is (1) a hydrogen atom, (2) a C_{1-6} alkyl-carbonyl group (e.g., methylcarbonyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, isobutylcarbonyl, tert-butylcarbonyl, neopentylcarbonyl) optionally substituted by 1 to 7 substituents selected from (i) a halogen atom (e.g., fluorine atom), (ii) a cyano group, (iii) a hydroxy group, (iv) a C_{3-10} cycloalkyl group (e.g., cyclopropyl), (v) a C_{1-6} alkoxy group (e.g., methoxy), (vi) a C_{6-14} aryl group (e.g., phenyl), (vii) a C_{6-14} aryloxy group (e.g., phenoxy), (viii) a pyrazolyl group, a thiazolyl group, a pyrimidinyl group, or a pyridazinyl group, each of which is optionally substituted by an oxo group, (ix) a pyrazolyloxy group optionally substituted by 1 to 3 C_{1-6} alkyl groups (e.g., methyl), (x) a C_{1-6} alkyl-carbonyl group (e.g., methylcarbonyl), (xi) a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl), (xii) a C_{1-6} alkyl-carbonyloxy group (e.g., methylcarbonyloxy), (xiii) a C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl), (xiv) a mono- or di-C_{1-6} alkylamino group (e.g., dimethylamino), (xv) a C_{1-6} alkyl-carbonylamino group (e.g., acetylamino) and (xvi) a (C_{1-6} alkyl) (C_{1-6} alkyl-carbonyl) amino group (e.g., N-acetyl-N-methylamino), (3) a C_{3-10} (preferably C_{3-6})cycloalkyl-carbonyl group (e.g., cyclopropanecarbonyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a cyano group, a hydroxy group, an oxo group and a C_{1-6} alkyl group (e.g., methyl), (4) a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl) optionally substituted by 1 to 6 substituents selected from deuterium, a halogen atom (e.g., fluorine atom) and a C_{6-14} aryl group (e.g., phenyl), (5) a C_{3-10} cycloalkyloxy-carbonyl group (e.g., cyclopropyloxycarbonyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group (e.g., methyl), (6) a C_{6-14} aryl-carbonyl group (e.g., phenylcarbonyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom, chlorine atom) and a C_{6-14} aryl group (e.g., phenyl), (7) a C_{6-14} aryloxy-carbonyl group (e.g., phenyloxycarbonyl), (8) a furylcarbonyl group, a thienylcarbonyl group, a pyrazolylcarbonyl group, a isoxazolylcarbonyl group, a pyridylcarbonyl group, each of which is optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group (e.g., methyl), (9) an azetidinylcarbonyl group, an oxetanylcarbonyl group, a pyrrolidinylcarbonyl group, a tetrahydrofuranylcarbonyl group, a tetrahydropyranylcarbonyl group, a morpholinylcarbonyl group, each of which is optionally substituted by 1 to 3 substituents selected from an oxo group, a C_{1-6} alkyl-carbonyl group (e.g., methylcarbonyl), a C_{1-6} alkoxy-carbonyl group (e.g.,

tert-butoxycarbonyl) and a C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl), (10) a mono- or di-C_{1-6} alkyl-carbamoyl group (e.g., methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, dimethylcarbamoyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a cyano group, a hydroxy group and a C_{1-6} alkoxy group (e.g., methoxy), (11) a mono- or di-C_{3-10} cycloalkyl-carbamoyl group (e.g., cyclopropylcarbamoyl), (12) a mono- or di-C_{6-14} aryl-carbamoyl group (e.g., phenylcarbamoyl), (13) a C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl), (14) a C_{3-10} cycloalkylsulfonyl group (e.g., cyclopropylsulfonyl), (15) a C_{6-14} arylsulfonyl group (e.g., phenylsulfonyl) optionally substituted by 1 to 3 halogen atoms (e.g., chlorine atom), (16) a thienylsulfonyl group, a pyrazolylsulfonyl group, a imidazolylsulfonyl group, a pyridylsulfonyl group, a dihydrochromenylsulfonyl group, each of which is optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group (e.g., methyl), (17) a mono- or di-C_{1-6} alkyl-sulfamoyl group (e.g., dimethylsulfamoyl) or (18) a C_{1-6} alkyl-carbonyl-carbonyl group (e.g., methylcarbonylcarbonyl).

[0043] In another embodiment of the present invention, R^1 is preferably a C_{1-6} alkyl-carbonyl group, a C_{1-6} alkoxy-carbonyl group, a C_{3-6} cycloalkyl-carbonyl group or a mono- or di-C_{1-6} alkyl-carbamoyl group optionally substituted by one hydroxy group.

[0044] In yet another embodiment of the present invention, R^1 is preferably a hydrogen atom.

[0045] In another embodiment of the present invention, R^1 is preferably (1) a hydrogen atom, (2) a C_{1-6} alkyl-carbonyl group optionally substituted by a hydroxy group, (3) a cyclopropanecarbonyl group, (4) a C_{1-6} alkoxy-carbonyl group or (5) a mono- or di-C_{1-6} alkyl-carbamoyl group.

[0046] In another embodiment of the present invention, R^1 is preferably (1) a C_{1-6} alkyl-carbonyl group optionally substituted by a hydroxy group, (2) a C_{1-6} alkoxy-carbonyl group or (3) a mono- or di-C_{1-6} alkyl-carbamoyl group.

[0047] In another embodiment of the present invention, R^1 is preferably a C_{1-6} alkoxy-carbonyl group (preferably methoxycarbonyl).

[0048] In another embodiment of the present invention, R^1 is preferably a C_{1-6} alkyl-carbonyl group optionally substituted by a hydroxy group.

[0049] In another embodiment of the present invention, R^1 is preferably a mono- or di-C_{1-6} alkyl-carbamoyl group.

[0050] In the present specification, when the C_{3-6} cycloalkyl group, pyrrolidinyl group,

piperidinyl group or dioxanyl group for R^2 has two substituents on one carbon constituting the C_{3-6} cycloalkyl group, pyrrolidinyl group, piperidinyl group or dioxanyl group, it includes an embodiment wherein said two substituents are bonded to each other to form a spiro ring system (e.g., 3H-spiro[2-benzofuran-1,1'-cyclohexane]-4'-yl, 1,4-dioxaspiro[4.5]dec-8-yl) together with the C_{3-6} cycloalkyl group, pyrrolidinyl group, piperidinyl group or dioxanyl group.

R^2 is a C_{3-6} cycloalkyl group, a pyrrolidinyl group, a piperidinyl group or a dioxanyl group, each of which is optionally substituted by 1 to 3 substituents selected from (1) deuterium, (2) a halogen atom, (3) a hydroxy group, (4) a C_{1-6} alkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom and a C_{6-14} aryl group, (5) a C_{3-10} cycloalkyl group, (6) a C_{1-6} alkoxy group optionally substituted by a C_{3-10} cycloalkyl group, (7) a C_{6-14} aryl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a cyano group, a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms and a hydroxy group, (8) a C_{6-14} aryloxy group, (9) a tri-C_{1-6} alkylsilyloxy group, (10) a pyrazolyl group, a thiazolyl group, a pyridyl group, a pyrimidinyl group, quinazolinyl group, a benzothiazolyl group or an isoquinolinyl group, each of which is optionally substituted by 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkyl group and a C_{1-6} alkoxy group, and (11) a C_{6-14} aryl-carbonyl group.

[0051] In another embodiment of the present invention, R^2 is preferably a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a pyrrolidinyl group, a piperidinyl group or a dioxanyl group, each of which is optionally substituted by 1 to 3 substituents selected from (1) deuterium, (2) a halogen atom, (3) a hydroxy group, (4) a C_{1-6} alkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom and a phenyl group, (5) a cyclohexyl group, (6) a C_{1-6} alkoxy group optionally substituted by a cyclopropyl group, (7) a phenyl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a cyano group, a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms and a hydroxy group, (8) a phenoxy group, (9) a tri-C_{1-6} alkylsilyloxy group, (10) a pyrazolyl group, a thiazolyl group, a pyridyl group, a pyrimidinyl group, a quinazolinyl group, a benzothiazolyl group or an isoquinolinyl group, each of which is optionally substituted by 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkyl group and a C_{1-6} alkoxy group, and (11) a benzoyl group.

[0052] In another embodiment of the present invention, R^2 is preferably (A) a cyclohexyl group optionally substituted by 1 to 3 substituents selected from (1) a C_{1-6} alkyl group and (2) a phenyl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms and a C_{1-6} alkoxy group or (B) a piperidinyl group optionally substituted by 1 to 3 pyrimidinyl groups.

[0053] In another embodiment of the present invention, R^2 is preferably a cyclohexyl group optionally substituted by 1 to 3 substituents selected from (1) a C_{1-6} alkyl group and (2) a

phenyl group optionally substituted by 1 to 3 halogen atoms.

[0054] In another embodiment of the present invention, R^2 is preferably a cyclohexyl group optionally substituted by a phenyl group.

[0055] In another embodiment of the present invention, R^2 is preferably a cyclohexyl group optionally substituted by a phenyl group optionally substituted by 1 to 3 halogen atoms.

[0056] In another embodiment of the present invention, R^2 is preferably a cyclohexyl group optionally substituted by a C_{1-6} alkyl group.

[0057] R^3 is a C_{1-6} alkyl group (e.g., methyl, ethyl, propyl, isopropyl, isobutyl), or a mono- or di-C_{1-6} alkylamino group (e.g., ethylamino, dimethylamino), more preferably, a C_{1-6} alkyl group (e.g., methyl), or a mono- or di-C_{1-6} alkylamino group (e.g., dimethylamino).

[0058] In another embodiment of the present invention, R^3 is preferably a C_{1-6} alkyl group or a di-C_{1-6} alkylamino group, more preferably a C_{1-6} alkyl group (preferably methyl).

[0059] As a preferable embodiment of compound (II), the following compounds can be mentioned.

[Compound II-2]

[0060] Compound (II) wherein R^1 is (1) a hydrogen atom, (2) a C_{1-6} alkyl-carbonyl group (e.g., methylcarbonyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, isobutylcarbonyl, tert-butylcarbonyl, neopentylcarbonyl) optionally substituted by 1 to 7 substituents selected from (i) a halogen atom (e.g., fluorine atom), (ii) a cyano group, (iii) a hydroxy group, (iv) a C_{3-10} cycloalkyl group (e.g., cyclopropyl), (v) a C_{1-6} alkoxy group (e.g., methoxy), (vi) a C_{6-14} aryl group (e.g., phenyl), (vii) a C_{6-14} aryloxy group (e.g., phenoxy), (viii) a pyrazolyl group, a thiazolyl group, a pyrimidinyl group, or a pyridazinyl group, each of which is optionally substituted by an oxo group, (ix) a pyrazolyloxy group optionally substituted by 1 to 3 C_{1-6} alkyl groups (e.g., methyl), (x) a C_{1-6} alkyl-carbonyl group (e.g., methylcarbonyl), (xi) a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl), (xii) a C_{1-6} alkyl-carbonyloxy group (e.g., methylcarbonyloxy), (xiii) a C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl), (xiv) a mono- or di-C_{1-6} alkylamino group (e.g., dimethylamino), (xv) a C_{1-6} alkyl-carbonylamino group (e.g., acetylamino) and (xvi) a (C_{1-6} alkyl) (C_{1-6} alkyl-carbonyl) amino group (e.g., N-acetyl-N-methylamino), (3) a C_{3-10} (preferably C_{3-6}) cycloalkyl-carbonyl group (e.g., cyclopropanecarbonyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom),

a cyano group, a hydroxy group, an oxo group and a C_{1-6} alkyl group (e.g., methyl), (4) a C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl) optionally substituted by 1 to 6 substituents selected from deuterium, a halogen atom (e.g., fluorine atom) and a C_{6-14} aryl group (e.g., phenyl), (5) a C_{3-10} cycloalkyloxy-carbonyl group (e.g., cyclopropyloxycarbonyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group (e.g., methyl), (6) a C_{6-14} aryl-carbonyl group (e.g., phenylcarbonyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom, chlorine atom) and a C_{6-14} aryl group (e.g., phenyl), (7) a C_{6-14} aryloxy-carbonyl group (e.g., phenyloxycarbonyl), (8) a furylcarbonyl group, a thienylcarbonyl group, a pyrazolylcarbonyl group, an isoxazolylcarbonyl group, or a pyridylcarbonyl group, each of which is optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group (e.g., methyl), (9) an azetidinylcarbonyl group, an oxetanylcarbonyl group, a pyrrolidinylcarbonyl group, a tetrahydrofuranylcarbonyl group, a tetrahydropyranylcarbonyl group, or a morpholinylcarbonyl group, each of which is optionally substituted by 1 to 3 substituents selected from an oxo group, a C_{1-6} alkyl-carbonyl group (e.g., methylcarbonyl), a C_{1-6} alkoxy-carbonyl group (e.g., tert-butoxycarbonyl) and a C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl), (10) a mono- or di-C_{1-6} alkyl-carbamoyl group (e.g., methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, dimethylcarbamoyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom), a cyano group, a hydroxy group and a C_{1-6} alkoxy group (e.g., methoxy), (11) a mono- or di-C_{3-10} cycloalkyl-carbamoyl group (e.g., cyclopropylcarbamoyl), (12) a mono- or di-C_{6-14} aryl-carbamoyl group (e.g., phenylcarbamoyl), (13) a C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl), (14) a C_{3-10} cycloalkylsulfonyl group (e.g., cyclopropylsulfonyl), (15) a C_{6-14} arylsulfonyl group (e.g., phenylsulfonyl) optionally substituted by 1 to 3 halogen atoms (e.g., chlorine atom), (16) a thienylsulfonyl group, a pyrazolylsulfonyl group, an imidazolylsulfonyl group, a pyridylsulfonyl group, a dihydrochromenylsulfonyl group, each of which is optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group (e.g., methyl), (17) a mono- or di-C_{1-6} alkyl-sulfamoyl group (e.g., dimethylsulfamoyl) or (18) a C_{1-6} alkyl-carbonyl-carbonyl group (e.g., methylcarbonylcarbonyl);

R^2 is a C_{3-6} cycloalkyl group (e.g., cyclobutyl, cyclopentyl, cyclohexyl) or a pyrrolidinyl group, a piperidinyl group, or a dioxanyl group, each of which is optionally substituted by 1 to 3 substituents selected from (1) deuterium, (2) a halogen atom (e.g., fluorine atom), (3) a hydroxy group, (4) a C_{1-6} alkyl group (e.g., methyl, isopropyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom) and a C_{6-14} aryl group (e.g., phenyl), (5) a C_{3-10} cycloalkyl group (e.g., cyclohexyl), (6) a C_{1-6} alkoxy group (e.g., methoxy) optionally substituted by a C_{3-10} cycloalkyl group (e.g., cyclopropyl), (7) a C_{6-14} aryl group (e.g., phenyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom, chlorine atom), a cyano group, a C_{1-6} alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom) and a C_{1-6} alkoxy group (e.g., methoxy) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine atom), (8) a C_{6-14}

aryloxy group (e.g., phenoxy), (9) a tri-C_{1-6} alkylsilyl group (e.g., tert-butyl(dimethyl)silyl) and (10) a pyrazolyl group, a thiazolyl group, a pyridyl group, a pyrimidinyl group, a quinazolinyl group, a benzothiazolyl group, or an isoquinolinyl group, each of which is optionally substituted by 1 to 3 substituents selected from a halogen atom (e.g., fluorine atom, chlorine atom), C_{1-6} alkyl group (e.g., methyl) and a C_{1-6} alkoxy group (e.g., methoxy); and

R^3 is a C_{1-6} alkyl group (e.g., methyl), or a mono- or di-C_{1-6} alkylamino group (e.g., dimethylamino).

[Compound II-7]

Compound (II), wherein R^1 is

[0061]

1. (1) a hydrogen atom,
2. (2) a C_{1-6} alkyl-carbonyl group optionally substituted by 1 to 7 substituents selected from (i) a halogen atom, (ii) a cyano group, (iii) a hydroxy group, (iv) a cyclopropyl group, (v) a C_{1-6} alkoxy group, (vi) a phenyl group, (vii) a phenoxy group, (viii) a pyrazolyl group, a thiazolyl group, a pyrimidinyl group or a pyridazinyl group, each of which is optionally substituted by an oxo group, (ix) a pyrazolyloxy group optionally substituted by 1 to 3 C_{1-6} alkyl groups, (x) a C_{1-6} alkyl-carbonyl group, (xi) a C_{1-6} alkoxy-carbonyl group, (xii) a C_{1-6} alkyl-carbonyloxy group, (xiii) a C_{1-6} alkylsulfonyl group, (xiv) a mono- or di-C_{1-6} alkylamino group, (xv) a C_{1-6} alkyl-carbonylamino group and (xvi) a (C_{1-6} alkyl) (C_{1-6} alkyl-carbonyl) amino group,
3. (3) a cyclopropanecarbonyl group, a cyclobutanecarbonyl group, a cyclopentanecarbonyl group or a cyclohexanecarbonyl group, each of which is optionally substituted by 1 to 3 substituents selected from a halogen atom, a cyano group, a hydroxy group, an oxo group and a C_{1-6} alkyl group,
4. (4) a C_{1-6} alkoxy-carbonyl group optionally substituted by 1 to 6 substituents selected from deuterium, a halogen atom and a phenyl group,
5. (5) a cyclopropyloxycarbonyl group optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group,
6. (6) a phenylcarbonyl group optionally substituted by 1 to 3 substituents selected from a halogen atom and a phenyl group,
7. (7) a phenyloxycarbonyl group,
8. (8) a furylcarbonyl group, a thienylcarbonyl group, a pyrazolylcarbonyl group, an isoxazolylcarbonyl group or a pyridylcarbonyl group, each of which is optionally

substituted by 1 to 3 C_{1-6} alkyl groups,

9. (9) an azetidinylcarbonyl group, an oxetanylcarbonyl group, a pyrrolidinylcarbonyl group, a tetrahydrofuranylcarbonyl group, a tetrahydropyranylcarbonyl group or a morpholinylcarbonyl group, each of which is optionally substituted by 1 to 3 substituents selected from an oxo group, a C_{1-6} alkyl-carbonyl group, a C_{1-6} alkoxy-carbonyl group and a C_{1-6} alkylsulfonyl group,
10. (10) a mono- or di-C_{1-6} alkyl-carbamoyl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a cyano group, a hydroxy group and a C_{1-6} alkoxy group,
11. (11) a cyclopropylcarbamoyl group,
12. (12) a phenylcarbamoyl group,
13. (13) a C_{1-6} alkylsulfonyl group,
14. (14) a cyclopropylsulfonyl group,
15. (15) a phenylsulfonyl group optionally substituted by 1 to 3 halogen atoms,
16. (16) a thienylsulfonyl group, a pyrazolylsulfonyl group, an imidazolylsulfonyl group, a pyridylsulfonyl group or a dihydrochromenylsulfonyl group, each of which is optionally substituted by 1 to 3 C_{1-6} alkyl groups,
17. (17) a dimethylsulfamoyl group or
18. (18) a C_{1-6} alkyl-carbonyl-carbonyl group;

R^2 is a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a pyrrolidinyl group, a piperidinyl group or a dioxanyl group, each of which is optionally substituted by 1 to 3 substituents selected from

1. (1) deuterium,
2. (2) a halogen atom,
3. (3) a hydroxy group,
4. (4) a C_{1-6} alkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom and a phenyl group,
5. (5) a cyclohexyl group,
6. (6) a C_{1-6} alkoxy group optionally substituted by a cyclopropyl group,
7. (7) a phenyl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a cyano group, a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, a C_{1-6} alkoxy group optionally substituted by 1 to 3 halogen atoms and a hydroxy group,
8. (8) a phenoxy group,
9. (9) a tri-C_{1-6} alkylsilyloxy group,
10. (10) a pyrazolyl group, a thiazolyl group, a pyridyl group, a pyrimidinyl group, a quinazolinyl group, a benzothiazolyl group or an isoquinolinyl group, each of which is optionally substituted by 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkyl group and a C_{1-6} alkoxy group, and
11. (11) a benzoyl group; and

R^3 is a C_{1-6} alkyl group, or a mono- or di-C_{1-6} alkylamino group.

[Compound II-10]

[0062]

Compound (II), wherein R^1 is a C_{1-6} alkoxy-carbonyl group;

R^2 is a cyclohexyl group optionally substituted by a phenyl group; and

R^3 is a C_{1-6} alkyl group.

[Compound II-11]

[0063]

Compound (II), wherein R^1 is a C_{1-6} alkyl-carbonyl group optionally substituted by a hydroxy group;

R^2 is a cyclohexyl group optionally substituted by a phenyl group optionally substituted by 1 to 3 halogen atoms; and

R^3 is a C_{1-6} alkyl group.

[Compound II-12]

[0064]

Compound (II), wherein R^1 is a mono- or di-C_{1-6} alkyl-carbamoyl group;

R^2 is a cyclohexyl group optionally substituted by a C_{1-6} alkyl group; and

R^3 is a C_{1-6} alkyl group.

[0065] Specific examples of compound (II) include the compounds of the below-mentioned Examples 1 - 372, of which

(2R,3S)-N-ethyl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide (Example 2),

N-((2R,3S)-1-acetyl-2-(((cis-4-phenylcyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (Example 4),

methyl (2R,3S)-3-((methylsulfonyl)amino)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)piperidine-1-carboxylate (Example 5),

N-((2R,3S)-1-acetyl-2-(((cis-4-(3,5-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (Example 8),

methyl (2R,3S)-2-(((cis-4-(2,5-difluorophenyl)cyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate (Example 11),

N-((2R,3S)-1-acetyl-2-(((cis-4-(2,6-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (Example 14),

N-((2R,3S)-1-(cyclopropylcarbonyl)-2-(((cis-4-(3-fluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (Example 16),

N-((2R,3S)-1-acetyl-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (Example 19),

methyl (2R,3S)-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate (Example 20),

N-((2R,3S)-1-acetyl-2-(((cis-4-(2,3,6-trifluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (Example 22),

N-((2R,3S)-1-acetyl-2-(((cis-4-(2-(trifluoromethyl)phenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (Example 24),

N-((2R,3S)-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)methyl)-1-glycoloylpiperidin-3-yl)methanesulfonamide (Example 25),

N-((2R,3S)-1-(cyclopropylcarbonyl)-2-(((cis-4-(2-methoxyphenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (Example 28),

isopropyl (2R,3S)-3-((dimethylsulfamoyl)amino)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate (Example 29),

(2R,3S)-N-ethyl-3-((methylsulfonyl)amino)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)piperidine-1-carboxamide (Example 30),

N-((2R,3S)-1-(cyclopropylcarbonyl)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (Example 31),

methyl (2R,3S)-3-((methylsulfonyl)amino)-2-(((cis-4-(2-(trifluoromethyl)phenyl)cyclohexyl)oxy)methyl)piperidine-1-carboxylate (Example 32),

N-((2R,3S)-2-(((cis-4-(3,5-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (Example 7),

N-((2R,3S)-2-(((cis-4-(2,6-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (Example 13),

N-((2R,3S)-2-(((cis-4-(3-fluorophenyl)cyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide (Example 15), and

N-((2R,3S)-1-glycoloyl-2-(((cis-4-(2,3,6-trifluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (Example 340)
are preferable.

[0066] As a salt of a compound represented by the formula (II), a pharmacologically acceptable salt is preferable, and examples 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.

[0067] Preferable examples of the salt with inorganic base include alkali metal salts such as sodium salt, potassium salt, alkaline earth metal salts such as calcium salt, magnesium salt, aluminum salt, or ammonium salt.

[0068] Preferable examples of the salt with organic base include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, tromethamine[tris(hydroxymethyl)methylamine], tert-butylamine, cyclohexylamine, benzylamine, dicyclohexylamine, N,N-dibenzylethylenediamine.

[0069] Preferable examples of the salt with inorganic acid include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid.

[0070] 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 acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid.

[0071] Preferable examples of the salt with basic amino acid include salts with arginine, lysine, ornithine.

[0072] Preferable examples of the salt with acidic amino acid include salts with aspartic acid, glutamic acid.

[0073] Compound (II) may be used as a prodrug. A prodrug of the compound (II) means a compound which is converted to the compound (II) of the present invention with a reaction due to an enzyme, an gastric acid under the physiological condition in the living body, that is, a compound which is converted to the compound (II) of the present invention with oxidation, reduction, hydrolysis according to an enzyme; a compound which is converted to the compound (II) of the present invention by hydrolysis due to gastric acid.

[0074] A prodrug of compound (II) may be a compound obtained by subjecting an amino group in compound (II) to an acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting an amino group in compound (II) to an eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation and tert-butylation); a compound obtained by subjecting a hydroxy group in compound (II) to an acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting an hydroxy group in compound (II) to an acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation, dimethylaminomethylcarbonylation); a compound obtained by subjecting a carboxyl group in compound (II) to an esterification or amidation (e.g., a compound obtained by subjecting a carboxyl group in compound (II) 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). Any of these compounds can be produced from compound (II) by a method known *per se.*

[0075] A prodrug for compound (II) may also be one which is converted into compound (II) under a physiological condition, such as those described in IYAKUHIN no KAIHATSU (Development of Pharmaceuticals), Vol.7, Design of Molecules, p.163-198, Published by HIROKAWA SHOTEN (1990).

[0076] 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 aforementioned formula (II) can be mentioned.

[0077] Compound (II) may be labeled with an isotope (e.g., ^{3}H, ^{13}C, ^{14}C, ^{18}F, ^{35}S, ^{125}I).

[0078] Compound (II) 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.

[0079] Furthermore, compound (II) may be a hydrate or a non-hydrate, or a non-solvate (e.g., anhydride), or a solvate (e.g., hydrate).

[0080] Compound (II) also encompasses a deuterium conversion form wherein ^{1}H is converted to $^{2}H(D)$.

[0081] Furthermore, compound (II) 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 cocrystallization method known per se.

[0082] Compound (II) (hereinafter sometimes to be simply abbreviated as the compound of the present invention) or a prodrug thereof is low in its toxicity and can be used as it is or in the form of a pharmaceutical composition (also referred to as a medicament) by mixing with a pharmacologically acceptable carrier 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.

[0083] 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, isotonicity agent, buffer and soothing agent for liquid preparations; and preparation additives such as preservative, antioxidant, colorant, sweetening agent can be added as necessary.

[0084] 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 aluminum silicate and magnesium alumino metasilicate.

[0085] Preferable examples of the lubricant include magnesium stearate, calcium stearate, talc and colloidal silica.

[0086] Preferable examples of the binder include gelatinated starch, sucrose, gelatin, gum arabic, methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, crystalline cellulose, sucrose, D-mannitol, trehalose, dextrin, pullulan, hydroxypropylcellulose, hydroxypropylmethylcellulose and polyvinylpyrrolidone.

[0087] Preferable examples of the disintegrant include lactose, sucrose, starch, carboxymethylcellulose, calcium carboxymethylcellulose, croscarmellose sodium, sodium carboxymethyl starch, light anhydrous silicic acid and low-substituted hydroxypropylcellulose.

[0088] Preferable examples of the solvent include water for injection, physiological brine, Ringer's solution, alcohol, propylene glycol, polyethylene glycol, sesame oil, corn oil, olive oil and cottonseed oil.

[0089] Preferable examples of the solubilizing agent include polyethylene glycol, propylene glycol, D-mannitol, trehalose, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, sodium salicylate and sodium acetate.

[0090] Preferable examples of the suspending agent include surfactants such as stearyltriethanolamine, sodium lauryl sulfate, lauryl aminopropionate, lecithin, benzalkonium chloride, benzethonium chloride, glycerol monostearate; hydrophilic polymers such as poly(vinyl alcohol), polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, polysorbates; and polyoxyethylene hydrogenated castor oil.

[0091] Preferable examples of the isotonicity agent include sodium chloride, glycerol, D-mannitol, D-sorbitol and glucose.

[0092] Preferable examples of the buffer include buffers of phosphate, acetate, carbonate, citrate.

[0093] Preferable examples of the soothing agent include benzyl alcohol.

[0094] Preferable examples of the preservative include p-oxybenzoate esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

[0095] Preferable examples of the antioxidant include sulfite salts and ascorbate salts.

[0096] 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), water insoluble lake dyes (e.g., aluminum salt of the aforementioned aqueous food tar color), natural dyes (e.g., β-carotene, chlorophyll, red iron oxide).

[0097] Preferable examples of the sweetening agent include saccharin sodium, dipotassium glycyrrhizinate, aspartame and stevia.

[0098] Examples of the dosage form of the aforementioned pharmaceutical composition include oral preparations such as tablet (including sugar-coated tablet, film-coated tablet, sublingual tablet, orally disintegrating tablet), capsule (including soft capsule, microcapsule), granule, powder, troche, syrup, emulsion, suspension, films (e.g., orally disintegrable films); and parenteral agents such as injection (e.g., subcutaneous injection, intravenous injection, intramuscular injection, intraperitoneal injection, drip infusion), external preparation (e.g., dermal preparation, ointment), suppository (e.g., rectal suppository, vaginal suppository), pellet, nasal preparation, pulmonary preparation (inhalant), eye drop, which can be respectively safely administered orally or parenterally (e.g., topical, rectal, intravenous administration).

[0099] These preparations may be a release control preparation (e.g., sustained-release microcapsule) such as an immediate-release preparation, a sustained-release preparation.

[0100] 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.

[0101] While the content of the compound of the present invention in the pharmaceutical composition of the present invention varies depending on the dosage form, dose of the compound of the present invention, it is, for example, about 0.1 to 100 wt%.

[0102] When an oral preparation is produced, coating may be applied where necessary for the purpose of taste masking, enteric solubility or sustainability.

[0103] Examples of the coating base used for coating include sugar coating base, water-soluble film coating base, enteric film coating base, and sustained-release film coating base.

[0104] As the sugar coating base, sucrose is used, and one or more kinds selected from talc, precipitated calcium carbonate, gelatin, gum arabic, pullulan, carnauba wax may be further used in combination.

[0105] Examples of the water-soluble film coating base include cellulose polymers such as hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, methylhydroxyethylcellulose; synthetic polymers such as polyvinyl acetal diethylaminoacetate, aminoalkylmethacrylate copolymer E [Eudragit E (trade name)], polyvinylpyrrolidone; and polysaccharides such as pullulan.

[0106] Examples of the enteric film coating base include cellulose polymers such as hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylethylcellulose, cellulose acetate phthalate; 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 copolymer S [Eudragit S (trade name)]; and naturally-occurring substances such as shellac.

[0107] Examples of the sustained-release film coating base include cellulose polymers such as ethylcellulose; and acrylic acid polymers such as aminoalkylmethacrylate copolymer RS [Eudragit RS (trade name)], ethyl acrylate-methyl methacrylate copolymer suspension [Eudragit NE (trade name)].

[0108] Two or more kinds of the above-mentioned coating bases may be used in a mixture at an appropriate ratio. In addition, for example, light shielding agents such as titanium oxide, red ferric oxide may also be used during coating.

[0109] Since the compound of the present invention shows low toxicity (e.g., acute toxicity,

chronic toxicity, genetic 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).

[0110] Orexin type 2 receptors have been considered to be involved in a wide range of biological functions. This suggests that this receptor plays a role in diverse disease processes in humans or other species. The compound of the present invention is useful for treating, preventing, or ameliorating the risk of one or more of the following symptoms or diseases of various neurological and psychiatric diseases associated with one or more orexin type 2 receptors. That is, narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, narcolepsy syndrome accompanied by narcolepsy-like symptoms, hypersomnia syndrome accompanied by daytime hypersomnia (e.g., 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, 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, hyperinsulinar obesity, hyperplasmic obesity, hypop hyseal adiposity, hypoplasmic 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, Alzheimer, disturbance of consciousness such as coma, 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, 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, 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, arrhythmia, myocardial infarction, congestive cardiac failure, cardiac failure, coronary heart disease, cardiovascular disorder, sudden death, polycysticovarian disease, craniopharingioma, Prader-Willi syndrome, Froelich's syndrome, growth hormone deficient, normal mutant short stature, Turner's syndrome, 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, 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, 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 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 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 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, 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, 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) .

[0111] Particularly, the compound of the present invention is useful as a therapeutic or prophylactic drug for narcolepsy, idiopathic hypersomnia, hypersomnia, sleep apnea syndrome, 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's, obesity, insulin resistance syndrome, cardiac failure, diseases related to bone loss, sepsis, disturbance of consciousness such as coma, side effects and complications due to anesthesia, or as an anesthetic antagonist.

[0112] While the dose of the compound of the present invention varies depending on the subject of administration, administration route, target disease, symptom, 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 preferably 0.5 to 20 mg/kg body weight per dose. This amount is desirably administered in one to 3 portions daily.

[0113] The compound of the present invention can be used in combination with other drugs (hereinafter to be abbreviated as concomitant drug).

[0114] By combining the compound of the present invention and a concomitant drug, a superior effect, for example,

1. (1) the dose can be reduced as compared to single administration of the compound of the present invention or a concomitant drug,
2. (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),
3. (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. (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. (5) a synergistic effect can be afforded by a combined use of the compound of the present invention and a concomitant drug, can be achieved.

[0115] 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".

[0116] 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.

[0117] 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).

[0118] 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.

[0119] 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.

[0120] 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.

[0121] The content of additives such as a carrier 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.

[0122] Similar contents may be employed even when the compound of the present invention and a concomitant drug are separately formulated into preparations.

[0123] Examples of the concomitant drug include, but are not limited to, the following. A therapeutic drug for narcolepsy (e.g., methylphenidate, amphetamine, pemoline, phenelzine, protriptyline, sodium oxybate, modafinil, caffeine), antiobesity drug (amphetamine, benzfetamine, bromocriptine, bupropion, diethylpropion, exenatide, fenfluramine, liothyronine, liraglutide, mazindol, methamphetamine, octreotide, octreotide, orlistat, phendimetrazine, phendimetrazine, phenmetrazine, phentermine, Qnexa (registered trade mark), phenylpropanolamine, pramlintide, propylhexedrine, recombinant leptin, sibutramine, topiramate, zimelidine, zonisamide, Lorcaserin, metformin), acetylcholine esterase inhibitor (e.g., donepezil, rivastigmine, galanthamine, zanapezil, 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-biphenylyl)methoxy-2-[2-(N,N-dimethylamino)ethyl]tetralin, 6-(4-biphenylyl)methoxy-2-(N,N-dimethylamino)methyltetralin, 6-(4-biphenylyl)methoxy-2-(N,N-dipropylamino)methyltetralin, 2-(N,N-dimethylamino)methyl-6-(4'-methoxybiphenyl-4-yl)methoxytetralin, 6-(4-biphenylyl)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 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, brain function enhancer (e.g., aniracetam, 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., trihexyphenidyl, biperiden), COMT inhibitor (e.g., entacapone)], therapeutic drug for amyotrophic lateral sclerosis (e.g., riluzole, neurotrophic factor), therapeutic drug for abnormal behavior accompanying progress of

dementia, wandering (e.g., sedative, anti-anxiety drug), apoptosis 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-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 agents (meloxicam, tenoxicam, indomethacin, ibuprofen, celecoxib, rofecoxib, aspirin, indomethacin), steroid drug (dexamethasone, hexestrol, cortisone acetate), disease-modifying anti-rheumatic drug (DMARDs), anti-cytokine drug (e.g., TNF inhibitor, MAP kinase inhibitor), therapeutic agent 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; atypical antipsychotic agents such as clozapine, olanzapine, risperidone, aripiprazole; medicament acting on metabotropic glutamate receptor or ion channel conjugated-type glutamate receptor; phosphodiesterase inhibitor), benzodiazepines medicament (chlordiazepoxide, diazepam, potassium clorazepate, lorazepam, clonazepam, alprazolam), L-type calcium channel inhibitor (pregabalin), tricyclic or tetracyclic antidepressant (imipramine hydrochloride, amitriptyline hydrochloride, desipramine hydrochloride, clomipramine hydrochloride), selective serotonin reuptake inhibitor (fluvoxamine maleate, fluoxetine hydrochloride, citalopram hydrobromide, sertraline hydrochloride, paroxetine hydrochloride, escitalopram oxalate), serotonin-noradrenaline reuptake inhibitor (venlafaxine hydrochloride, duloxetine hydrochloride, desvenlafaxine hydrochloride), noradrenaline reuptake inhibitor (reboxetine mesylate), mirtazapine, trazodone hydrochloride, nefazodone hydrochloride, bupropion hydrochloride, setiptiline maleate, 5-HT_{1A} agonist, (buspirone hydrochloride, tandospirone citrate, osemozotan hydrocloride), 5-HT_{2A} antagonist, 5-HT_{2A} inverse agonist, 5-HT_3 antagonist (cyamemazine), heart non-selective β inhibitor (propranolol hydrochloride, oxprenolol hydrochloride), histamine H_1 antagonist (hydroxyzine hydrochloride), CRF antagonist, other antianxiety drug (meprobamate), tachykinin antagonist (MK-869, saredutant), medicament that acts on metabotropic glutamate receptor, CCK antagonist, β3 adrenaline antagonist (amibegron hydrochloride), GAT-1 inhibitor (tiagabine hydrochloride), N-type calcium channel inhibitor, carbonic anhydrase II inhibitor, NMDA glycine moiety agonist, NMDA antagonist (memantine), 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 sulfate, tranylcypromine sulfate, moclobemide), COMT inhibitor (entacapone), therapeutic drug for

bipolar disorder (lithium carbonate, sodium valproate, lamotrigine, riluzole, felbamate), cannabinoid CB1 antagonist (rimonabant), FAAH inhibitor, sodium channel inhibitor, anti-ADHD drug (methylphenidate hydrochloride, methamphetamine hydrochloride), 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, 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, 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 ALS (riluzole, neurotrophic factor), therapeutic drug for lipid abnormality such as cholesterol-lowering drug (statin series (pravastatin sodium, atorvastatin, simvastatin, rosuvastatin), fibrate (clofibrate), squalene synthetase inhibitor), therapeutic drug for abnormal behavior or suppressant of dromomania due to dementia (sedatives, antianxiety drug), antiobesity drug, 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.

[0124] Two or more kinds of the above-mentioned concomitant drug may be used in a mixture at an appropriate ratio.

[0125] 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 combined with a gene therapy method and applied as a combination therapy, or can also be used in combination with a treatment in psychiatric field without using drugs.

[0126] Examples of the antibody and vaccine preparation include vaccine preparation against angiotensin II, vaccine preparation against CETP, CETP antibody, antibody against TNFα 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. In addition, it can be used in combination with biologics relating to growth factors such as GH, IGF.

[0127] 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 NFκB decoy, 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 (e.g., growth factors such as HGF, VEGF), a treatment method using a gene relating to a protein involved in glucose metabolism and insulin resistance, antisense against cytokines such as TNF.

[0128] 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.

[0129] It can also be used in combination with various organ regeneration methods such as cardiac regeneration, renal regeneration, pancreatic regeneration, revascularization, 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).

[0130] The compound of the present invention can be administered orally, parenterally (e.g., intramuscular, intraperitoneal, intravenous, intraarterial, intraventricular, intracisternal injection or infusion; subcutaneous injection; or implant), and by topical route such as inhalation spray, intratracheal, nasal, vaginal, rectal, sublingual, subdermal, transdermal and ocular instillation administration, in a suitable unit dosage form containing a pharmaceutically acceptable conventional nontoxic carrier, adjuvant and vehicle suitable for each administration route. In addition to the treatment of warm-blooded animals such as mouse, rat, horse, bovine, sheep, dog, cat, monkey, the compound of the present invention is effective for use in human.

[0131] A pharmaceutical composition for the administration of the compound of the present invention may conveniently be given in a unit dosage form and may be prepared by any of the methods well known in the pharmaceutical field. All methods include a step of mixing the active ingredient and one or more carriers constituting the auxiliary components. Generally, a pharmaceutical composition is prepared by uniformly and completely admixing the active ingredient with liquid carrier or finely-divided solid carrier or both, and then molding the product into a desirable dosage form as necessary. In a pharmaceutical composition, the active compound of interest is included in an amount sufficient to produce a desired effect on the process or condition of a disease. As used herein, the term "composition" is intended to encompass a product comprising specified amounts of specified ingredients and all products obtained directly or indirectly from the combination of the specified amounts of the specified ingredients.

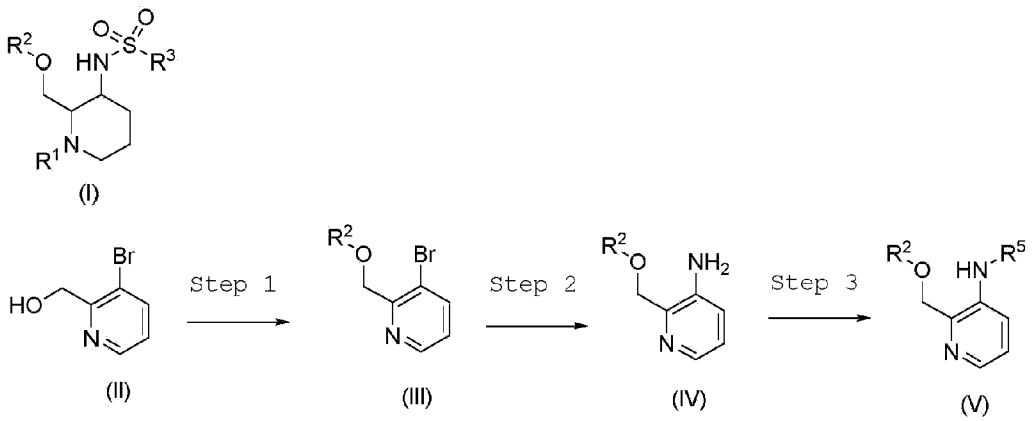
[0132] A pharmaceutical composition for oral use may be prepared according to any method known in the field relating to the manufacture of pharmaceutical compositions, and such composition may contain one or more agents selected from the group consisting of sweetener, flavor, colorant and preservative to provide a preparation having pharmaceutically high quality and good taste. A tablet contains an active ingredient in admixture with a pharmaceutically

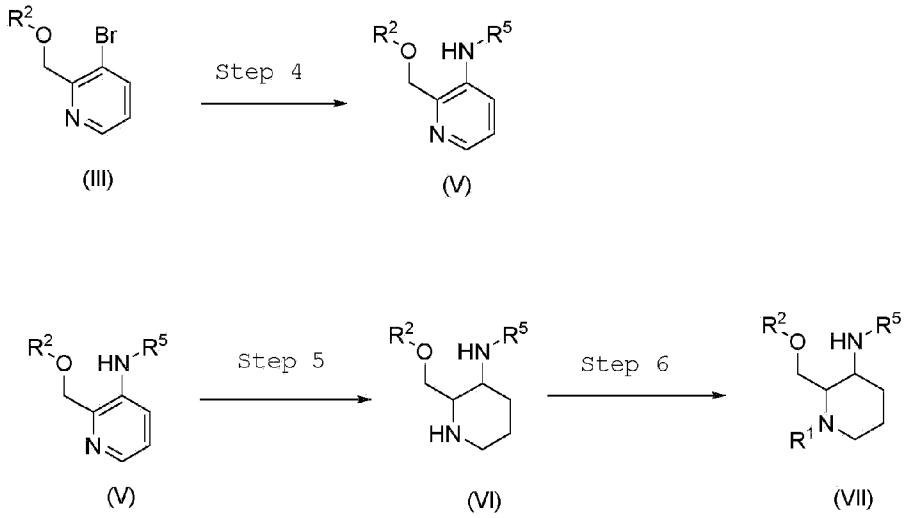
acceptable nontoxic excipient suitable for the manufacture of tablets. These excipients may be, for example, inert diluents such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, sodium phosphate; granulating agent and disintegrant such as cornstarch, alginic acid; binder such as starch, gelatin, acacia; and lubricant such as magnesium stearate, stearic acid, talc. Tablets may not be coated or coated by a known technique for delaying disintegration and absorption in the gastrointestinal tract, whereby a sustained action is provided over a longer period of time. A composition for oral use may also be provided as a hard gelatin capsule wherein the active ingredient is mixed with an inert solid diluent such as calcium carbonate, calcium phosphate and kaolin, or as a soft gelatin capsule wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin and olive oil. An aqueous suspension contains an active material in admixture with excipients suitable for the manufacture of an aqueous suspension. An oily suspension may be formulated by suspending the active ingredient in a suitable oil. An oil-in-water emulsion may also be adopted. Dispersible powders and granules suitable for the preparation of an aqueous suspension by the addition of water provide an active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. The pharmaceutical composition of the present compound may be in the form of a sterile injectable aqueous or oily suspension. The compound of the invention may also be administered in the form of a suppository for rectal administration. For topical use, cream, ointment, jelly, solution, suspension containing the compound of the present invention may be employed. The compound of the present invention may also be formulated for the administration by inhalation. The compound of the present invention may also be administered by a transdermal patch according to a method known in this field.

[0133] While various production methods of the compound (II) of the present invention or a salt thereof (hereinafter to be simply referred to as compound (II)) are considered, a representative example thereof is shown in the following scheme 1. In the explanation of the following production method, a compound and a reaction product thereof to be the starting materials may form a salt which does not adversely influence the reaction.

[0134] Compound (II) is produced, for example, by the method shown in the following scheme 1.

(Scheme 1)





[0135] wherein R^5 is a carbonyl group or a sulfonyl group substituted by R^3, and other symbols are as defined above.

[0136] As compound (II) to be a starting material, for example, a commercially available compound or a compound known per se or a compound produced by a method analogous to the production method thereof can be used (e.g., Organic Letters 2008, V10(13), 2701-2704).

[0137] Step 1 can be performed by a method known per se or a method analogous thereto. For example, alkylation reaction (e.g., S.R. Sandler and W. Karo, Organic Functional Group Preparations I, 2nd ed., Academic Press, 1983, Chapter 13)) can be used.

[0138] For step 2, for example, a method known per se (e.g., Journal of Organic Chemistry, 77(16), 6908-6916; 2012) can be used.

[0139] Step 3 shows the production of compound (V) by reaction of compound (IV) with sulfonyl chloride, acyl chloride or isocyanate in the presence of a base.

[0140] As the base, organic bases (e.g., triethylamine, pyridine, diethylisopropylamine, sodium methoxide, sodium ethoxide), inorganic bases (e.g., sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, cesium carbonate, sodium hydride, metal sodium) are used. The amount of the base to be used is generally 1 to 10 mol, preferably 1 to 3 mol, per 1 mol of compound (IV). As the kind of the base, an organic base is preferable, and triethylamine, pyridine, diethylisopropylamine, particularly pyridine, are preferable.

[0141] This reaction can be advantageously performed in a solvent. As the solvent, hydrocarbons (e.g., pentane, hexane, cyclohexane, benzene, toluene), ethers (e.g., diethyl

ether, tetrahydrofuran, dioxane), amides (e.g., N,N-dimethylformamide, hexamethylphosphoric acid triamide), halogenated hydrocarbons (e.g., dichloromethane, chloroform), sulfoxides (e.g., dimethyl sulfoxide), ureas (e.g., 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidine) are used. When the aforementioned organic base is a liquid (e.g., triethylamine, pyridine, diethylisopropylamine), it can also be used as a solvent. These solvents may be used alone or two or more kinds thereof may be mixed at a suitable ratio and used. The amount of the solvent to be used is generally 1 to 100 ml, preferably 5 to 20 ml, per 1 g of compound (IV). The reaction temperature is generally -20°C to the boiling point of the solvent to be used for the reaction, preferably 0°C to 60°C. While the reaction time varies depending on the kind and amount of the base to be used, it is 10 min to 3 days, preferably 1 hr to 24 hr.

[0142] Step 4 can be performed according to, for example, a method known per se (e.g., Organic Letters 2011, V13(10), 2564-2567).

[0143] Step 5 can be performed according to, for example, a method known per se (e.g., WO 2011119541 A1).

[0144] Step 6 can be performed according to a method known per se (e.g., S.R. Sandler and W. Karo, Organic Functional Group Preparations II, 2nd ed., Academic Press, 1989, Chapter 6).

[0145] In the thus-obtained compound (VII), 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, reduction reaction, alkylation reaction, acylation reaction, ureation reaction, hydrolysis reaction, amination reaction, esterification reaction, aryl coupling reaction, deprotection reaction.

[0146] 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 obtained by removing the protecting group as necessary after the reaction.

[0147] Examples of the amino-protecting group include formyl group, C_{1-6} alkyl-carbonyl group, C_{1-6} alkoxy-carbonyl group, benzoyl group, C_{7-10} aralkyl-carbonyl group (e.g., benzylcarbonyl), C_{7-14} aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl), trityl group, phthaloyl group, N,N-dimethylaminomethylene group, substituted silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl), C_{2-6} alkenyl group (e.g., 1-allyl). These groups may be substituted by 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkoxy group and a nitro group.

[0148] Examples of the carboxyl-protecting group include C_{1-6} alkyl group, C_{7-10} aralkyl group (e.g., benzyl), phenyl group, trityl group, substituted silyl group (e.g., trimethylsilyl, triethylsilyl,

dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl), C_{2-6} alkenyl group (e.g., 1-allyl). These groups may be substituted by 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkoxy group and a nitro group.

[0149] Examples of the hydroxy-protecting group include C_{1-6} alkyl group, phenyl group, trityl group, C_{7-10} aralkyl group (e.g., benzyl), formyl group, C_{1-6} alkyl-carbonyl group, benzoyl group, a C_{7-10} aralkyl-carbonyl group (e.g., benzylcarbonyl), 2-tetrahydropyranyl group, 2-tetrahydrofuranyl group, substituted silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl), C_{2-6} alkenyl group (e.g., 1-allyl). These groups may be substituted by 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group and a nitro group.

[0150] Examples of the carbonyl-protecting group include cyclic acetal (e.g., 1,3-dioxane), non-cyclic acetal (e.g., di-C_{1-6} alkylacetal).

[0151] Examples of the mercapto-protecting group include C_{1-6} alkyl group, phenyl group, trityl group, C_{7-10} aralkyl group (e.g., benzyl), C_{1-6} alkyl-carbonyl group, benzoyl group, C_{7-10} aralkyl-carbonyl group (e.g., benzylcarbonyl), C_{1-6} alkoxy-carbonyl group, C_{6-14} aryloxy-carbonyl group (e.g., phenyloxycarbonyl), C_{7-14} aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl), 2-tetrahydropyranyl group, C_{1-6} alkylamino-carbonyl group (e.g., methylaminocarbonyl, ethylaminocarbonyl). These groups may be substituted by 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group and a nitro group.

[0152] The above-mentioned protecting groups can be removed by a deprotection reaction known per se.

[0153] Compound (II) obtained by the above-mentioned production method can be isolated and purified by a known means, such as solvent extraction, liquid conversion, phase transfer, crystallization, recrystallization, chromatography.

[0154] When compound (II) contains optical isomer, stereoisomer, regio isomer and rotamer, these compounds are also included in compound (II), and each can be obtained as a single product by a synthesis method or a separation method known per se. For example, when an optical isomer exists in compound (II), an optical isomer resolved from the compound is also encompassed in compound (II).

[0155] Here, an optical isomer can be produced by a method known per se.

[0156] Compound (II) may be a crystal.

[0157] A crystal of compound (II) (hereinafter sometimes to be abbreviated as the crystal of

the present invention) can be produced by crystallizing compound (II), by applying a crystallization method known per se.

[0158] The crystal of the present invention is superior in the physicochemical properties (e.g., melting point, solubility, stability) and biological properties (e.g., pharmacokinetics (absorbability, distribution, metabolism, excretion), efficacy expression), and is extremely useful as a medicament.

[Example]

[0159] 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 present invention can be modified within the scope of the present invention. The compounds of Examples 80, 82, 103, 104, and 353-372 are provided for reference purposes.

[0160] The "room temperature" in the following Examples is generally about 10°C to about 35°C. The ratio for a mixed solvent is, unless otherwise specified, a volume mixing ratio and % means wt% unless otherwise specified.

[0161] The elution by column chromatography in the Examples was performed under the observation by TLC (Thin Layer Chromatography) unless otherwise specified. In the observation by TLC, 60 F_{254} 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 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 of elution solvents is, unless otherwise specified, a volume mixing ratio.

[0162] In the following Examples, the following abbreviations are used.

[0163] THF: tetrahydrofuran, DMSO: dimethylsulfoxide, DME: 1,2-dimethoxyethane, IPE: isopropyl ether, $PdCl_2$(dppf): 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride, NMP: 1-methyl-2-pyrrolidone, MPa: megapascal, psi: psi, $CDCl_3$: deuterochloroform, DMSO-d_6: deuterodimethyl sulfoxide

[0164] ^{1}H NMR (proton nuclear magnetic resonance) was measured by Fourier transform NMR. For the analysis of ^{1}H NMR, ACD/SpecManager (trade name) software were used. Very mild peaks of protons of hydroxyl group, amino group are not described sometimes.

[0165] MS (mass spectrum) was measured by LC/MS (liquid chromatograph mass

spectrometer). As the ionization method, ESI (electrospray ionization) method, or APCI (atomospheric pressure chemical ionization) method was used. The data indicates those found. While molecular ion peak is generally observed, a fragment ion is sometimes observed. In the case of a salt, a molecular ion peak or fragment ion peak of free form is generally observed. Peaks by powder X-ray diffraction in the Examples mean peaks measured at room temperature by using Ultima IV (Rigaku Corporation, Japan) using Cu Kα 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

The crystallinity by powder X-ray diffraction in the Examples was calculated by the Hermans method.

Example 1

N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide A) 3-bromo-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)pyridine

[0166] To a suspension of 60% sodium hydride (7.00 g) in THF (80 ml) was added cis-4-isopropylcyclohexanol (19.91 g) at room temperature. The reaction mixture was stirred at room temperature overnight, 3-bromo-2-(bromomethyl)pyridine (17.56 g) was added to the reaction mixture, and the mixture was stirred overnight at room temperature. To the mixture was added saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by NH silica gel chromatography (ethyl acetate/hexane) to give the title compound (17.30 g). MS, found: 312.2,314.2.

B) N-(2-(((cis-4-isopropylcyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide

[0167] A mixture of 3-bromo-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)pyridine (3.0 g), methanesulfonamide (1.097 g), di-tert-butyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (0.408 g), tris(dibenzylideneacetone)dipalladium(0) (0.440 g), cesium carbonate (4.70 g) and THF (40 ml) was stirred with heating under microwave radiation at 120°C for 20 min. The reaction mixture was filtered through celite, and the filtrate was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium

sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (2.310 g).
MS, found: 327.3.

C) N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0168] A mixture of N-(2-(((cis-4-isopropylcyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide (2.285 g), platinum oxide (0.079 g), methanol (15 ml) and acetic acid (15 ml) was stirred overnight under a 0.6 MPa hydrogen atmosphere at 50°C. The mixture was filtrated, and the filtrate was neutralized with saturated aqueous sodium hydrogen carbonate solution at 0°C and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by NH silica gel chromatography (ethyl acetate/hexane) to give the title compound (1.630 g).

[0169] ^{1}H NMR (300 MHz,$CDCl_3$)δ 0.78-0.90(6H,m), 0.96-1.15(1H,m), 1.20-1.48(8H,m), 1.48-1.77(9H,m), 1.79-1.90(2H,m), 1.91-2.03(1H,m), 2.67(1H,td,J=11.8,2.8Hz), 2.86(1H,ddd,J=7.9,4.5,1.9Hz), 3.04(1H,dt,J=11.4,2.4Hz), 3.33(1H,dd,J=9.4,7.9Hz), 3.46(2H,dd,J=9.4,4.5Hz), 3.59(1H,brs), 5.36(1H,d,J=8.3Hz).

Example 2

(2R,3S)-N-ethyl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide

[0170] To a solution of (2S,3S)-2,3-bis((4-methylbenzoyl)oxy)succinic acid (579 mg) in ethanol (4 ml) was added a solution of N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (498 mg) in ethanol (4 ml) at room temperature, and the solution was left standing overnight. The resulting solid was collected by filtration, and washed with acetonitrile to give a solid (270 mg). To a solution of the obtained solid (100 mg) and triethylamine (0.078 ml) in THF (2 ml) was added ethylisocyanate (14.83 mg) at 0°C, and the mixture was stirred at room temperature overnight. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (54 mg).

^{1}H NMR (300 MHz,$CDCl_3$)δ 0.86(6H,d,J=6.8Hz), 1.20-1.25(1H,m), 1.34-1.53(5H,m), 1.56-1.71(8H,m), 1.71-1.81(1H,m), 1.89(2H,d,J=13.4Hz), 2.82(1H,td,J=12.7,2.7Hz), 3.00(3H,s), 3.25(2H,qd,J=7.2,5.4Hz), 3.48-3.61(3H,m), 3.66-3.79(1H,m), 3.87(1H,dd,J=9.3,7.8Hz), 4.44-

4.56(1H,m), 4.66(1H,t,J=4.9Hz), 5.73(1H,d,J=7.7Hz).

Example 3

N-((2R,3S)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

A) 3-bromo-2-(((cis-4-phenylcyclohexyl)oxy)methyl)pyridine

[0171] To a solution of cis-4-phenylcyclohexanol (50.8 g) in THF (300 ml) was added 60% sodium hydride (17.29 g) at 0°C, and the mixture was stirred for 30 min. To the reaction mixture was added 3-bromo-2-(bromomethyl)pyridine (72.3 g), and the mixture was stirred at room temperature overnight. Saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (84.43 g).
MS, found: 346.0,348.0.

B) N-(2-(((cis-4-phenylcyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide

[0172] To a mixture of 3-bromo-2-(((cis-4-phenylcyclohexyl)oxy)methyl)pyridine (38 g) in DME (450 ml) were added di-tert-butyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (9.32 g), tris(dibenzylideneacetone)dipalladium(0) (10.05 g), cesium carbonate (53.6 g) and methanesulfonamide (12.53 g) at room temperature and the reaction mixture was stirred under a nitrogen atmosphere at 100°C for 5 hr. Water was added to the reaction mixture at room temperature, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give pale orange solid, which was recrystallized from ethyl acetate/hexane to give the title compound (17.19 g).
MS, found: 361.2.

C) N-((2R,3S)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0173] A mixture of N-(2-(((cis-4-phenylcyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide (6.48 g), 5% rhodium/carbon (7.40 g), and ethanol/acetic acid (9:1)

solution (222.22 ml) was stirred under a hydrogen atmosphere for 23.5 hr. The reaction mixture was filtered through celite, and the solvent was evaporated under reduced pressure. The residue was diluted with ethyl acetate, washed successively with saturated aqueous sodium hydrogen carbonate solution, and saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. To a solution of the obtained residue (6.80 g) in ethyl acetate (48 ml) was added a solution of (+)-mandelic acid (2.82 g) in ethyl acetate (20 ml) at 60°C, and the mixture was stirred at the same temperature for 1 hr. Seed crystal was added to the reaction mixture at 50°C, and the mixture was gradually cooled to room temperature and stirred at room temperature overnight. The salt was collected by filtration, and washed with a mixed solvent of ethyl acetate/IPE (2:3). The solid was recrystallized from a mixed solvent of ethyl acetate/acetonitrile (1:1). The obtained crystal was dissolved in ethyl acetate-10% aqueous potassium carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to give the title compound (1.09 g).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.47-1.86(10H,m), 1.92-2.08(3H,m), 2.53(1H,tt,J=11.4,3.7Hz), 2.69(1H,td,J=11.6,2.8Hz), 2.86-2.94(1H,m), 2.98(3H,s), 3.02-3.12(1H,m), 3.32-3.42(1H,m), 3.51(1H,dd,J=9.3,4.4Hz), 3.57-3.68(2H,m), 5.38(1H,d,J=7.2Hz), 7.13-7.37(5H,m).

Example 4

N-((2R,3S)-1-acetyl-2-(((cis-4-phenylcyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0174] A reaction mixture of N-((2R,3S)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (220 mg), pyridine (4 ml), and acetic anhydride (1 ml) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate/hexane) to give the title compound (249 mg).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.48-2.65(15H,m), 2.94-3.16(4H,m), 3.43-5.20(7H,m), 5.31-6.22(1H,m), 7.13-7.36(5H,m).

Example 5

Methyl (2R,3S)-3-((methylsulfonyl)amino)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)piperidine-1-carboxylate

[0175] To a reaction mixture of N-((2R,3S)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)piperidin-3-

yl)methanesulfonamide (58 mg), triethylamine (0.044 ml) in THF (3 ml) was added methyl chloroformate (0.024 ml) at room temperature, and the mixture was stirred overnight under a calcium chloride tube dry atmosphere. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (64 mg). ^{1}H NMR (300 MHz,$CDCl_3$)δ 1.48-1.58(2H,m), 1.59-1.67(2H,m), 1.68-1.89(6H,m), 2.01-2.12(3H,m), 2.47-2.61(1H,m), 2.73-2.88(1H,m), 2.99(3H,s), 3.53-3.63(2H,m), 3.64-3.69(1H,m), 3.70-3.77(3H,m), 4.00-4.10(1H,m), 4.48-4.73(1H,m), 6.00(1H,brs), 7.14-7.26(3H,m), 7.27-7.35(2H,m).

Example 5A

Methyl (2R,3S)-3-((methylsulfonyl)amino)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)piperidine-1-carboxylate

[0176] To a solution of N-((2R,3S)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (1.09 g) in THF (25 ml) were added methyl chloroformate (337 mg) and triethylamine (0.622 ml) at room temperature, and the mixture was stirred over weekend. Saturated aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was dissolved in hot ethanol (3 ml), and the solution was stirred at room temperature for 10 min. After crystals started to precipitate, water (3 ml) was added to the solution and then stirred overnight. The crystals were collected by filtration to give crystals of the title compound (1.023 g).

[0177] X-ray powder diffraction patterns of the obtained crystals were generated using Ultima IV with Cu Kα radiation.

[0178] The obtained crystal showed a powder X-ray diffraction pattern having characteristic peaks at the diffraction angle (2θ) of 8.8°, 11.0°, 13.4°, 15.3°, 17.6°, 19.2°, 20.4°and 23.4°.

Example 6

N-(cis-2-(((cis-4-(3,5-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide acetate

A) 3-bromo-2-(((cis-4-(3,5-difluorophenyl)cyclohexyl)oxy)methyl)pyridine

[0179] A solution of cis-4-(3,5-difluorophenyl)cyclohexanol (1.91 g) in THF (40 ml) was cooled to 0°C, 60% sodium hydride (0.720 g) was added, and the mixture was stirred at room temperature under a calcium chloride tube dry atmosphere for 2 hr. To the reaction mixture was added 3-bromo-2-(bromomethyl)pyridine (2.416 g), and the mixture was stirred at room temperature for 30 min, and at 70°C for 3 hr. To the mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (3.33 g).
MS, found: 382.0,384.0.

B) N-(2-(((cis-4-(3,5-difluorophenyl)cyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide

[0180] A mixture of 3-bromo-2-(((cis-4-(3,5-difluorophenyl)cyclohexyl)oxy)methyl)pyridine (3.3 g), methanesulfonamide (0.985 g), di-tert-butyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (0.440 g), tris(dibenzylideneacetone)dipalladium(0) (0.395 g), cesium carbonate (4.22 g) and DME (40 ml) was heated under reflux at 95°C under a nitrogen atmosphere for 6 hr. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (3.20 g).
MS, found: 397.2.

C) N-(cis-2-(((cis-4-(3,5-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide acetate

[0181] A mixture of N-(2-(((cis-4-(3,5-difluorophenyl)cyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide (1.95 g), 5% rhodium/carbon (2.025 g), ethanol (45 ml) and acetic acid (5.0 ml) was stirred at room temperature under a hydrogen atmosphere for 6 hr. The mixture was filtrated, toluene was added to the filtrate, and the mixture was concentrated under reduced pressure. The residue was washed with IPE to give the title compound (1.5045 g).
MS, found: 403.2.

Example 7

N-((2R,3S)-2-(((cis-4-(3,5-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0182] N-(cis-2-(((cis-4-(3,5-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide acetate (1.15 g) was dissolved in ethyl acetate and the mixture was basified with 1 mol/l aqueous sodium hydroxide solution. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. From the residue (0.976 g) was separated 295.5 mg by HPLC (column: CHIRALPAK AD (LF001), 50 mmID×500 mmL, manufactured by Daicel Corporation, mobile phase: hexane/2-propanol/diethylamine=700/300/1) and a fraction having a shorter retention time was obtained as the title compound (0.143 g).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.45-1.59(3H,m), 1.60-1.77(6H,m), 1.81-1.89(1H,m), 1.89-2.04(2H,m), 2.52(1H,tt,J=11.1,4.0Hz), 2.64-2.76(1H,m), 2.90(1H,ddd,J=8.1,4.4,1.9Hz), 2.94-3.01(3H,m), 3.07(1H,dt,J=11.5,2.4Hz), 3.30-3.42(1H,m), 3.46-3.55(1H,m), 3.56-3.67(2H,m), 3.71-3.79(1H,m), 5.35(1H,d,J=8.0Hz), 6.61(1H,tt,J=8.9,2.3Hz), 6.69-6.79(2H,m).

Example 8

N-((2R,3S)-1-acetyl-2-(((cis-4-(3,5-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0183] To a solution of N-((2R,3S)-2-(((cis-4-(3,5-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (200 mg) and triethylamine (0.138 ml) in THF (5 ml) was added acetyl chloride (0.068 ml) at room temperature, and the mixture was stirred under a calcium chloride tube dry atmosphere for 30 min. To the mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (218 mg).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.52(1H,brs), 1.58-1.88(7H,m), 1.97-2.25(6H,m), 2.44-2.66(1H,m), 2.92-3.14(4H,m), 3.39-3.75(4.5H,m), 3.84-4.08(1H,m), 4.38(0.5H,brs), 5.11(1H,brs), 5.24-6.18(1H,m), 6.62(1H,tt,J=9.0,2.3Hz), 6.76(2H,d,J=6.8Hz).

Example 9

N-(cis-2-(((cis-4-(2,5-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

A) 8-(2,5-difluorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene

[0184] To a mixed solution of (2,5-difluorophenyl)boronic acid (4.11 g), 1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (5 g), sodium carbonate (7.35 g), and lithium chloride (0.037 g) in DME (60 ml)-water (15.00 ml) was added tetrakis(triphenylphosphine)palladium(0) (1.002 g) at room temperature. The mixture was heated under reflux at 100°C under a nitrogen atmosphere overnight. To the mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (3.582 g).
MS, found: 253.0.

B) 8-(2,5-difluorophenyl)-1,4-dioxaspiro[4.5]decane

[0185] To a solution of 8-(2,5-difluorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene (800 mg) in ethanol (15 ml) was added 10% palladium/carbon (337 mg) at room temperature. The mixture was stirred at room temperature under a hydrogen atmosphere for 1 hr. The mixture was filtered, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (754 mg).
MS, found: 255.0.

C) 4-(2,5-difluorophenyl)cyclohexanone

[0186] To a solution of 8-(2,5-difluorophenyl)-1,4-dioxaspiro[4.5]decane (4.15 g) in acetone (30 ml) was added 2 mol/l hydrochloric acid (30 ml) at room temperature. The mixture was stirred at 60°C for 2 hr. The reaction mixture was partitioned by adding ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (3.32 g).
MS, found: 211.0.

D) cis-4-(2,5-difluorophenyl)cyclohexanol

[0187] To a solution of 4-(2,5-difluorophenyl)cyclohexanone (3.32 g) in THF (150 ml) was added lithium tri-(sec-butyl)borohydride 1 mol/l THF solution (46.0 ml) at -78°C. The mixture

was stirred at 0°C for 3 hr. To the mixture was added dropwise 30% hydrogen peroxide water at 0°C, and the mixture was stirred for 5 min. To the reaction mixture were added acetone (22 ml), water (52 ml), 30% hydrogen peroxide water (22 ml) in this order, and the mixture was stirred for 5 min and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (2.85 g).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.31(1H,d,J=2.3Hz), 1.64-1.99(8H,m), 2.75-2.98(1H,m), 4.07-4.23(1H,m), 6.74-7.06(3H,m).

E) 3-bromo-2-(((cis-4-(2,5-difluorophenyl)cyclohexyl)oxy)methyl)pyridine

[0188] A solution of cis-4-(2,5-difluorophenyl)cyclohexanol (2.85 g) in THF (60 ml) was cooled to 0°C, 60% sodium hydride (1.074 g) was added, and the mixture was stirred under a calcium chloride tube dry atmosphere at room temperature for 2 hr. To the reaction mixture was added 3-bromo-2-(chloromethyl)pyridine (3.60 g), and the mixture was stirred at room temperature for 30 min and at 70°C for 3 hr. Water was added to the mixture at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (4.33 g).
MS, found: 382.0,383.9.

F) N-(2-(((cis-4-(2,5-difluorophenyl)cyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide

[0189] To a mixed solution of 3-bromo-2-(((cis-4-(2,5-difluorophenyl)cyclohexyl)oxy)methyl)pyridine (4.33 g), methanesulfonamide (1.293 g), di-tert-butyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (0.962 g), and cesium carbonate (5.54 g) in DME (65 ml) was added tris(dibenzylideneacetone)dipalladium(0) (1.037 g) at room temperature. The mixture was heated under reflux at 100°C under a nitrogen atmosphere for 6 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (3.95 g).
MS, found: 397.1.

G) N-(cis-2-(((cis-4-(2,5-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0190] To a mixed solution of N-(2-(((cis-4-(2,5-difluorophenyl)cyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide (3.76 g) in ethanol (99 ml) and acetic acid (11.00 ml) was added 5% rhodium/carbon (3.90 g) at room temperature. The mixture was stirred at room temperature under a hydrogen atmosphere for 11 hr. The mixed solution was filtered, and the solvent was evaporated under reduced pressure. After washing with IPE-methanol, the residue was suspended in saturated aqueous sodium hydrogen carbonate solution, and the suspension was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to give the title compound (2.015 g).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.44-1.65(7H,m), 1.69-1.82(3H,m), 2.02(3H,d,J=13.3Hz), 2.59-2.75(1H,m), 2.80-2.94(2H,m), 2.96-3.00(3H,m), 3.08(1H,dt,J=11.5,2.4Hz), 3.31-3.42(1H,m), 3.51(1H,dd,J=9.3,4.4Hz), 3.62(2H,d,J=2.7Hz), 5.37(1H,d,J=6.1Hz), 6.73-6.87(1H,m), 6.89-7.02(2H,m).

Example 10

N-((2R,3S)-2-(((cis-4-(2,5-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0191] N-(cis-2-(((cis-4-(2,5-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide was separated by HPLC (column: CHIRALPAK AD(LF001), 50 mmID×500 mmL, manufactured by Daicel Corporation, mobile phase: hexane/2-propanol/diethylamine=700/300/1) and a fraction having a shorter retention time was obtained as the title compound (0.718 g).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.48-1.65(6H,m), 1.70-1.83(4H,m), 1.93-2.12(3H,m), 2.70(1H,td,J=11.6,2.8Hz), 2.80-2.95(2H,m), 2.98(3H,s), 3.09(1H,dt,J=11.5,2.2Hz), 3.30-3.43(1H,m), 3.48-3.55(1H,m), 3.59-3.70(2H,m), 5.30-5.60(1H,m), 6.76-6.87(1H,m)6.88-7.04(2H,m).

Example 11

methyl (2R,3S)-2-(((cis-4-(2,5-difluorophenyl)cyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate

[0192] To a solution of N-((2R,3S)-2-(((cis-4-(2,5-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (300 mg) and triethylamine (0.207 ml) in THF (5 ml) was added methyl chloroformate (0.115 ml) at room temperature, and the mixture was stirred for 1 hr. Water was added to the mixture at room

temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (329 mg).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.50-1.56(1H,m), 1.59-1.91(8H,m), 2.03(1H,brs), 2.08(2H,brs), 2.70-2.95(2H,m), 3.01(3H,s), 3.53-3.71(3H,m), 3.73(3H,s), 3.84-4.08(2H,m), 4.63(1H,brs), 5.96(1H,brs), 6.77-6.88(1H,m), 6.89-7.06(2H,m).

Example 12

N-(cis-2-(((cis-4-(2,6-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

A) cis-4-(2,6-difluorophenyl)cyclohexanol

[0193] To a solution of 4-(2,6-difluorophenyl)cyclohexanone (2.71 g) in THF (120 ml) was added lithium tri(sec-butyl)borohydride 1 mol/l THF solution (37.0 ml) at -78°C. The mixture was warmed to 0°C over 3 hr. To the mixture were added dropwise acetone, water and 30% hydrogen peroxide water at 0°C and the mixture was stirred for 5 min and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (2.69 g).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.40(1H,d,J=4.5Hz), 1.56-1.74(4H,m), 1.84-2.01(2H,m), 2.25(2H,d,J=14.0Hz), 3.02(1H,tt,J=12.6,3.3Hz), 4.13(1H,brs), 6.73-6.92(2H,m), 7.01-7.20(1H,m).

B) 3-bromo-2-(((cis-4-(2,6-difluorophenyl)cyclohexyl)oxy)methyl)pyridine

[0194] A solution of cis-4-(2,6-difluorophenyl)cyclohexanol (2.69 g) in THF (60 ml) was cooled to 0°C, 60% sodium hydride (1.014 g) was added, and the mixture was stirred under a calcium chloride tube dry atmosphere for 2 hr. To the reaction mixture was added 3-bromo-2-(chloromethyl)pyridine (3.40 g), and the mixture was stirred at room temperature for 30 min, and at 70°C overnight. Water was added to the mixture at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (3.96 g).

MS, found: 382.0,384.0.

C) N-(2-(((cis-4-(2,6-difluorophenyl)cyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide

[0195] A mixture of 3-bromo-2-(((cis-4-(2,6-difluorophenyl)cyclohexyl)oxy)methyl)pyridine (3.96 g), methanesulfonamide (1.183 g), di-tert-butyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (0.880 g), tris(dibenzylideneacetone)dipalladium(0) (0.949 g), cesium carbonate (5.06 g) and DME (60 ml) was heated under reflux at 100°C under a nitrogen atmosphere for 6 hr. Water was added to the reaction mixture at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (3.76 g).
MS, found: 397.1.

D) N-(cis-2-(((cis-4-(2,6-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0196] A mixture of N-(2-(((cis-4-(2,6-difluorophenyl)cyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide (3.76 g), 5% rhodium/carbon (3.90 g), ethanol (99 ml) and acetic acid (11.0 ml) was stirred at room temperature under a hydrogen atmosphere for 9 hr. The mixture was filtered, and the solvent was evaporated under reduced pressure. The residue was washed with IPE. The obtained solid was dissolved in saturated aqueous sodium hydrogen carbonate solution and then neutralized, and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by NH silica gel chromatography (ethyl acetate/hexane) to give the title compound (1.84 g).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.40-1.80(8H,m), 1.92-2.22 (5H,m), 2.71(1H,td,J=11.7,2.6Hz), 2.89-3.13(6H,m), 3.35-3.44(1H,m), 3.45-3.53(1H,m), 3.63(2H,brs), 5.40(1H,brs), 6.69-6.94(2H,m), 7.01-7.22(1H,m).

Example 13

N-((2R,3S)-2-(((cis-4-(2,6-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0197] N-(cis-2-(((cis-4-(2,6-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-

yl)methanesulfonamide (1800 mg) was separated by HPLC (column: CHIRALPAK AD(LF001), 50 mmID×500 mmL, manufactured by Daicel Corporation, mobile phase: hexane/2-propanol/diethylamine=800/200/1) and a fraction having a shorter retention time was obtained as the title compound (593.2 mg).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.51(4H,dd,J=9.8,4.2Hz), 1.65-1.82(4H,m), 1.93-2.28(5H,m), 2.71(1H,td,J=11.6,2.8Hz), 2.85-3.13(6H,m), 3.31-3.44(1H,m), 3.44-3.51(1H,m), 3.63(2H,brs), 5.40(1H,brs), 6.70-6.94(2H,m), 7.10(1H,tt,J=8.3,6.4Hz).

Example 14

N-((2R,3S)-1-acetyl-2-(((cis-4-(2,6-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0198] To a solution of N-((2R,3S)-2-(((cis-4-(2,6-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (51.9 mg) in pyridine (2.0 ml) was added acetic anhydride (0.036 ml) at room temperature, and the mixture was stirred under a calcium chloride tube dry atmosphere for 30 min. Toluene was added to the mixture, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (53.1 mg).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.56-1.65(3H,m), 1.68-2.24(11H,m), 2.60-3.35(5H,m), 3.44-3.81(4H,m), 3.82-3.95(1H,m), 4.26-4.66(1H,m), 4.98-5.47(1H,m), 5.72(1H,d,J=8.3Hz), 6.82(2H,t,J=8.5Hz), 7.11(1H,tt,J=8.3,6.3Hz).

Example 15

N-((2R,3S)-2-(((cis-4-(3-fluorophenyl)cyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide

A) 8-(3-fluorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene

[0199] To a mixed solution of (3-fluorophenyl)boronic acid (7.28 g), 1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (10 g), sodium carbonate (7.35 g), and lithium chloride (0.147 g) in DME (150 ml)-water (30.0 ml) was added tetrakis(triphenylphosphine)palladium(0) (2.005 g) at room temperature. The mixture was heated under reflux at 100°C under a nitrogen atmosphere for 3 hr. Water was added to the mixture at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced

pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (5.13 g).
MS, found: 235.0.

B) 8-(3-fluorophenyl)-1,4-dioxaspiro[4.5]decane

[0200] To a solution of 8-(3-fluorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene (2.40 g) in ethanol (30 ml) was added 10% palladium/carbon (1.090 g) at room temperature. The mixture was stirred at room temperature under a hydrogen atmosphere for 2 hr. The mixed solution was filtered, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (1.900 g).
MS, found: 237.0.

C) 4-(3-fluorophenyl)cyclohexanone

[0201] To a solution of 8-(3-fluorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene (3.96 g) in acetone (30 ml) was added 6 mol/l hydrochloric acid (3 ml) at room temperature. The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure. To the mixture was added saturated brine, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (3.01 g).
MS, found: 193.1.

D) cis-4-(3-fluorophenyl)cyclohexanol

[0202] To 4-(3-fluorophenyl)cyclohexanone (380 mg) in THF (15 ml) was added lithium tri(sec-butyl)borohydride 1 mol/l THF solution (3.95 ml) at -78°C. The mixture was stirred at 0°C for 2 hr. To the reaction mixture was added saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (325 mg).
^{1}H NMR (300 MHz,$CDCl_3$)δ 1.31(1H,s),1.60-1.76(4H,m), 1.77-1.98(4H,m), 2.45-2.62(1H,m), 4.10-4.18(1H,m), 6.82-6.97(2H,m), 7.01(1H,d,J=7.6Hz), 7.18-7.26(1H,m).

E) 3-bromo-2-(((cis-4-(3-fluorophenyl)cyclohexyl)oxy)methyl)pyridine

[0203] A solution of cis-4-(3-fluorophenyl)cyclohexanol (1.0 g) in THF (20 ml) was cooled to 0°C, 60% sodium hydride (0.412 g) was added, and the mixture was stirred under a calcium chloride tube dry atmosphere for 1 hr. To the reaction mixture was added 3-bromo-2-(chloromethyl)pyridine (1.382 g), and the mixture was stirred at room temperature for 2 hr, and at 70°C for 2.5 hr. To the mixture was added saturated aqueous ammonium chloride solution at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (1.580 g).
MS, found: 363.9,365.9.

F) N-(2-(((cis-4-(3-fluorophenyl)cyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide

[0204] To a solution of 3-bromo-2-(((cis-4-(3-fluorophenyl)cyclohexyl)oxy)methyl)pyridine (1.15 g), methanesulfonamide (0.601 g), di-tert-butyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (0.134 g), and cesium carbonate (2.057 g) in DME (20 ml) was added tris(dibenzylideneacetone)dipalladium(0) (0.289 g) at room temperature. The mixture was stirred under microwave radiation at 120°C for 2 hr. The reaction mixture was filtered through celite, and the filtrate was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (1.100 g).
MS, found: 379.0.

G) N-((2R,3S)-2-(((cis-4-(3-fluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0205] To a mixed solution of a solution of N-(2-(((cis-4-(3-fluorophenyl)cyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide (2.82 g) in ethanol (40 ml) and acetic acid (2.105 ml) was added 5% rhodium/carbon (3.07 g) at room temperature. The mixture was stirred at room temperature under a hydrogen atmosphere overnight. The mixed solution was filtered, and the solvent was evaporated under reduced pressure. The residue was dissolved in saturated aqueous sodium hydrogen carbonate solution, extracted with ethyl acetate, and the solvent was evaporated under reduced pressure. The residue was separated by HPLC (column: CHIRALPAK AD(AF003), 50 mmID×500 mmL, manufactured by Daicel Corporation, mobile phase: hexane/2-propanol/diethylamine=650/350/1) and a fraction having a shorter retention time was obtained as the title compound (1.040 g).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.50-1.76(10H,m), 1.92-2.07(3H,m), 2.54(1H,tt,J=11.4,4.0Hz), 2.69(1H,td,J=11.7,2.7Hz), 2.90(1H,ddd,J=8.0,4.3,2.1Hz), 2.97(3H,s), 3.07(1H,dt,J=11.5,2.4Hz), 3.29-3.42(1H,m), 3.49-3.54(1H,m), 3.49-3.54(1H,m), 3.56-3.66(2H,m), 5.38(1H,d,J=7.6Hz), 6.82-6.95(2H,m), 6.99(1H,d,J=7.6Hz), 7.18-7.26(1H,m).

Example 16

N-((2R,3S)-1-(cyclopropylcarbonyl)-2-(((cis-4-(3-fluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0206] To a solution of N-((2R,3S)-2-(((cis-4-(3-fluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (60 mg), triethylamine (0.043 ml) in THF (4 ml) was added cyclopropanecarbonyl chloride (0.028 ml) at room temperature, and the mixture was stirred for 1 hr. Water was added to the mixture at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (59.3 mg).

^{1}H NMR (300 MHz,$CDCl_3$)δ 0.80(2H,dd,J=7.8,3.6Hz), 0.92-1.05(2H,m), 1.52(1H,d,J=2.3Hz), 1.59-2.25(12H,m), 2.54(1H,dt,J=15.0,7.7Hz), 2.92-3.20(4H,m), 3.43-3.73(3H,m), 4.00(1H,t,J=9.1Hz), 4.50(1H,brs), 4.65-5.23(1H,m), 5.42-6.37(1H,m), 6.81-6.97(2H,m), 7.01(1H,d,J=7.6Hz), 7.19-7.26(1H,m).

Example 17

N-(cis-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

A) 8-(2,3-difluorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene

[0207] To a solution of 1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (20.0 g) in DME/water (4:1) (250 ml) were added 2,3-difluorophenylboronic acid (16.45 g), lithium chloride (1.0 g), and sodium carbonate (29.8 g). Tetrakis(triphenylphosphine)palladium(0) (6.42 g) was added, and the reaction mixture was stirred with heating under reflux for 16 hr. The reaction mixture was diluted with ethyl acetate and filtered through celite. The filtrate was successively washed with water and saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (11.0 g).

^{1}H NMR (400 MHz, DMSO-d_6)δ 1.80(2H,t,J=6.4Hz), 2.38(2H,s),2.50(2H,brs), 3.93(4H,s),5.88(1H,s),7.12-7.19(1H,m), 7.25-7.34(1H,m), 7.41(1H,t,J=7.6Hz).

B) 8-(2,3-difluorophenyl)-1,4-dioxaspiro[4.5]decane

[0208] A solution of 8-(2,3-difluorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene (10.0 g) in ethanol (500 ml) was deaerated with an argon stream for 15 min, and 10% palladium/carbon (1 g) was added. The reaction mixture was stirred under normal pressure hydrogen atmosphere at room temperature for 2 hr. The reaction mixture was filtered through celite, and the residue was washed with ethanol. The filtrate was concentrated under reduced pressure to give the title compound (8.0 g).

^{1}H NMR (400 MHz,DMSO-d_6)δ 1.61-1.78(8H,m), 2.90-2.93(1H,m), 3.89(4H,s),7.11-7.18(1H,m), 7.21(1H,m), 7.40(1H,t,J=8.1Hz).

C) 4-(2,3-difluorophenyl)cyclohexanone

[0209] To a solution of 8-(2,3-difluorophenyl)-1,4-dioxaspiro[4.5]decane (8.0 g) in THF/water (1:1) (100 ml) was added concentrated sulfuric acid (6.4 ml) at 0°C, and the mixture was stirred at room temperature for 16 hr. To the reaction mixture was added aqueous sodium carbonate solution at 0°C, and the mixture was extracted with ethyl acetate. The extract was successively washed with water and saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (6.0 g).

^{1}H NMR (400 MHz, DMSO-d_6)δ 1.87-1.98(2H,m), 2.03-2.07(2H,m), 2.26-2.29(2H,m), 2.59-2.67(2H,m), 3.35-3.44(1H,m), 7.14-7.22(1H,m), 7.25-7.31(1H,m), 7.41(1H,t,J=7.7Hz).

D) cis-4-(2,3-difluorophenyl)cyclohexanol

[0210] To a solution of 4-(2,3-difluorophenyl)cyclohexanone (3.0 g) in THF (20 ml) was added lithium tri(sec-butyl)borohydride 1 mol/l THF solution (21.43 ml) at -78°C, and the mixture was stirred at the same temperature for 30 min. The reaction mixture was gradually warmed to 0°C, and stirred at 0°C for 2 hr. To the reaction mixture were successively added dropwise at 0°C water and 1 mol/l aqueous sodium hydroxide solution, and the mixture was extracted with ethyl acetate. The extract was successively washed with water and saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.3 g).

^{1}H NMR (400 MHz,DMSO-d_6)δ 1.49-1.59(4H,m), 1.73-1.77(2H,m), 1.82-1.91(2H,m), 2.80-2.86(1H,m), 3.90-3.91(1H,m), 4.38-4.39(1H,m), 7.12-7.26(3H,m).

E) 3-bromo-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)methyl)pyridine

[0211] To a solution of cis-4-(2,3-difluorophenyl)cyclohexanol (1.3 g) in THF (5 ml) was added 60% sodium hydride (610 mg) at 0°C, and the mixture was stirred with heating under reflux for 2 hr. To the reaction mixture was slowly added a solution of 3-bromo-2-(bromomethyl)pyridine (2.31 g) in THF (5 ml) at room temperature, and the reaction mixture was stirred with heating under reflux for 4 hr. To the reaction mixture was added water, and the mixture was neutralized with 1 mol/l hydrochloric acid and extracted with ethyl acetate. The extract was successively washed with water and saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (810 mg).

^{1}H NMR (400 MHz,DMSO-d_6)δ 1.52-1.60(4H,m), 1.75-1.85(2H,m), 2.00-2.03(2H,m), 2.86-2.92(1H,m), 3.78(1H,s),4.60(2H,s),7.10-7.20(2H,m), 7.22-7.26(1H,m), 7.32-7.35(1H,m), 8.10(1H,dd,J=8.1,1.1Hz), 8.55(1H,dd,J=4.5,1.2Hz).

F) N-(2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide

[0212] To a solution of 3-bromo-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)methyl)pyridine (800 mg) in dioxane (5 ml) were added methanesulfonamide (345 mg) and cesium carbonate (1.02 g). The reaction mixture was aerated with an argon stream for 20 min, di-tert-butyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (178 mg) and tris(dibenzylideneacetone)dipalladium(0) (192 mg) were added, and the mixture was sealed and stirred under an argon atmosphere at 120°C for 4 hr. The reaction mixture was filtered through celite, and the residue was washed with ethyl acetate. The filtrate was successively washed with water and saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (620 mg).

^{1}H NMR (400 MHz,DMSO-d_6)δ 1.53-1.61(4H,m), 1.70-1.76(2H,m), 1.99-2.05(2H,m), 2.87-2.93(1H,m), 3.10(3H,s), 3.79(1H,brs), 4.75(2H,s),7.10-7.15(2H,m), 7.22-7.24(1H,m), 7.37-7.41(1H,m), 7.79(1H,d,J=8.0Hz), 8.37-8.38(1H,m), 9.11(1H,brs) .

G) N-(cis-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0213] To a solution of N-(2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide (600 mg) in methanol/acetic acid (10:1) (66 ml) was added platinum oxide (60 mg). The reaction mixture was stirred under a 40 psi hydrogen atmosphere for 16 hr at room temperature. The reaction mixture was filtered through celite, and the residue was washed with methanol. The filtrate was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate and the mixture was successively washed with saturated

aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate/hexane) to give the title compound (400 mg).

[0214] ^{1}H NMR (400 MHz,DMSO-d_6)δ 1.35-1.38(1H,m), 1.50-1.56(5H,m), 1.68-1.98(7H,m), 2.54-2.57(1H,m), 2.84-2.90(3H,m), 2.93(3H,s), 3.36-3.40(2H,m), 3.51(1H,brs), 3.59(1H,brs), 6.72(1H,brs), 7.11-7.18(2H,m), 7.19-7.26(1H,m).

Example 18

N-((2R,3S)-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0215] N-(cis-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (3.5 g) was separated by HPLC (column: CHIRALPAK AD(LF001), 50 mmID×500 mmL, manufactured by Daicel Corporation, mobile phase: hexane/2-propanol/diethylamine=700/100/1), and a fraction having a shorter retention time was obtained as the title compound (1.57 g).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.48-1.64(6H,m), 1.70-1.86(3H,m), 2.69(1H,td,J=11.7,2.7Hz), 2.85-1.96(2H,m), 2.97-3.00(3H,m), 3.07(1H,dt,J=11.5,2.4Hz), 3.28-3.56(3H,m), 3.63(2H,d,J=2.7Hz), 5.38(1H,dt,J=8.3Hz), 6.90-7.06(3H,m).

Example 19

N-((2R,3S)-1-acetyl-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0216] To a solution of N-((2R,3S)-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (300 mg) in THF (15 ml) were added acetyl chloride (0.079 ml) and triethylamine (0.208 ml) at room temperature, and the mixture was stirred at the same temperature for 4 hr. To the reaction mixture was added saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was successively washed with saturated aqueous ammonium chloride solution and saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (315 mg).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.59-1.90(8H,m), 1.95-2.24(6H,m), 2.79-4.43(10H,m), 4.48-

6.25(2H,m), 6.87-7.16(3H,m).

Example 20

methyl (2R,3S)-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate

[0217] To a solution of N-((2R,3S)-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (50 mg) in THF (5 ml) were added methyl chloroformate (18 mg) and triethylamine (38 mg) at room temperature, and the mixture was stirred at the same temperature overnight. To the reaction mixture was added saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (52 mg).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.51-2.12(12H,m), 2.74-2.86(1H,m), 2.87-2.98(1H,m), 3.00(3H,s), 3.54-3.65(2H,m), 3.68(1H,t,J=2.5Hz), 3.72(3H,s), 3.90-4.07(2H,m), 4.64(1H,brs), 6.02(1H,brs), 6.86-7.16(3H,m).

Example 21

N-((2R,3S)-2-(((cis-4-(2,3,6-trifluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

A) 8-(2,3,6-trifluorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene

[0218] To a mixed solution of 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dioxaspiro[4.5]dec-7-ene (1 g), 2-bromo-1,3,4-trifluorobenzene (1.189 g), and sodium hydrogen carbonate (0.631 g) in DME (15 ml)-water (3.00 ml) was added $PdCl_2$(dppf) (0.275 g) at room temperature. The mixture was heated under reflux at 100°C under a nitrogen atmosphere overnight. The mixture was filtered through celite, and the filtrate was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (0.970 g).

MS, found: 271.0.

B) 8-(2,3,6-trifluorophenyl)-1,4-dioxaspiro[4.5]decane

[0219] To a solution of 8-(2,3,6-trifluorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene (6.94 g) in ethanol (60 ml) was added 10% palladium/carbon (2.73 g) at room temperature. The mixture was stirred at room temperature under a hydrogen atmosphere for 7 hr. The mixed solution was filtered, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (4.23 g).
MS, found: 273.0.

C) 4-(2,3,6-trifluorophenyl)cyclohexanone

[0220] To a mixed solution of 8-(2,3,6-trifluorophenyl)-1,4-dioxaspiro[4.5]decane (6.49 g) in acetone (100 ml) and water (20 ml) was added 6 mol/l hydrochloric acid (7.95 ml) at room temperature. The mixture was stirred at 70°C for 1 hr. The solvent was evaporated under reduced pressure, saturated brine was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (5.24 g).
MS, found: 229.1.

D) cis-4-(2,3,6-trifluorophenyl)cyclohexanol

[0221] To a solution of 4-(2,3,6-trifluorophenyl)cyclohexanone (3.98 g) in THF (50 ml) was added lithium tri(sec-butyl)borohydride 1 mol/l THF solution (22.67 ml) at -78°C. The mixture was stirred at -78°C under a nitrogen atmosphere for 1 hr. To the mixture was added dropwise 30% hydrogen peroxide water at -78°C, and the mixture was warmed to room temperature and stirred for 5 min. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride solution, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (3.66 g).
^{1}H NMR (300 MHz,$CDCl_3$)δ 1.39(1H,d,J=3.0Hz), 1.54(1H,d,J=2.7Hz), 1.58-1.74(3H,m), 1.84-1.98(2H,m), 2.15-2.37(2H,m), 3.02(1H,tt,J=12.6,3.3Hz), 4.11-4.19(1H,m), 6.76(1H,tdd,J=9.5,4.2,2.3Hz), 6.95(1H,qd,J=9.1,4.9Hz).

E) 3-bromo-2-(((cis-4-(2,3,6-trifluorophenyl)cyclohexyl)oxy)methyl)pyridine

[0222] A solution of cis-4-(2,3,6-trifluorophenyl)cyclohexanol (3.66 g) in THF (100 ml) was cooled to 0°C, 60% sodium hydride (1.272 g) was added, and the mixture was stirred under a calcium chloride tube dry atmosphere at room temperature for 10 min. To the reaction mixture was added 3-bromo-2-(chloromethyl)pyridine (4.92 g), and the mixture was stirred at 70°C for 3 hr. Water was added to the mixture at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (3.73 g).
MS, found: 401.0,403.0.

F) N-(2-(((cis-4-(2,3,6-trifluorophenyl)cyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide

[0223] To a mixed solution of 3-bromo-2-(((cis-4-(2,3,6-trifluorophenyl)cyclohexyl)oxy)methyl)pyridine (4.0 g), methanesulfonamide (1.901 g), di-tert-butyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (0.424 g), and cesium carbonate (6.51 g) in DME (100 ml) was added tris(dibenzylideneacetone)dipalladium(0) (0.915 g) at room temperature. The mixture was heated under reflux at 100°C under a nitrogen atmosphere overnight. The reaction mixture was filtered through celite, and the filtrate was washed with water and saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (3.97 g).
MS, found: 415.2.

G) N-((2R,3S)-2-(((cis-4-(2,3,6-trifluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0224] To a mixed solution of N-(2-(((cis-4-(2,3,6-trifluorophenyl)cyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide (3.95 g) in ethanol (100 ml) and acetic acid (11.11 ml) was added 5% rhodium/carbon (3.92 g) at room temperature. The mixture was stirred at room temperature under a hydrogen atmosphere for 6 hr. The mixed solution was filtered, and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate-hexane, and the resulting precipitate was collected by filtration. The obtained precipitate was dissolved in saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was separated by HPLC (column: CHIRALPAK AD(AF003), 50 mmID×500 mmL, manufactured by Daicel Corporation, mobile phase: hexane/2-propanol/diethylamine=700/300/1), and a fraction having a shorter retention time was obtained as the title compound (1.02 g).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.39-1.85(12H,m), 1.89-2.04(2H,m), 2.06-2.24(2H,m),

2.70(1H,td,J=11.7,2.7Hz), 2.92(1H,ddd,J=8.2,4.4,2.1Hz), 3.00-3.14(2H,m), 3.33-3.43(1H,m), 3.45-3.55(1H,m), 3.63(2H,d,J=2.3Hz), 5.37(1H,brs), 6.68-6.80(1H,m), 6.94(1H,qd,J=9.1,4.9Hz).

Example 22

N-((2R,3S)-1-acetyl-2-(((cis-4-(2,3,6-trifluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0225] To a solution of N-((2R,3S)-2-(((cis-4-(2,3,6-trifluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (900 mg) and triethylamine (0.893 ml) in THF (15 ml) was added acetyl chloride (0.303 ml) at room temperature, and the mixture was stirred for 1 hr. Water was added to the mixture at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (920 mg).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.45-1.57(3H,m), 1.58-1.69(3H,m), 1.74-2.10(6H,m), 2.18(2H,s),2.97-3.06(4H,m), 3.06-3.30(1H,m), 3.51-3.79(4H,m), 3.81-3.96(1H,m), 4.24-4.64(1H,m), 4.98-5.28(1H,m), 5.67(1H,d,J=8.7Hz), 6.68-6.82(1H,m), 6.88-7.03(1H,m).

Example 23

N-((2R,3S)-2-(((cis-4-(2-(trifluoromethyl)phenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

A) cis-4-(2-(trifluoromethyl)phenyl)cyclohexanol

[0226] To a solution of 4-(2-(trifluoromethyl)phenyl)cyclohexanone (2.56 g) in THF (50 ml) was added dropwise over 4 min at -78°C lithium tri(sec-butyl)borohydride 1 mol/l THF solution (13.74 ml). The mixture was stirred at -78°C for 2 hr, and at 0°C overnight. To the mixture were added dropwise acetone, water and 30% hydrogen peroxide water at 0°C, and the mixture was stirred at room temperature for 1 hr, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (2.13 g).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.31(1H,d,J=2.3Hz), 1.58-1.79(4H,m), 1.83-2.01(4H,m),

2.95(1H,t,J=11.2Hz), 4.14-4.25(1H,m), 7.22-7.31(1H,m), 7.46-7.65(3H,m).

B) 3-bromo-2-(((cis-4-(2-(trifluoromethyl)phenyl)cyclohexyl)oxy)methyl)pyridine

[0227] To a solution of cis-4-(2-(trifluoromethyl)phenyl)cyclohexanol (9.36 g) in THF (150 ml) was added at 0°C potassium hexamethyl disilazide 1.0 mol/l tert-butyl methyl ether solution (57.5 ml), and the mixture was stirred for 30 min. To the reaction mixture was added 3-bromo-2-(bromomethyl)pyridine (19.26 g), and the mixture was stirred under a calcium chloride tube dry atmosphere at 60°C for 5 hr, potassium carbonate (15.89 g) and 2-mercaptoacetic acid (5.32 ml) were added at room temperature, and the mixture was stirred overnight. Water was added to the mixture at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1 mol/l aqueous sodium hydroxide solution and saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by NH silica gel chromatography and silica gel column chromatography (ethyl acetate/hexane) to give the title compound (3.87 g).
MS, found: 414.1,416.1.

C) N-(2-(((cis-4-(2-(trifluoromethyl)phenyl)cyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide

[0228] To a solution of 3-bromo-2-(((cis-4-(2-(trifluoromethyl)phenyl)cyclohexyl)oxy)methyl)pyridine (3.87 g) in DME (25 ml) were added methanesulfonamide (1.066 g), di-tert-butyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (0.159 g), tris(dibenzylideneacetone)dipalladium(0) (0.171 g) and cesium carbonate (4.57 g) at room temperature. The mixture was stirred at 80°C under a nitrogen atmosphere overnight. Water was added to the reaction mixture at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (3.85 g).
MS, found: 429.2.

D) N-((2R,3S)-2-(((cis-4-(2-(trifluoromethyl)phenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0229] A mixture of N-(2-(((cis-4-(2-(trifluoromethyl)phenyl)cyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide (0.93 g), 5% rhodium/carbon (0.893 g), ethanol (27 ml) and acetic acid (3.00 ml) was stirred at room temperature under a hydrogen atmosphere for 11 hr. The mixture was filtered, and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, the organic layer was washed with 1 mol/l aqueous sodium

hydroxide solution and saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was washed with IPE, and recrystallized from ethanol/hexane to give a white solid (361 mg). The mother liquor was concentrated under reduced pressure. The residue was purified by NH silica gel chromatography (ethyl acetate/hexane) to give a white solid (208 mg). The obtained white solids (361 mg and 208 mg) were combined, and separated by HPLC (column: CHIRALPAK AD(LF001), 50 mmID×500 mmL, manufactured by Daicel Corporation, mobile phase: hexane/2-propanol/diethylamine=900/100/1), and a fraction having a shorter retention time was obtained as the title compound (0.257 g).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.51(2H,brs), 1.57-1.88(8H,m), 2.03(3H,d,J=13.0Hz), 2.71(1H,td,J=12.0,2.8Hz), 2.86-2.96(2H,m), 2.99(3H,s), 3.09(1H,d,J=11.0Hz), 3.39(1H,dd,J=9.3,7.8Hz), 3.54(1H,dd,J=9.5,4.5Hz), 3.60-3.69(2H,m), 5.35(1H,d,J=7.6Hz), 7.27-7.33(1H,m), 7.43-7.54(2H,m), 7.61(1H,s).

Example 24

N-((2R,3S)-1-acetyl-2-(((cis-4-(2-(trifluoromethyl)phenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0230] To a solution of N-((2R,3S)-2-(((cis-4-(2-(trifluoromethyl)phenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (97.2 mg) and triethylamine (0.094 ml) in THF (5 ml) was added acetic anhydride (0.042 ml) at room temperature, and the mixture was stirred under a calcium chloride tube dry atmosphere overnight. Water was added to the mixture at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography and NH silica gel column chromatography (ethyl acetate/hexane) to give the title compound (87.8 mg).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.48-2.31(14H,m), 2.50-3.22(5H,m), 3.31-3.79(3H,m), 3.84-4.06(1H,m), 4.30-4.65(1H,m), 5.17(1H,dt,J=9.0,4.4Hz), 5.63(1H,brs), 6.31(1H,d,J=7.6Hz), 7.20-7.29(1H,m), 7.47-7.64(3H,m).

Example 25

N-((2R,3S)-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)methyl)-1-glycoloylpiperidin-3-yl)methanesulfonamide

[0231] To a solution of N-((2R,3S)-2-(((cis-4-(2,3-

difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (100.2 mg) in pyridine (2 ml) was added 2-chloro-2-oxoethyl acetate (51 mg) at room temperature. The mixture was stirred under a calcium chloride tube dry atmosphere at the same temperature overnight. To the reaction mixture was added 1 mol/l hydrochloric acid at room temperature, and the mixture was extracted with ethyl acetate. The extract was successively washed with saturated aqueous sodium hydrogen carbonate solution, and saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (2 ml), 1 mol/l aqueous sodium hydroxide solution (1.25 ml) was added at 0°C, and the mixture was stirred at room temperature for 1 hr. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (104 mg).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.58-2.23(11H,m), 2.70-3.00(2H,m), 3.01(3H,s), 3.05-3.37(1H,m), 3.44-4.00(5H,m), 4.01-4.62(3H,m), 4.79-5.29(1H,m), 5.89(1H,d,J=7.95Hz), 6.81-7.15(3H,m).

Example 26

N-(cis-2-(((cis-4-(2-methoxyphenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

A) 8-(2-methoxyphenyl)-1,4-dioxaspiro[4.5]dec-7-ene

[0232] To a mixed solution of 1,4-dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (3.00 g), (2-methoxyphenyl)boronic acid (2.37 g), sodium carbonate (4.41 g) and lithium chloride (22 mg) in DME (40 ml)/water (10 ml) was added tetrakis(triphenylphosphine)palladium(0) (601 mg), and the mixture was stirred under a nitrogen atmosphere at 90°C for 2 hr. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The obtained organic layer was washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.60 g).
MS, found: 247.1.

B) 4-(2-methoxyphenyl)cyclohexanone

[0233] To a solution of 8-(2-methoxyphenyl)-1,4-dioxaspiro[4.5]dec-7-ene (1.60 g) in ethanol (25 ml) was added 10% palladium/carbon (346 mg), and the mixture was stirred under a

hydrogen atmosphere (normal pressure) at room temperature for 2 hr. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. To a solution of the residue in acetone (15 ml) was added 2 mol/l hydrochloric acid (15 ml), and the mixture was stirred at 60°C for 2 hr. The reaction mixture was extracted with ethyl acetate. The obtained organic layer was washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.02 g).
MS, found: 205.1.

C) cis-4-(2-methoxyphenyl)cyclohexanol

[0234] Under a nitrogen atmosphere, to a solution of 4-(2-methoxyphenyl)cyclohexanone (1.00 g) in THF (20 ml) was added dropwise lithium tri(sec-butyl)borohydride 1 mol/l THF solution (6.4 ml) at 0°C, and the mixture was stirred at the same temperature for 1 hr. To the reaction mixture were successively added water and 30% hydrogen peroxide water at 0°C, and the mixture was stirred at the same temperature for 5 min and extracted with ethyl acetate. The obtained organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (893 mg).
^{1}H NMR (300 MHz,DMSO-d_6)δ 1.36-1.59(4H,m), 1.66-1.87 (4H,m), 2.80-2.95(1H,m), 3.76(3H,s), 3.86-3.94(1H,m), 4.22-4.39(1H,m), 6.76-7.00(2H,m), 7.04-7.27(2H,m).

D) 3-bromo-2-(((cis-4-(2-methoxyphenyl)cyclohexyl)oxy)methyl)pyridine

[0235] To a solution of cis-4-(2-methoxyphenyl)cyclohexanol (889 mg) in THF (20 ml) was added 60% sodium hydride (345 mg) at 0°C, and the mixture was stirred at under a nitrogen atmosphere at room temperature for 2 hr. To the reaction mixture was added 3-bromo-2-(chloromethyl)pyridine (1.16 g), and the mixture was stirred at room temperature for 2 hr, and at 70°C for 3 hr. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The obtained organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (743 mg).
MS, found: 376.0,378.0.

E) N-(2-(((cis-4-(2-methoxyphenyl)cyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide

[0236] A mixture of 3-bromo-2-(((cis-4-(2-methoxyphenyl)cyclohexyl)oxy)methyl)pyridine (740 mg), methanesulfonamide (224 mg), di-tert-butyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (100 mg), tris(dibenzylideneacetone)dipalladium(0) (90 mg), cesium carbonate (961 mg) and DME (10 ml) was heated under reflux under a nitrogen atmosphere for 6 hr. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The obtained organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (723 mg).
MS, found: 391.2.

F) N-(cis-2-(((cis-4-(2-methoxyphenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0237] To a mixed solution of N-(2-(((cis-4-(2-methoxyphenyl)cyclohexyl)oxy)methyl)pyridin-3-yl)methanesulfonamide (669 mg) in ethanol (9 ml)/acetic acid (1 ml) was added 5% rhodium/carbon (705 mg), and the mixture was stirred under a hydrogen atmosphere (normal pressure) at room temperature for 20 hr. Rhodium/carbon was filtered off, toluene was added, and the solvent was evaporated under reduced pressure. The residue was washed with diisopropyl ether, and the obtained solid was dissolved in ethyl acetate. Saturated aqueous sodium hydrogen carbonate solution was added, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by NH silica gel column chromatography (ethyl acetate/hexane) to give the title compound (123 mg).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.48-1.89(9H,m), 1.94-2.11(4H,m), 2.59-2.76(1H,m), 2.84-3.15(6H,m), 3.28-3.43(1H,m), 3.45-3.54(1H,m), 3.56-3.69(2H,m), 3.82(3H,s), 5.27-5.54(1H,m), 6.81-6.88(1H,m), 6.89-6.98(1H,m), 7.09-7.24(2H,m).

Example 27

N-((2R,3S)-2-(((cis-4-(2-methoxyphenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0238] N-(cis-2-(((cis-4-(2-methoxyphenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (2.0 g) was separated by HPLC (column: CHIRALPAK AD(AF003), 50 mmID×500 mmL, manufactured by Daicel Corporation, mobile phase: hexane/2-propanol/diethylamine=700/300/1), and a fraction having a shorter retention time was obtained as the title compound (783 mg) .

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.45-1.83(9H,m), 1.90-2.10(4H,m), 2.62-2.76(1H,m), 2.86-

3.13(6H,m), 3.32-3.42(1H,m), 3.46-3.55(1H,m), 3.56-3.68(2H,m), 3.82(3H,s), 5.30-5.51(1H,m), 6.82-6.88(1H,m), 6.88-6.97(1H,m), 7.10-7.24(2H,m).

Example 28

N-((2R,3S)-1-(cyclopropylcarbonyl)-2-(((cis-4-(2-methoxyphenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0239] To a solution of N-((2R,3S)-2-(((cis-4-(2-methoxyphenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (200 mg) and triethylamine (102 mg) in THF (5 ml) was added cyclopropanecarbonyl chloride (79 mg) at room temperature, and the mixture was stirred at the same temperature for 30 min. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (227 mg).

^{1}H NMR (300 MHz,DMSO-d_6)δ 0.57-0.87(4H,m), 1.31-1.81(10H,m), 1.83-2.07(3H,m), 2.56-3.07(4H,m), 3.10-3.88(8H,m), 3.99-5.01(2H,m), 6.80-7.39(5H,m).

Example 29 isopropyl cis-3-((dimethylsulfamoyl)amino)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate A) tert-butyl 4-((3-bromopyridin-2-yl)methoxy)piperidine-1-carboxylate

[0240] A solution of tert-butyl 4-hydroxypiperidine-1-carboxylate (9.63 g) in THF (100 ml) was cooled to 0°C, 60% sodium hydride (3.19 g) was added, and the mixture was stirred for 20 min. To the reaction mixture was added a solution of 3-bromo-2-(bromomethyl)pyridine (10.00 g) in THF (100 ml), and the mixture was stirred at room temperature under an argon atmosphere overnight. To the mixture was added water at 0°C, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (13.12 g).
MS, found: 371.1,373.1.

B) tert-butyl 4-((3-((dimethylsulfamoyl)amino)pyridin-2-yl)methoxy)piperidine-1-carboxylate

[0241] To a mixed solution of tert-butyl 4-((3-bromopyridin-2-yl)methoxy)piperidine-1-

carboxylate (5 g), N,N-dimethylsulfuric acid diamide (2.007 g), di-tert-butyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (0.686 g), and cesium carbonate (6.58 g) in DME (50 ml) was added tris(dibenzylideneacetone)dipalladium(0) (0.617 g) at room temperature. The mixture was heated under reflux at 100°C under an argon atmosphere for 20 hr. The reaction mixture was neutralized with 1 mol/l hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with saturated brine, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane, methanol/ethyl acetate) and NH silica gel chromatography (ethyl acetate/hexane) to give the title compound (4.10 g).
MS, found: 415.2.

C) tert-butyl 4-((cis-3-((dimethylsulfamoyl)amino)piperidin-2-yl)methoxy)piperidine-1-carboxylate

[0242] To a mixed solution of tert-butyl 4-((3-((dimethylsulfamoyl)amino)pyridin-2-yl)methoxy)piperidine-1-carboxylate (4.00 g) in ethanol (100 ml) and acetic acid (10.00 ml) was added 5% rhodium/carbon (3.97 g) at room temperature. The mixture was stirred at room temperature under a hydrogen atmosphere overnight. The mixed solution was filtered, and the solvent was evaporated under reduced pressure. To the residue were added ethyl acetate and hexane and the precipitated solid was collected by filtration. The obtained solid was dissolved in saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to give the title compound (1.870 g).
MS, found: 421.2.

D) isopropyl cis-2-(((1-(tert-butoxycarbonyl)piperidin-4-yl)oxy)methyl)-3-((dimethylsulfamoyl)amino)piperidine-1-carboxylate

[0243] To a solution of tert-butyl 4-((cis-3-((dimethylsulfamoyl)amino)piperidin-2-yl)methoxy)piperidine-1-carboxylate (100 mg) and N,N-diisopropylethylamine (0.164 ml) in THF (3 ml) was added isopropyl chloroformate (29.1 mg) at room temperature, and the mixture was stirred for 2 days. Water was added to the mixture at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (120 mg).
MS, found: 407.2.

E) isopropyl cis-3-((dimethylsulfamoyl)amino)-2-((piperidin-4-yloxy)methyl)piperidine-1-carboxylate hydrochloride

[0244] To isopropyl cis-2-(((1-(tert-butoxycarbonyl)piperidin-4-yl)oxy)methyl)-3-((dimethylsulfamoyl)amino)piperidine-1-carboxylate (120 mg) was added 4 mol/l hydrogen chloride ethyl acetate solution (5 ml) at room temperature, and the mixture was stirred for 2 hr. The solvent in the mixture was evaporated under reduced pressure to give the title compound (106 mg).
MS, found: 407.2.

F) isopropyl cis-3-((dimethylsulfamoyl)amino)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate

[0245] To a solution of isopropyl cis-3-((dimethylsulfamoyl)amino)-2-((piperidin-4-yloxy)methyl)piperidine-1-carboxylate hydrochloride (106 mg) and cesium carbonate (235 mg) in NMP (2 ml) was added 2-chloropyrimidine (41.2 mg), and the mixture was stirred at 90°C for 2 hr. Water was added to the mixture at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (89 mg)
.

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.24(3H,s), 1.26(3H,s), 1.42-1.58(2H,m), 1.60-1.66(1H,m), 1.67-1.79(2H,m), 1.88-2.00(2H,m), 2.00-2.11(1H,m), 2.69-2.78(1H,m), 2.80(6H,s), 3.35-3.54(3H,m), 3.62(1H,tt,J=8.2,3.9Hz), 3.70(1H,dd,J=9.7,4.4Hz), 3.96(2H,dd,J=9.8,8.3Hz), 4.26(2H,dt,J=13.3,5.1Hz), 4.46-4.69(1H,m), 4.93(1H,spt,J=6.2Hz), 5.51(1H,d,J=8.0Hz), 6.47(1H,t,J=4.7Hz), 8.29(2H,d,J=4.5Hz).

Example 30

(2R,3S)-N-ethyl-3-((methylsulfonyl)amino)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)piperidine-1-carboxamide

[0246] To a solution of N-[cis-2-(4-phenyl-cyclohexyloxymethyl)-piperidin-3-yl]-methanesulfonamide (280 mg), triethylamine (0.319 ml) in THF (2 ml) was added ethylisocyanate (81 mg) at 0°C, and the mixture was stirred at room temperature overnight. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane). The obtained compound was separated by HPLC (column: CHIRALPAK IC(ME001), 50 mmID×500 mmL, manufactured by Daicel Corporation, mobile phase: hexane/2-propanol =200/800), and a fraction having a longer retention time was obtained as the title compound (153 mg).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.14(3H,t,J=7.2Hz), 1.56-1.80(9H,m), 1.98-2.10(3H,m), 2.45-2.59(1H,m), 2.84(1H,qd,J=12.7,2.8Hz), 3.01(3H,s), 3.26(2H,qd,J=7.2,5.3Hz), 3.52-3.81(4H,m), 3.93(1H,dd,J=9.2,7.7Hz), 4.48-4.59(1H,m), 4.70(1H,t,J=5.1Hz), 5.74(1H,d,J=7.7Hz), 7.14-7.35(5H,m).

Example 31

N-((2R,3S)-1-(cyclopropylcarbonyl)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

[0247] To a solution of N-((2R,3S)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (58 mg), triethylamine (0.044 ml) in THF (3 ml) was added cyclopropanecarbonyl chloride (0.022 ml) at room temperature, and the mixture was stirred under a calcium chloride tube dry atmosphere overnight. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (62 mg).

^{1}H NMR (300 MHz,$CDCl_3$)δ 0.74-0.85(2H,m), 0.94-1.05(2H,m), 1.58-1.88(10H,m), 2.01-2.23(3H,m), 2.45-2.63(1H,m), 2.92-3.18(4H,m), 3.41-3.77(3H,m), 3.89-4.60(2H,m), 4.69-5.23(1H,m), 5.46-6.39(1H,m), 7.13-7.25(3H,m), 7.27-7.34(2H,m).

Example 32 methyl (2R,3S)-3-((methylsulfonyl)amino)-2-(((cis-4-(2-(trifluoromethyl)phenyl)cyclohexyl)oxy)methyl)piperidine-1-carboxylate

[0248] To a solution of N-((2R,3S)-2-(((cis-4-(2-(trifluoromethyl)phenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (51.2 mg) and triethylamine (0.049 ml) in THF (2 ml) was added methyl chloroformate (0.018 ml) at room temperature, and the mixture was stirred under a calcium chloride tube dry atmosphere overnight. Water was added to the mixture at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (56.3 mg).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.55-1.89(9H,m), 1.97-2.19(3H,m), 2.80(1H,td,J=13.3,3.0Hz), 2.88-3.10(4H,m), 3.44-3.71(3H,m), 3.72-3.78(3H,m), 4.02(2H,t,J=9.1Hz), 4.67(1H,brs), 6.15(1H,brs), 7.19-7.31(1H,m), 7.47-7.67(3H,m).

Example 340

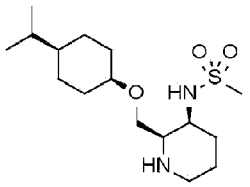
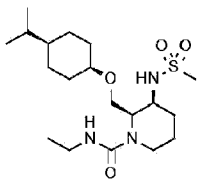
N-((2R,3S)-1-glycoloyl-2-(((cis-4-(2,3,6-trifluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide

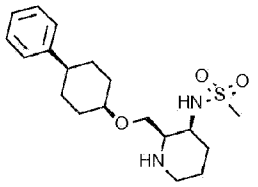
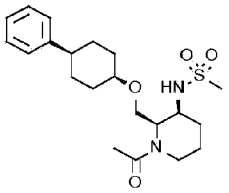
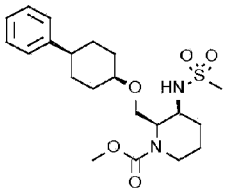
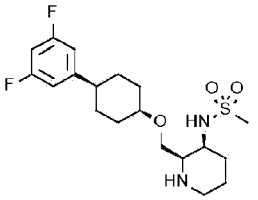
[0249] To a mixture of N-((2R,3S)-2-(((cis-4-(2,3,6-trifluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide (100.8 mg) and pyridine (2.0 ml) was added 2-chloro-2-oxoethyl acetate (49.1 mg) at room temperature. The mixture was stirred at room temperature overnight. To the mixture was added 1 mol/l hydrochloric acid at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. To a mixture of the residue and methanol (2.0 ml) was added 1 mol/l aqueous sodium hydroxide solution at 0°C. The mixture was stirred at room temperature for 1 hr. Water was added to the mixture at room temperature, 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 (108.1 mg).

^{1}H NMR (300 MHz,$CDCl_3$)δ 1.48-1.68(6H,m), 1.85-2.19(6H,m), 2.75-3.12(4H,m), 3.13-3.89(6H,m), 3.93-4.66(3H,m), 4.87-5.16(1H,m), 5.40(1H,d,J=8.7Hz), 6.66-6.83(1H,m), 6.96(1H,qd,J=9.1,4.9Hz) .

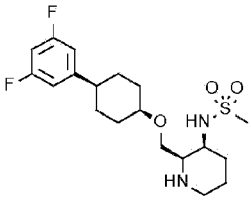
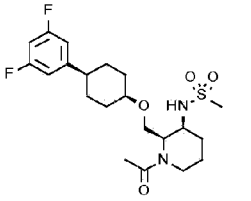
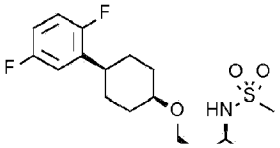
[0250] The compounds of Examples 33-339 and 341-372 were produced according to the aforementioned production methods, a method shown in the Examples, or a method analogous thereto. The Example compounds produced are shown in the following Tables. The compounds of Examples 80, 82, 103, 104, and 353-372 are provided for reference purposes. In the Tables, MS shows measured values.

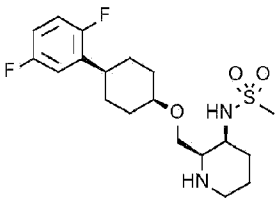
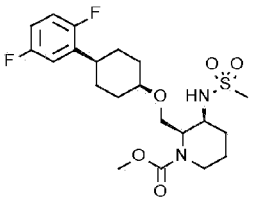
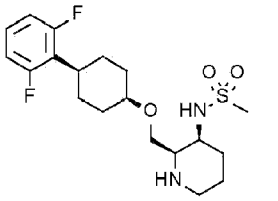
[Table 1-1]

Ex. No.	IUPAC name	Structure	MS
1	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		333.2
2	(2R,3S)-N-ethyl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide		404.2

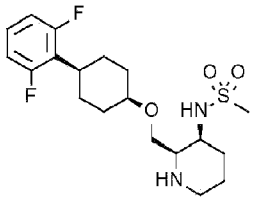
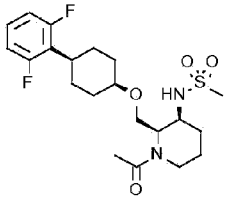
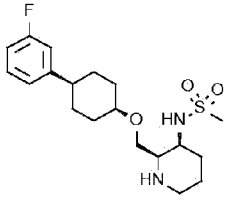
Ex. No.	IUPAC name	Structure	MS
3	N-((2R,3S)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		367.1
4	N-((2R,3S)-1-acetyl-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		409.2
5	methyl (2R,3S)-3-((methylsulfonyl)amino)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidine-1-carboxylate		425.1
6	N-(cis-2-(((cis-4-(3,5-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide acetate		403.2

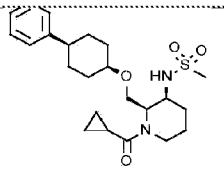
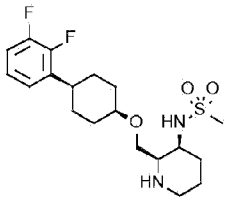
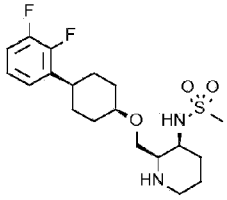
[Table 1-2]

Ex. No.	IUPAC name	Structure	MS
7	N-((2R,3S)-2-(((cis-4-(3,5-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		403.2
8	N-((2R,3S)-1-acetyl-2-(((cis-4-(3,5-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		445.3
9	N-(cis-2-(((cis-4-(2,5-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		403.2

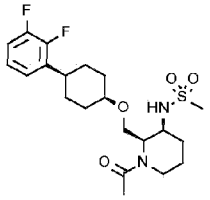
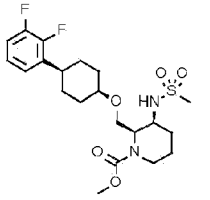
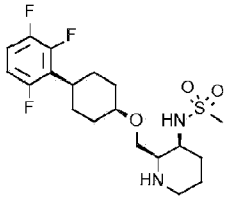
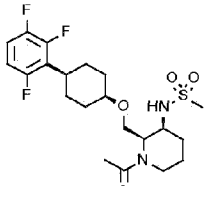
Ex. No.	IUPAC name	Structure	MS
			
10	N-((2R,3S)-2-(((cis-4-(2,5-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		403.2
11	methyl (2R,3S)-2-(((cis-4-(2,5-difluorophenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		461.2
12	N-(cis-2-(((cis-4-(2,6-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		403.2

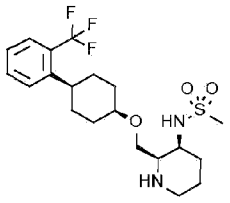
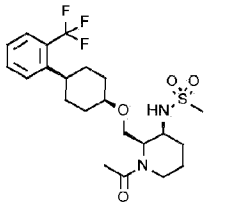
[Table 1-3]

Ex. No.	IUPAC name	Structure	MS
13	N-((2R,3S)-2-(((cis-4-(2,6-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		403.2
14	N-((2R,3S)-1-acetyl-2-(((cis-4-(2,6-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		445.2
15	N-((2R,3S)-2-(((cis-4-(3-fluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		385.1
16	N-((2R,3S)-1-(cyclopropylcarbonyl)-2-(((cis-4-(3-fluorophenyl)cyclohexyl)oxy)-		453.2

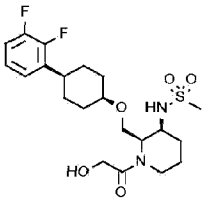
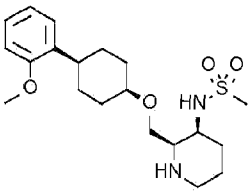
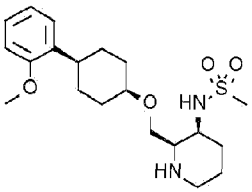
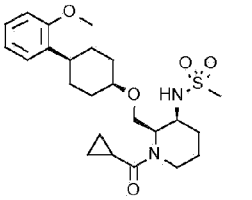
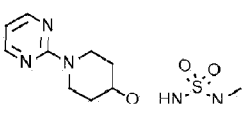
Ex. No.	IUPAC name	Structure	MS
	methyl)piperidin-3-yl)methanesulfonamide		
17	N-(cis-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		403.1
18	N-((2R,3S)-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		403.2

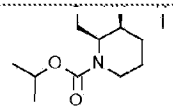
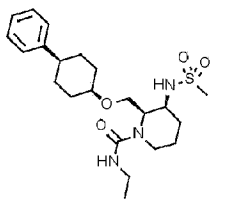
[Table 1-4]

Ex. No.	IUPAC name	Structure	MS
19	N-((2R,3S)-1-acetyl-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		445.2
20	methyl (2R,3S)-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		459.2
21	N-((2R,3S)-2-(((cis-4-(2,3,6-trifluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		421.1
22	N-((2R,3S)-1-acetyl-2-(((cis-4-(2,3,6-trifluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		463.2

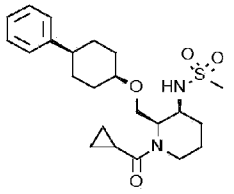
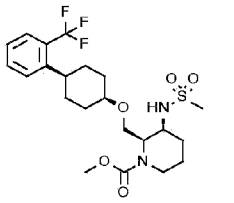
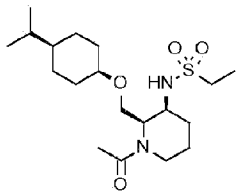
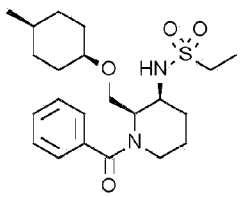
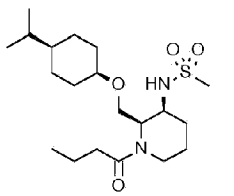
Ex. No.	IUPAC name	Structure	MS
23	N-((2R,3S)-2-(((cis-4-(2-(trifluoromethyl)phenyl)-cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		435.1
24	N-((2R,3S)-1-acetyl-2-(((cis-4-(2-(trifluoromethyl)phenyl)-cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		477.2

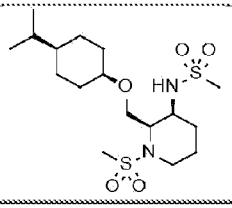
[Table 1-5]

Ex. No.	IUPAC name	Structure	MS
25	N-((2R,3S)-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)-methyl)-1-glycoloylpiperidin-3-yl)methanesulfonamide		461.2
26	N-(cis-2-(((cis-4-(2-methoxyphenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		397.2
27	N-((2R,3S)-2-(((cis-4-(2-methoxyphenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		397.2
28	N-((2R,3S)-1-(cyclopropylcarbonyl)-2-(((cis-4-(2-methoxyphenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		465.2
29	isopropyl cis-3-((dimethylsulfamoyl)amino)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		485.2

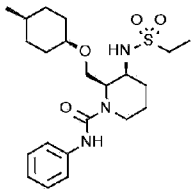
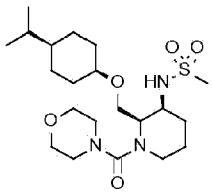
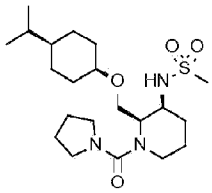
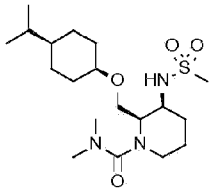
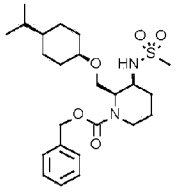
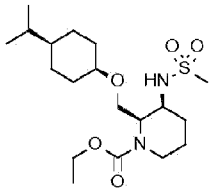
Ex. No.	IUPAC name	Structure	MS
			
30	(2R,3S)-N-ethyl-3-((methylsulfonyl)amino)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidine-1-carboxamide		438.3

[Table 1-6]

Ex. No.	IUPAC name	Structure	MS
31	N-((2R,3S)-1-(cyclopropylcarbonyl)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		435.2
32	methyl (2R,3S)-3-((methylsulfonyl)amino)-2-(((cis-4-(2-(trifluoromethyl)phenyl)-cyclohexyl)oxy)methyl)piperidine-1-carboxylate		493.2
33	N-((2R,3S)-1-acetyl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)ethanesulfonamide		389.2
34	N-(cis-1-benzoyl-2-(((cis-4-methylcyclohexyl)oxy)methyl)-piperidin-3-yl)ethanesulfonamide		423.2
35	N-(cis-1-butyryl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		403.2
36	N-(cis-2-(((cis-4-		409.2

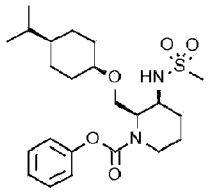
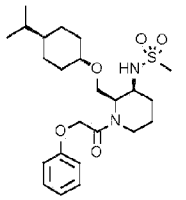
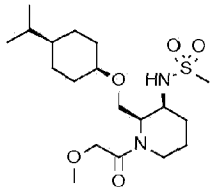
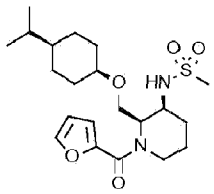
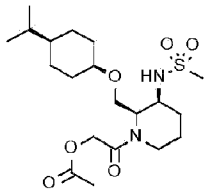
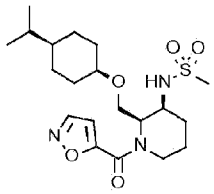
Ex. No.	IUPAC name	Structure	MS
	isopropylcyclohexyl)oxy)methyl)-1-(methylsulfonyl)piperidin-3-yl)methanesulfonamide		

[Table 1-7]

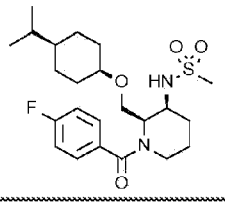
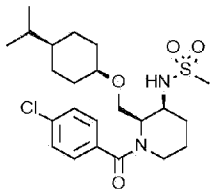
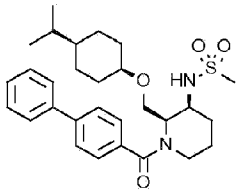
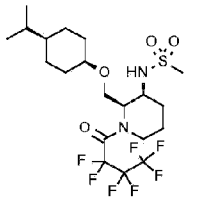
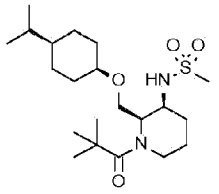
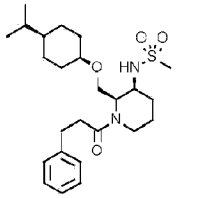
Ex. No.	IUPAC name	Structure	MS
37	cis-3-((ethylsulfonyl)amino)-2-(((cis-4-methylcyclohexyl)oxy)methyl)-N-phenylpiperidine-1-carboxamide		438.1
38	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-(morpholin-4-ylcarbonyl)piperidin-3-yl)methanesulfonamide		446.2
39	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-(pyrrolidin-1-ylcarbonyl)piperidin-3-yl)methanesulfonamide		430.2
40	cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-N,N-dimethyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide		404.2
41	benzyl cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		465.1
42	ethyl cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		403.2

Ex. No.	IUPAC name	Structure	MS

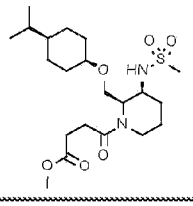
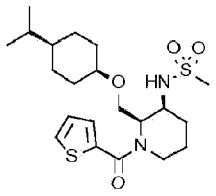
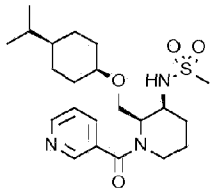
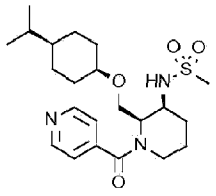
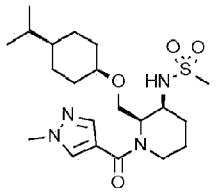
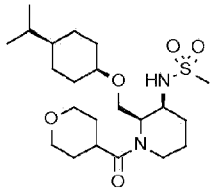
[Table 1-8]

Ex. No.	IUPAC name	Structure	MS
43	phenyl cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		453.2
44	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-(phenoxyacetyl)piperidin-3-yl)methanesulfonamide		467.2
45	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-(methoxyacetyl)piperidin-3-yl)methanesulfonamide		405.2
46	N-(cis-1-(2-furoyl)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		427.2
47	2-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidin-1-yl)-2-oxoethyl acetate		431.1
48	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-(1,2-oxazol-5-ylcarbonyl)piperidin-3-yl)methanesulfonamide		426.2

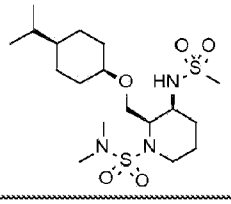
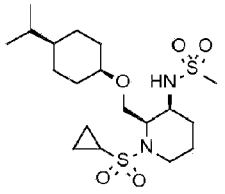
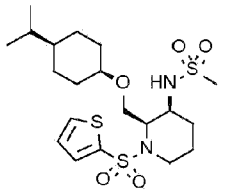
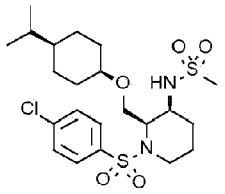
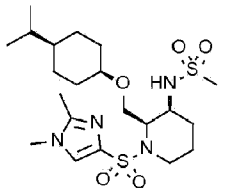
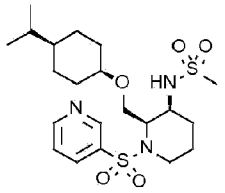
[Table 1-9]

Ex. No.	IUPAC name	Structure	MS
49	N-(cis-1-(4-fluorobenzoyl)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		453.1
50	N-(cis-1-(4-chlorobenzoyl)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		469.1
51	N-(cis-1-(biphenyl-4-ylcarbonyl)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		513.2
52	N-(cis-1-(2,2,3,3,4,4,4-heptafluorobutanoyl)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		527.1
53	N-(cis-1-(2,2-dimethylpropanoyl)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		415.1
54	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-(3-phenylpropanoyl)piperidin-3-yl)methanesulfonamide		465.2

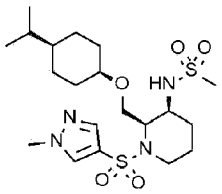
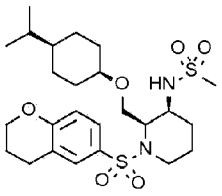
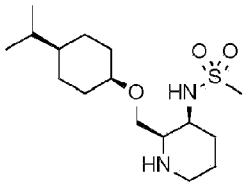
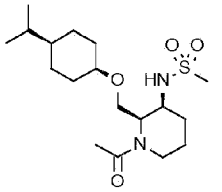
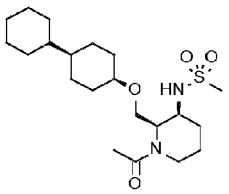
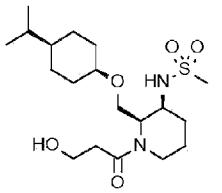
[Table 1-10]

Ex. No.	IUPAC name	Structure	MS
55	methyl 4-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidin-1-yl)-4-oxobutanoate		447.2
56	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-(2-thienylcarbonyl)piperidin-3-yl)methanesulfonamide		441.1
57	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-(pyridin-3-ylcarbonyl)piperidin-3-yl)methanesulfonamide		438.2
58	N-(cis-1-isonicotinoyl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		438.1
59	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-((1-methyl-1H-pyrazol-4-yl)carbonyl)piperidin-3-yl)methanesulfonamide		441.3
60	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-(tetrahydro-2H-pyran-4-ylcarbonyl)piperidin-3-yl)methanesulfonamide		445.3

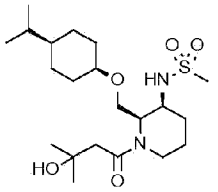
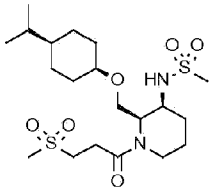
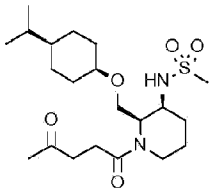
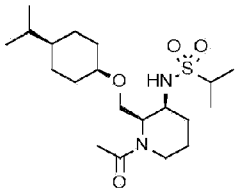
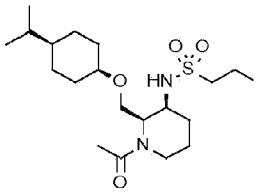
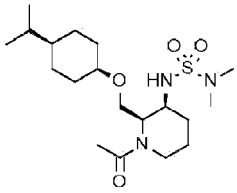
[Table 1-11]

Ex. No.	IUPAC name	Structure	MS
61	cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-N,N-dimethyl-3-((methylsulfonyl)amino)piperidine-1-sulfonamide		438.1
62	N-(cis-1-(cyclopropylsulfonyl)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		435.1
63	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-(2-thienylsulfonyl)piperidin-3-yl)methanesulfonamide		477
64	N-(cis-1-((4-chlorophenyl)sulfonyl)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		505.1
65	N-(cis-1-((1,2-dimethyl-1H-imidazol-4-yl)sulfonyl)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		491.2
66	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-(pyridin-3-ylsulfonyl)piperidin-3-yl)methanesulfonamide		474.2

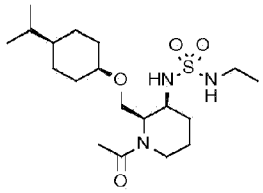
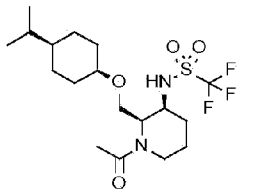
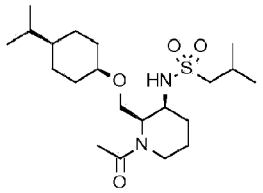
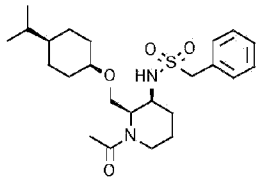
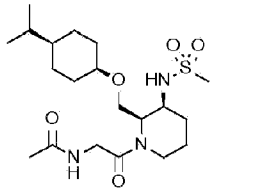
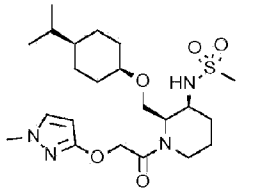
[Table 1-12]

Ex. No.	IUPAC name	Structure	MS
67	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-((1-methyl-1H-pyrazol-4-yl)sulfonyl)piperidin-3-yl)methanesulfonamide		475.1
68	N-(cis-1-(3,4-dihydro-2H-chromen-6-ylsulfonyl)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		527.2
69	N-((2R,3S)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide ((2S,3S)-2,3-bis((4-methylbenzoyl)oxy)succinate		333.1
70	N-((2R,3S)-1-acetyl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		375.1
71	N-(cis-1-acetyl-2-(((1s,4s)-1,1'-bi(cyclohexyl)-4-yloxy)methyl)piperidin-3-yl)methanesulfonamide		415.1
72	N-(cis-1-(3-hydroxypropanoyl)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		405.2

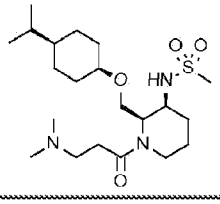
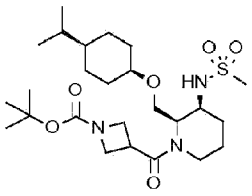
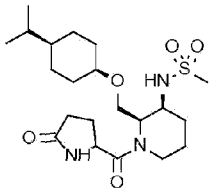
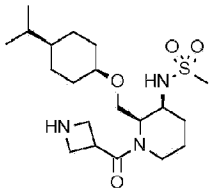
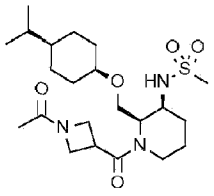
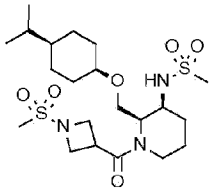
[Table 1-13]

Ex. No.	IUPAC name	Structure	MS
73	N-(cis-1-(3-hydroxy-3-methylbutanoyl)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		433.1
74	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-(3-(methylsulfonyl)-propanoyl)piperidin-3-yl)methanesulfonamide		467.2
75	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-(4-oxopentanoyl)piperidin-3-yl)methanesulfonamide		429.1
76	N-(cis-1-acetyl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)propane-2-sulfonamide		403.1
77	N-(cis-1-acetyl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)propane-1-sulfonamide		403.2
78	N'-(cis-1-acetyl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)-N,N-dimethylsulfuric diamide		404.2

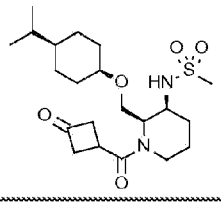
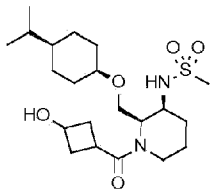
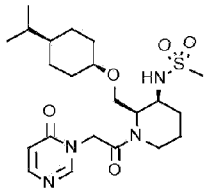
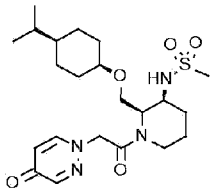
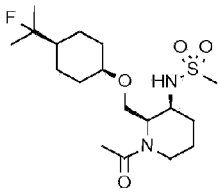
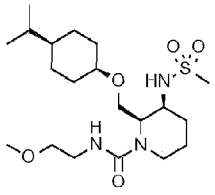
[Table 1-14]

Ex. No.	IUPAC name	Structure	MS
79	N-(cis-1-acetyl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)-N'-ethylsulfuric diamide		404.2
80	N-(cis-1-acetyl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)-1,1,1-trifluoromethanesulfonamide		429.2
81	N-(cis-1-acetyl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)-2-methylpropane-1-sulfonamide		417.2
82	N-(cis-1-acetyl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)-1-phenylmethanesulfonamide		451.2
83	N-(2-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidin-1-yl)-2-oxoethyl)acetamide		432.1
84	N-((2R,3S)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-(((1-methyl-1H-pyrazol-3-yl)oxy)acetyl)piperidin-3-yl)methanesulfonamide		471.2

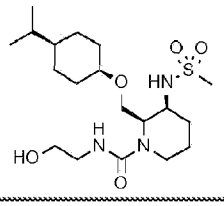
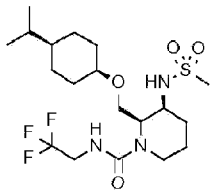
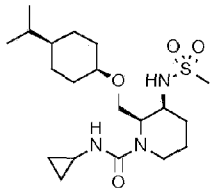
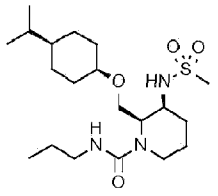
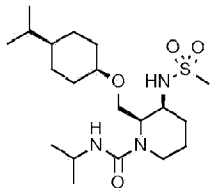
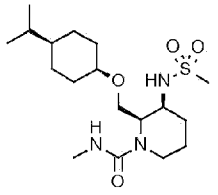
[Table 1-15]

Ex. No.	IUPAC name	Structure	MS
85	N-(cis-1-(N,N-dimethyl-beta-alanyl)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		430.2
86	tert-butyl 3-((cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidin-1-yl)carbonyl)azetidine-1-carboxylate		514.1
87	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-(5-oxoprolyl)piperidin-3-yl)methanesulfonamide		444.2
88	N-(cis-1-(azetidin-3-ylcarbonyl)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		416.2
89	N-(cis-1-((1-acetylazetidin-3-yl)carbonyl)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		458.2
90	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-((1-(methylsulfonyl)azetidin-3-yl)carbonyl)piperidin-3-yl)methanesulfonamide		494.2

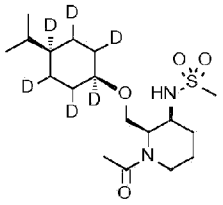
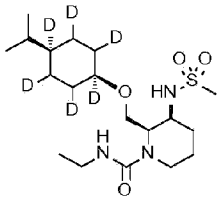
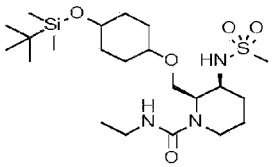
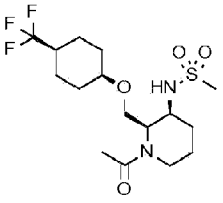
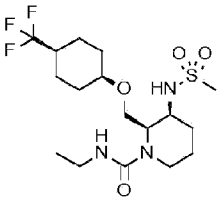
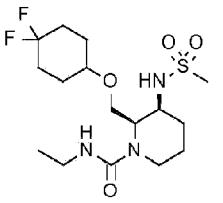
[Table 1-16]

Ex. No.	IUPAC name	Structure	MS
91	N-((2R,3S)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-((3-oxocyclobutyl)carbonyl)piperidin-3-yl)methanesulfonamide		427.1
92	N-((2R,3S)-1-((3-hydroxycyclobutyl)carbonyl)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		431.2
93	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-((6-oxopyrimidin-1(6H)-yl)acetyl)piperidin-3-yl)methanesulfonamide		467
94	N-(cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-((4-oxopyridazin-1(4H)-yl)acetyl)piperidin-3-yl)methanesulfonamide		469.2
95	N-(cis-1-acetyl-2-(((cis-4-(2-fluoropropan-2-yl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		391
96	cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-N-(2-methoxyethyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide		434.2

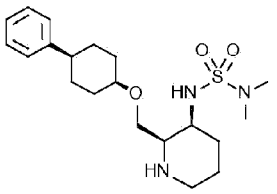
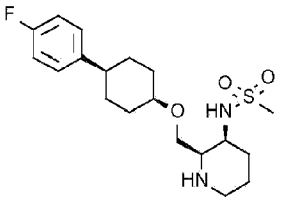
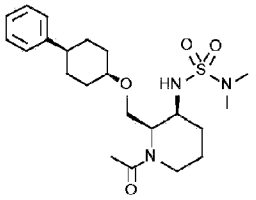
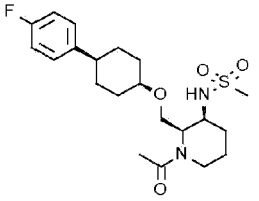
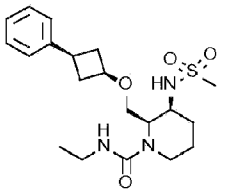
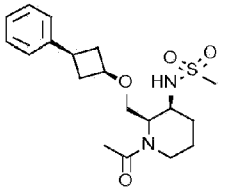
[Table 1-17]

Ex. No.	IUPAC name	Structure	MS
97	cis-N-(2-hydroxyethyl)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide		420.2
98	cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)-N-(2,2,2-trifluoroethyl)piperidine-1-carboxamide		456
99	cis-N-cyclopropyl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide		416.2
100	cis-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)-N-propylpiperidine-1-carboxamide		418.2
101	cis-N-isopropyl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide		418.2
102	(2R,3S)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-N-methyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide		390.2

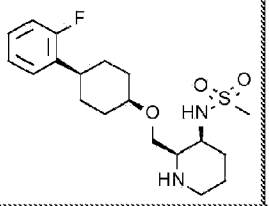
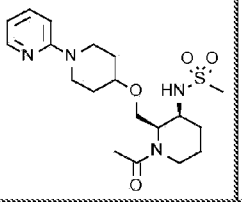
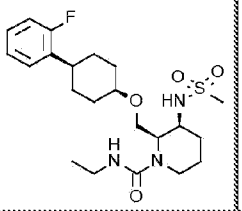
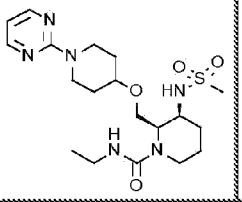
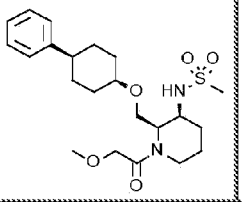
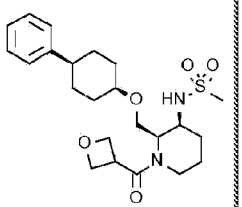
[Table 1-18]

Ex. No.	IUPAC name	Structure	MS
103	N-(cis-1-acetyl-2-(((cis-4-isopropyl(1,2,3,4,5,6-d6)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		381.2
104	cis-N-ethyl-2-(((cis-4-isopropyl(1,2,3,4,5,6-d6)cyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide		410.3
105	cis-2-(((4-((tert-butyl(dimethyl)silyl)oxy)-cyclohexyl)oxy)methyl)-N-ethyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide		492.3
106	N-(cis-1-acetyl-2-(((cis-4-(trifluoromethyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		400.9
107	cis-N-ethyl-3-((methylsulfonyl)amino)-2-(((cis-4-(trifluoromethyl)cyclohexyl)oxy)-methyl)piperidine-1-carboxamide		430
108	cis-2-(((4,4-difluorocyclohexyl)oxy)methyl)-N-ethyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide		398.1

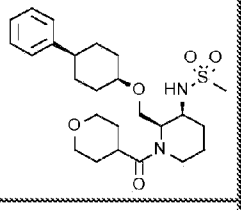
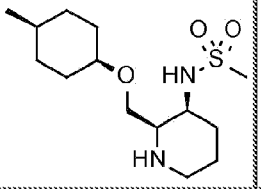
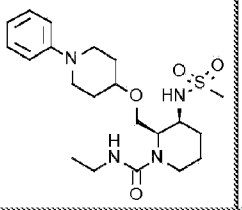
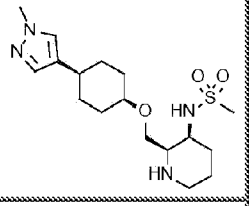
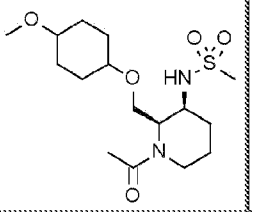
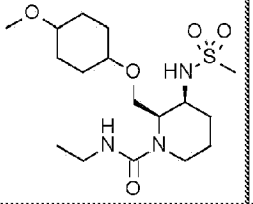
[Table 1-19]

Ex. No.	IUPAC name	Structure	MS
109	N,N-dimethyl-N'-(cis-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)sulfuric diamide		396.2
110	N-(cis-2-(((cis-4-(4-fluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		385
111	N'-(cis-1-acetyl-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)-N,N-dimethylsulfuric diamide		438.1
112	N-(cis-1-acetyl-2-(((cis-4-(4-fluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		427.1
113	cis-N-ethyl-3-((methylsulfonyl)amino)-2-(((cis-3-phenylcyclobutyl)oxy)methyl)-piperidine-1-carboxamide		410.1
114	N-(cis-1-acetyl-2-(((cis-3-phenylcyclobutyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		381

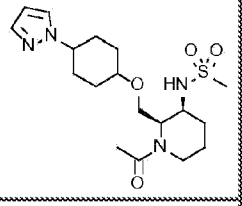
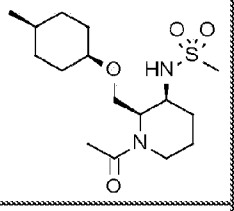
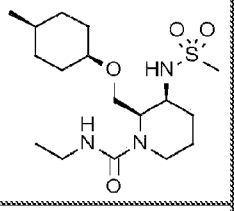
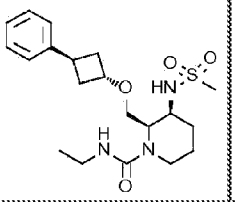
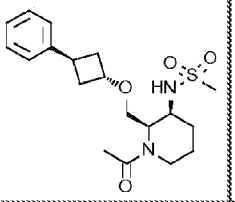
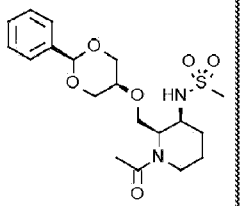
[Table 1-20]

Ex. No.	IUPAC name	Structure	MS
115	N-(cis-2-(((cis-4-(2-fluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		385
116	N-(cis-1-acetyl-2-(((1-(pyridin-2-yl)piperidin-4-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		411.1
117	cis-N-ethyl-2-(((cis-4-(2-fluorophenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide		456.1
118	cis-N-ethyl-3-((methylsulfonyl)amino)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxamide		441.1
119	N-(cis-1-(methoxyacetyl)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		439.1
120	N-(cis-1-(oxetan-3-ylcarbonyl)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		451

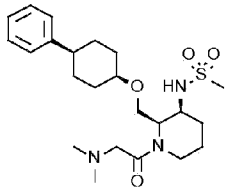
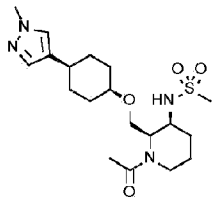
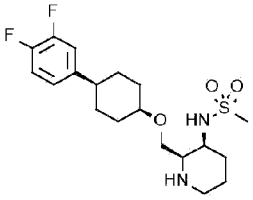
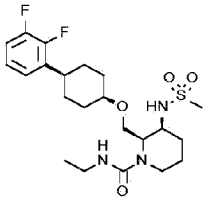
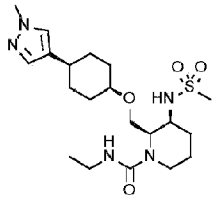
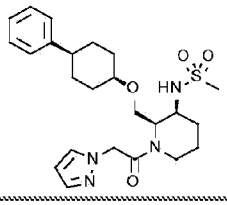
[Table 1-21]

Ex. No.	IUPAC name	Structure	MS
121	N-(cis-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-1-(tetrahydro-2H-pyran-4-ylcarbonyl)piperidin-3-yl)methanesulfonamide		479.1
122	N-(cis-2-(((cis-4-methylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		305.1
123	cis-N-ethyl-3-((methylsulfonyl)amino)-2-(((1-phenylpiperidin-4-yl)oxy)methyl)piperidine-1-carboxamide		439.1
124	N-(cis-2-(((cis-4-(1-methyl-1H-pyrazol-4-yl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		371.1
125	N-(cis-1-acetyl-2-(((4-methoxycyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		363.1
126	cis-N-ethyl-2-(((4-methoxycyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide		392.1

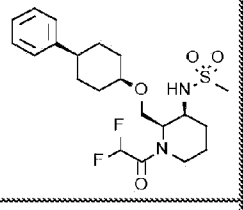
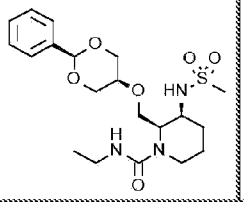
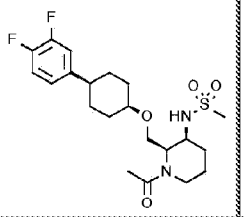
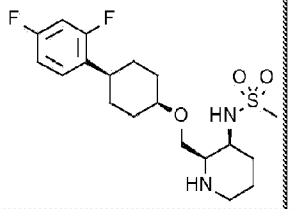
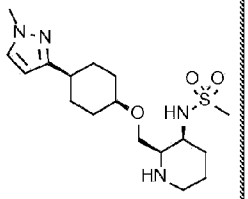
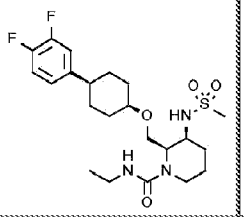
[Table 1-22]

Ex. No.	IUPAC name	Structure	MS
127	N-(cis-1-acetyl-2-(((4-(1H-pyrazol-1-yl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		399
128	N-(cis-1-acetyl-2-(((cis-4-methylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		347.1
129	cis-N-ethyl-2-(((cis-4-methylcyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide		376.1
130	cis-N-ethyl-3-((methylsulfonyl)amino)-2-(((trans-3-phenylcyclobutyl)oxy)methyl)-piperidine-1-carboxamide		410.1
131	N-(cis-1-acetyl-2-(((trans-3-phenylcyclobutyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		381.1
132	N-(cis-1-acetyl-2-(((cis-2-phenyl-1,3-dioxan-5-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		413.1

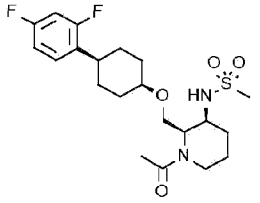
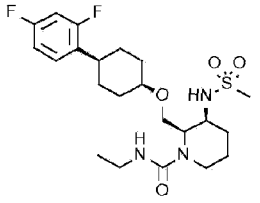
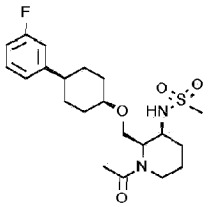
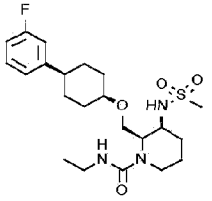
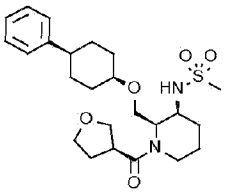
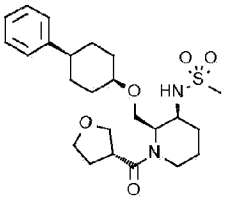
[Table 1-23]

Ex. No.	IUPAC name	Structure	MS
133	N-(cis-1-(N,N-dimethylglycyl)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		452.2
134	N-(cis-1-acetyl-2-(((cis-4-(1-methyl-1H-pyrazol-4-yl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		413.1
135	N-(cis-2-(((cis-4-(3,4-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		403.2
136	cis-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)-methyl)-N-ethyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide		474.1
137	cis-N-ethyl-2-(((cis-4-(1-methyl-1H-pyrazol-4-yl)cyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide		442.1
138	N-(cis-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-1-(1H-pyrazol-1-ylacetyl)piperidin-3-yl)methanesulfonamide		475.1

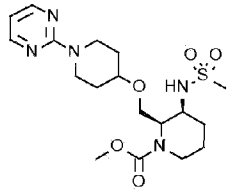
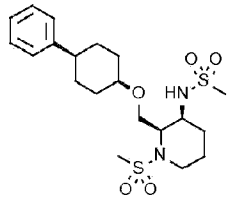
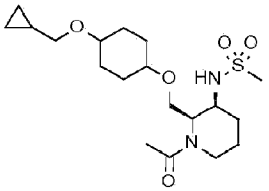
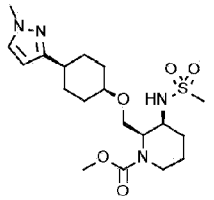
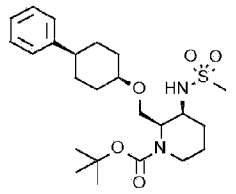
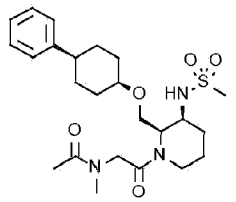
[Table 1-24]

Ex. No.	IUPAC name	Structure	MS
139	N-(cis-1-(difluoroacetyl)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		443.2
140	cis-N-ethyl-3-((methylsulfonyl)amino)-2-(((cis-2-phenyl-1,3-dioxan-5-yl)oxy)methyl)piperidine-1-carboxamide		442.1
141	N-(cis-1-acetyl-2-(((cis-4-(3,4-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		445.1
142	N-(cis-2-(((cis-4-(2,4-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		403
143	N-(cis-2-(((cis-4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		369
144	cis-2-(((cis-4-(3,4-difluorophenyl)cyclohexyl)oxy)-methyl)-N-ethyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide		474.1

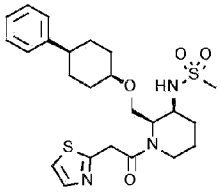
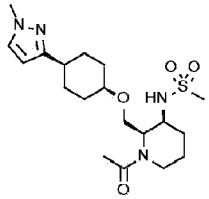
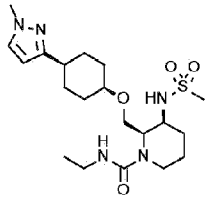
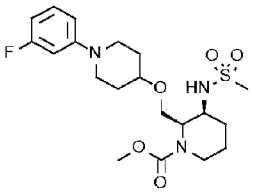
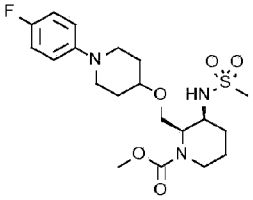
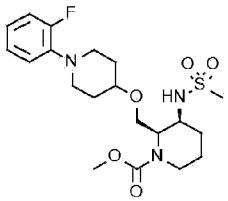
[Table 1-25]

Ex. No.	IUPAC name	Structure	MS
145	N-(cis-1-acetyl-2-(((cis-4-(2,4-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		445.2
146	cis-2-(((cis-4-(2,4-difluorophenyl)cyclohexyl)oxy)-methyl)-N-ethyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide		474.1
147	N-((2R,3S)-1-acetyl-2-(((cis-4-(3-fluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		427.2
148	(2R,3S)-N-ethyl-2-(((cis-4-(3-fluorophenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide		456
149	N-(cis-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-1-((3S)-tetrahydrofuran-3-ylcarbonyl)piperidin-3-yl)methanesulfonamide		465.1
150	N-(cis-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-1-((3R)-tetrahydrofuran-3-ylcarbonyl)piperidin-3-yl)methanesulfonamide		465.1

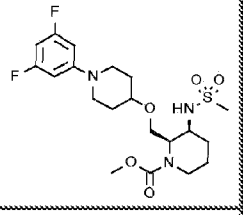
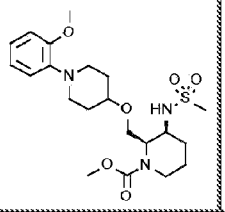
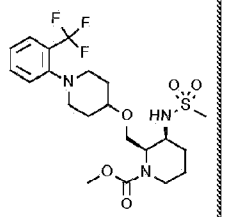
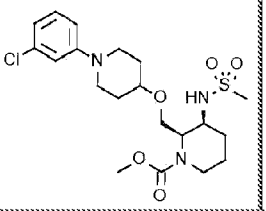
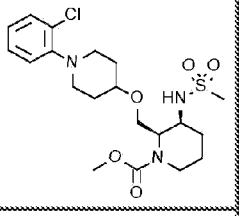
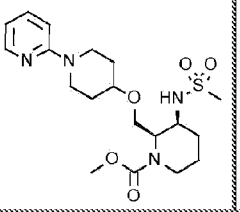
[Table 1-26]

Ex. No.	IUPAC name	Structure	MS
151	methyl cis-3-((methylsulfonyl)amino)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		428.1
152	N-(cis-1-(methylsulfonyl)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		443.1
153	N-(cis-1-acetyl-2-(((4-(cyclopropylmethoxy)cyclohexyl)-oxy)methyl)piperidin-3-yl)methanesulfonamide		403.2
154	methyl cis-2-(((cis-4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		429.3
155	tert-butyl cis-3-((methylsulfonyl)amino)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidine-1-carboxylate		465.2
156	N-methyl-N-(2-(cis-3-((methylsulfonyl)amino)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-1-yl)-2-oxoethyl) acetamide		480.3

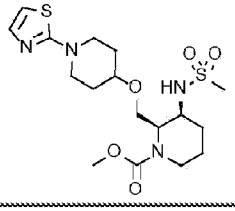
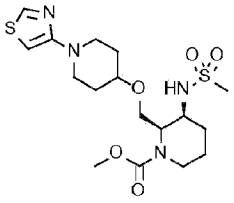
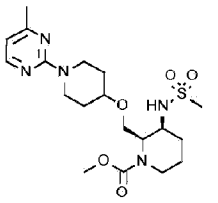
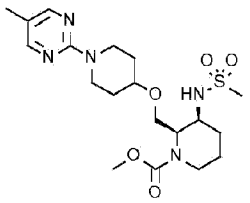
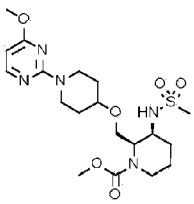
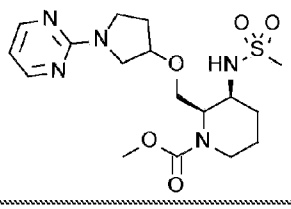
[Table 1-27]

Ex. No.	IUPAC name	Structure	MS
157	N-(cis-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-1-(1,3-thiazol-2-ylacetyl)piperidin-3-yl)methanesulfonamide		492.2
158	N-(cis-1-acetyl-2-(((cis-4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		413.2
159	cis-N-ethyl-2-(((cis-4-(1-methyl-1H-pyrazol-3-yl)cyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide		442.2
160	methyl cis-2-(((1-(3-fluorophenyl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		444.2
161	methyl cis-2-(((1-(4-fluorophenyl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		444.2
162	methyl cis-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		444.2

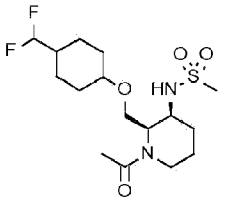
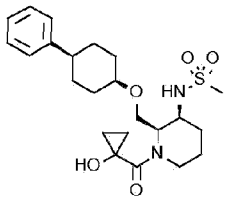
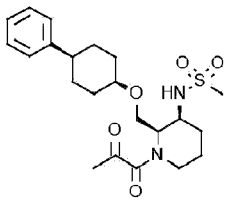
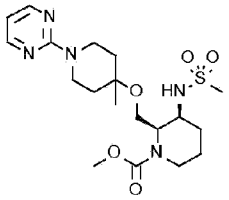
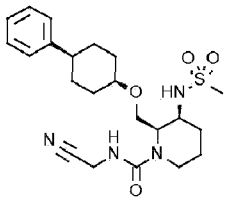
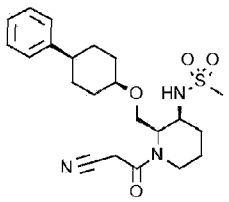
[Table 1-28]

Ex. No.	IUPAC name	Structure	MS
163	methyl cis-2-(((1-(3,5-difluorophenyl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		462.2
164	methyl cis-2-(((1-(2-methoxyphenyl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		456.1
165	methyl cis-3-((methylsulfonyl)amino)-2-(((1-(2-(trifluoromethyl)phenyl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		494.2
166	methyl cis-2-(((1-(3-chlorophenyl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		460.3
167	methyl cis-2-(((1-(2-chlorophenyl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		460.2
168	methyl cis-3-((methylsulfonyl)amino)-2-(((1-(pyridin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		427.2

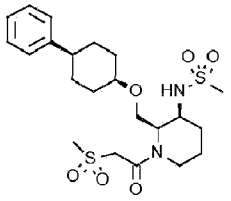
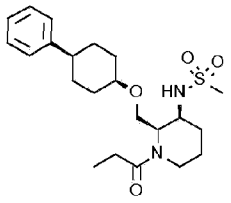
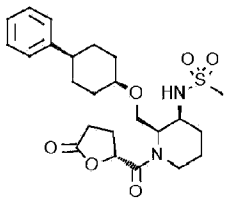
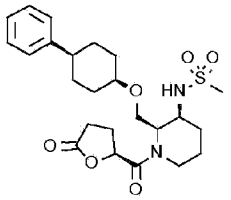
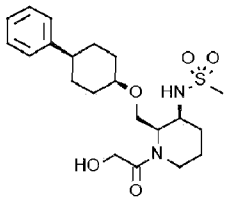
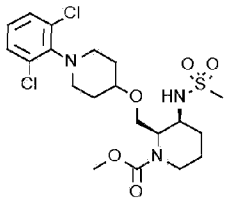
[Table 1-29]

Ex. No.	IUPAC name	Structure	MS
169	methyl cis-3-((methylsulfonyl)amino)-2-(((1-(1,3-thiazol-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		433.1
170	methyl cis-3-((methylsulfonyl)amino)-2-(((1-(1,3-thiazol-4-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		433.1
171	methyl cis-2-(((1-(4-methylpyrimidin-2-yl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate hydrochloride		442.2
172	methyl cis-2-(((1-(5-methylpyrimidin-2-yl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate hydrochloride		442.2
173	methyl cis-2-(((1-(4-methoxypyrimidin-2-yl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate hydrochloride		458.2
174	methyl cis-3-((methylsulfonyl)amino)-2-(((1-(pyrimidin-2-yl)pyrrolidin-3-yl)oxy)methyl)piperidine-1-carboxylate		414.2

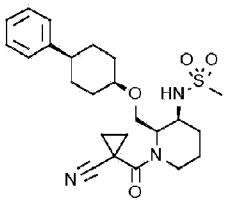
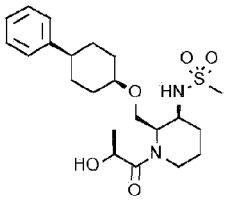
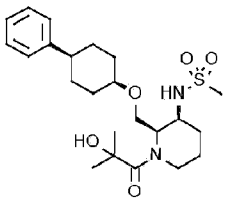
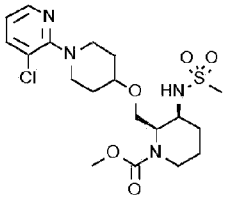
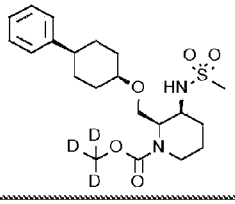
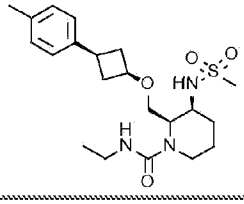
[Table 1-30]

Ex. No.	IUPAC name	Structure	MS
175	N-(cis-1-acetyl-2-(((4-(difluoromethyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		383.1
176	N-(cis-1-((1-hydroxycyclopropyl)carbonyl)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		451.1
177	N-(cis-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-1-pyruvoylpiperidin-3-yl)methanesulfonamide		435.1
178	methyl cis-2-(((4-methyl-1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate hydrochloride		442.2
179	cis-N-(cyanomethyl)-3-((methylsulfonyl)amino)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidine-1-carboxamide		447.1
180	N-((2R,3S)-1-(cyanoacetyl)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		432.1

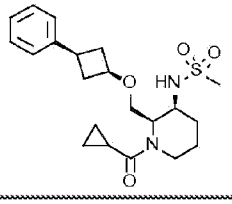
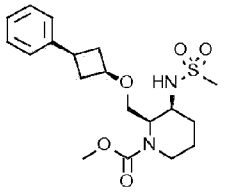
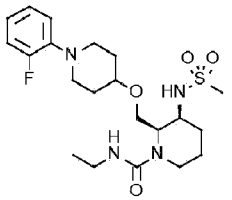
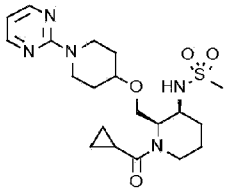
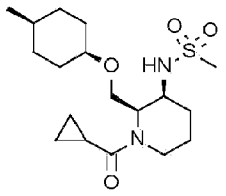
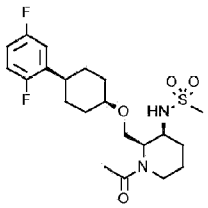
[Table 1-31]

Ex. No.	IUPAC name	Structure	MS
181	N-((2R,3S)-1-((methylsulfonyl)acetyl)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		485.1
182	N-((2R,3S)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-1-propionylpiperidin-3-yl)methanesulfonamide		423.2
183	N-((2R,3S)-1-(((2R)-5-oxotetrahydrofuran-2-yl)carbonyl)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		479.2
184	N-((2R,3S)-1-(((2S)-5-oxotetrahydrofuran-2-yl)carbonyl)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		479.2
185	N-((2R,3S)-1-glycoloyl-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		425.1
186	methyl cis-2-(((1-(2,6-dichlorophenyl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		494

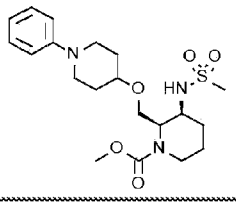
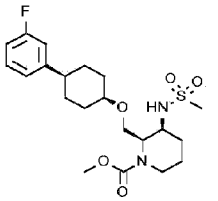
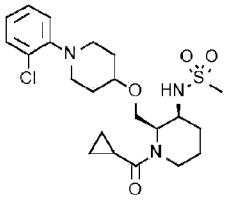
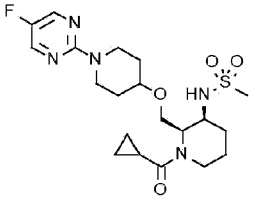
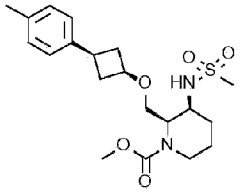
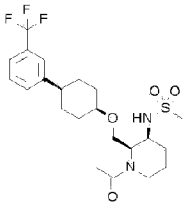
[Table 1-32]

Ex. No.	IUPAC name	Structure	MS
187	N-((2R,3S)-1-((1-cyanocyclopropyl)carbonyl)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		460.3
188	N-((2R,3S)-1-((2S)-2-hydroxypropanoyl)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		439.2
189	N-(cis-1-(2-hydroxy-2-methylpropanoyl)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		453.2
190	methyl cis-2-(((1-(3-chloropyridin-2-yl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		461.2
191	methyl-d3 (2R,3S)-3-((methylsulfonyl)amino)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidine-1-carboxylate		428.3
192	cis-N-ethyl-2-(((cis-3-(4-methylphenyl)cyclobutyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide		424.2

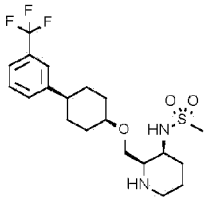
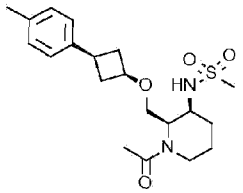
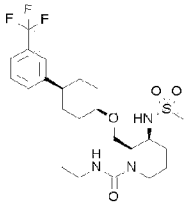
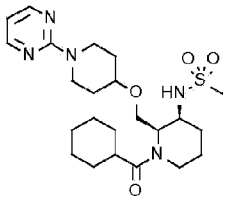
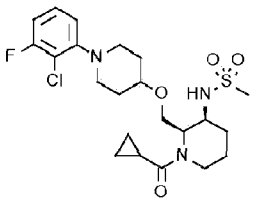
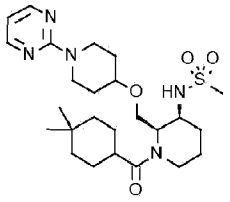
[Table 1-33]

Ex. No.	IUPAC name	Structure	MS
193	N-(cis-1-(cyclopropylcarbonyl)-2-(((cis-3-phenylcyclobutyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		407.2
194	methyl cis-3-((methylsulfonyl)amino)-2-(((cis-3-phenylcyclobutyl)oxy)methyl)-piperidine-1-carboxylate		395.1
195	cis-N-ethyl-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide		457.2
196	N-(cis-1-(cyclopropylcarbonyl)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		438.2
197	N-(cis-1-(cyclopropylcarbonyl)-2-(((cis-4-methylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		371.2
198	N-(cis-1-acetyl-2-(((cis-4-(2,5-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		445.3

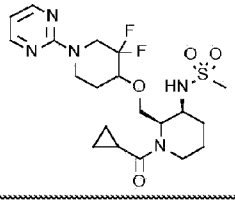
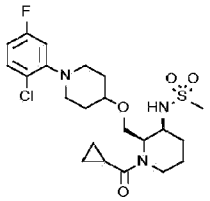
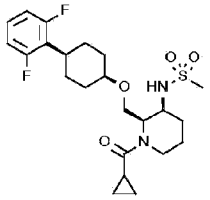
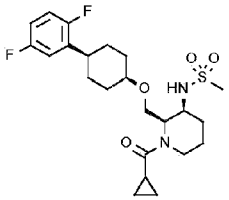
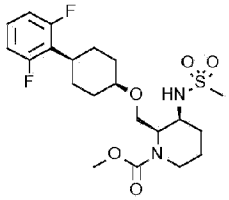
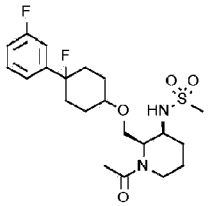
[Table 1-34]

Ex. No.	IUPAC name	Structure	MS
199	methyl cis-3-((methylsulfonyl)amino)-2-(((1-phenylpiperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		426.2
200	methyl (2R,3S)-2-(((cis-4-(3-fluorophenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		441
201	N-(cis-2-(((1-(2-chlorophenyl)piperidin-4-yl)oxy)methyl)-1-(cyclopropylcarbonyl)piperidin-3-yl)methanesulfonamide		470.3
202	N-(cis-1-(cyclopropylcarbonyl)-2-(((1-(5-fluoropyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		456.2
203	methyl cis-2-(((cis-3-(4-methylphenyl)cyclobutyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		409.1
204	N-(cis-1-acetyl-2-(((cis-4-(3-(trifluoromethyl)phenyl)-cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		477.2

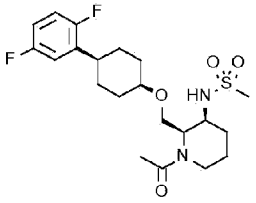
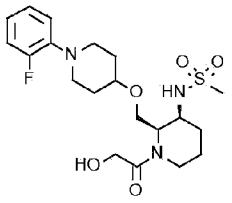
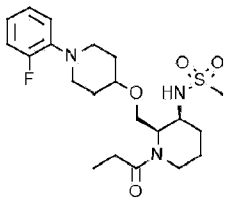
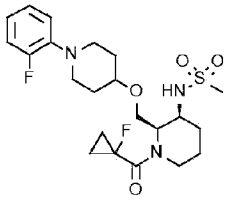
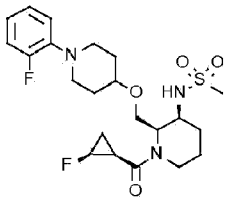
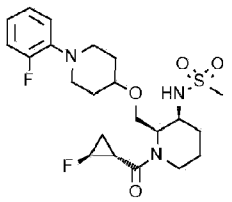
[Table 1-35]

Ex. No.	IUPAC name	Structure	MS
205	N-(cis-2-(((cis-4-(3-(trifluoromethyl)phenyl)-cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		435.2
206	N-(cis-1-acetyl-2-(((cis-3-(4-methylphenyl)cyclobutyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		395.3
207	cis-N-ethyl-3-((methylsulfonyl)amino)-2-(((cis-4-(3-(trifluoromethyl)phenyl)-cyclohexyl)oxy)methyl)piperidine-1-carboxamide		506.2
208	N-(cis-1-(cyclohexylcarbonyl)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		480.3
209	N-(cis-2-(((1-(2-chloro-3-fluorophenyl)piperidin-4-yl)oxy)methyl)-1-(cyclopropylcarbonyl)piperidin-3-yl)methanesulfonamide		488.1
210	N-(cis-1-((4,4-dimethylcyclohexyl)carbonyl)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		508.3

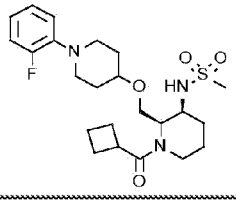
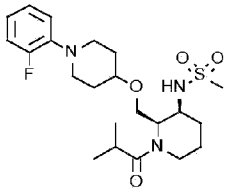
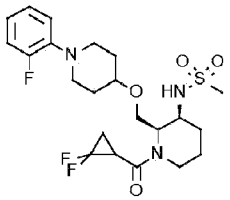
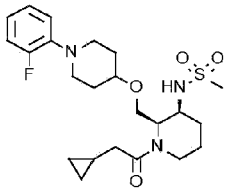
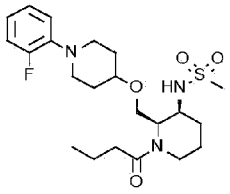
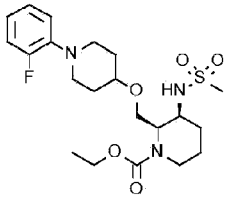
[Table 1-36]

Ex. No.	IUPAC name	Structure	MS
211	N-(cis-1-(cyclopropylcarbonyl)-2-(((3,3-difluoro-1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		474.2
212	N-(cis-2-(((1-(2-chloro-5-fluorophenyl)piperidin-4-yl)oxy)methyl)-1-(cyclopropylcarbonyl)piperidin-3-yl)methanesulfonamide		488.1
213	N-((2R,3S)-1-(cyclopropylcarbonyl)-2-(((cis-4-(2,6-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		471.2
214	N-((2R,3S)-1-(cyclopropylcarbonyl)-2-(((cis-4-(2,5-difluorophenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		471.2
215	methyl (2R,3S)-2-(((cis-4-(2,6-difluorophenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		461.3
216	N-(cis-1-acetyl-2-(((4-fluoro-4-(3-fluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		445.2

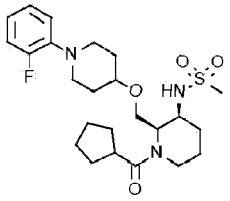
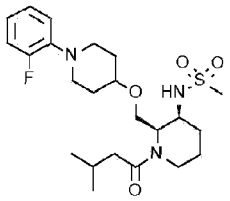
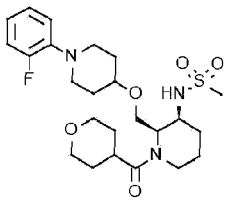
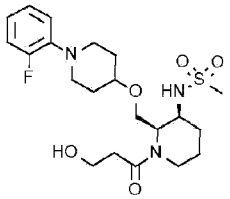
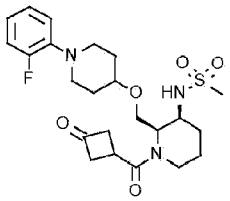
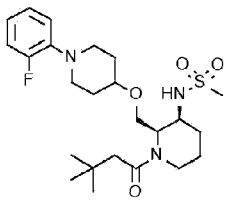
[Table 1-37]

Ex. No.	IUPAC name	Structure	MS
217	N-((2R,3S)-1-acetyl-2-(((cis-4-(2,5-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		445.2
218	N-(cis-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)-1-glycoloylpiperidin-3-yl)methanesulfonamide		444.2
219	N-(cis-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)-1-propionylpiperidin-3-yl)methanesulfonamide		442.2
220	N-(cis-1-((1-fluorocyclopropyl)carbonyl)-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		472.2
221	N-(cis-1-(((1S,2S)-2-fluorocyclopropyl)carbonyl)-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		472.2
222	N-(cis-1-(((1R,2S)-2-fluorocyclopropyl)carbonyl)-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		472.2

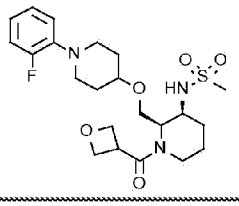
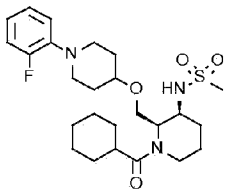
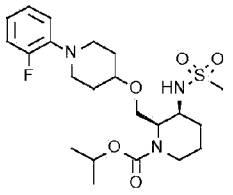
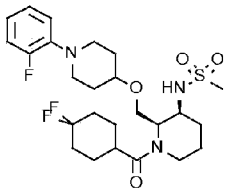
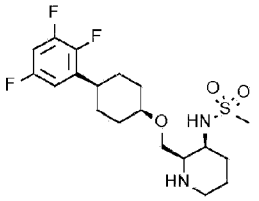
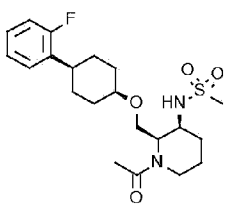
[Table 1-38]

Ex. No.	IUPAC name	Structure	MS
223	N-(cis-1-(cyclobutylcarbonyl)-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		468.2
224	N-(cis-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)-1-isobutyrylpiperidin-3-yl)methanesulfonamide		456.3
225	N-(cis-1-((2,2-difluorocyclopropyl)carbonyl)-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		490.2
226	N-(cis-1-(cyclopropylacetyl)-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		468.2
227	N-(cis-1-butyryl-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		456.2
228	ethyl cis-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		458.2

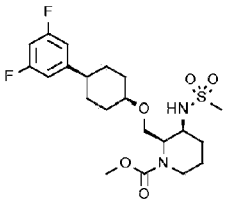
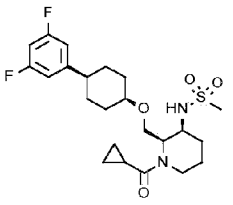
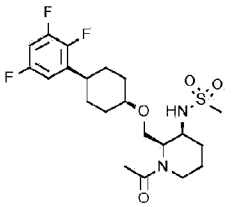
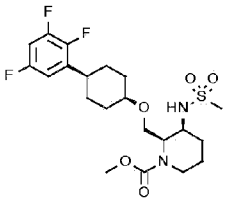
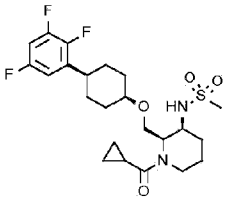
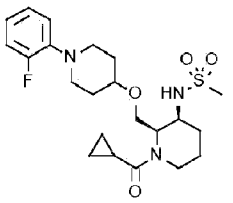
[Table 1-39]

Ex. No.	IUPAC name	Structure	MS
229	N-(cis-1-(cyclopentylcarbonyl)-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		482.2
230	N-(cis-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)-1-(3-methylbutanoyl)piperidin-3-yl)methanesulfonamide		470.2
231	N-(cis-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)-1-(tetrahydro-2H-pyran-4-ylcarbonyl)piperidin-3-yl)methanesulfonamide		498.2
232	N-(cis-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)-1-(3-hydroxypropanoyl)piperidin-3-yl)methanesulfonamide		458.2
233	N-(cis-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)-1-((3-oxocyclobutyl)carbonyl)piperidin-3-yl)methanesulfonamide		482.2
234	N-(cis-1-(3,3-dimethylbutanoyl)-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		484.3

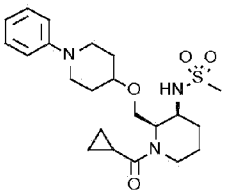
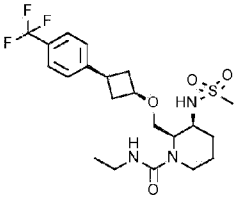
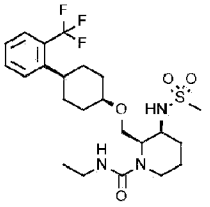
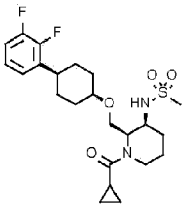
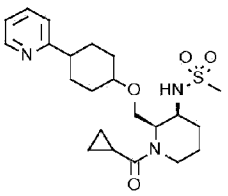
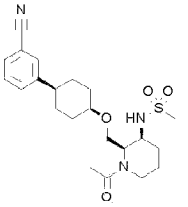
[Table 1-40]

Ex. No.	IUPAC name	Structure	MS
235	N-(cis-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)-1-(oxetan-3-ylcarbonyl)piperidin-3-yl)methanesulfonamide		470.2
236	N-(cis-1-(cyclohexylcarbonyl)-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		496.3
237	isopropyl cis-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		472.2
238	N-(cis-1-((4,4-difluorocyclohexyl)carbonyl)-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		532.3
239	N-((2R,3S)-2-(((cis-4-(2,3,5-trifluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		421.2
240	N-((2R,3S)-1-acetyl-2-(((cis-4-(2-fluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		427.1

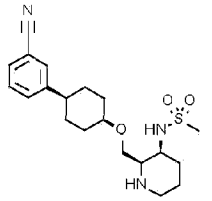
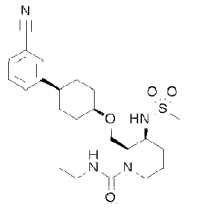
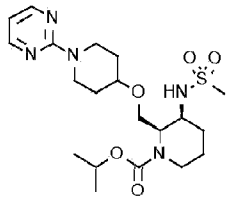
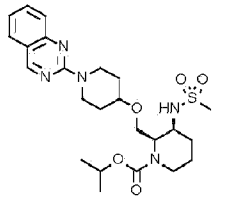
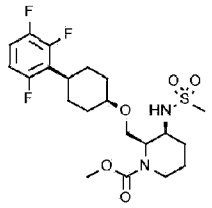
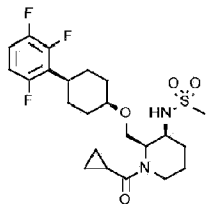
[Table 1-41]

Ex. No.	IUPAC name	Structure	MS
241	methyl (2R,3S)-2-(((cis-4-(3,5-difluorophenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		459.1
242	N-((2R,3S)-1-(cyclopropylcarbonyl)-2-(((cis-4-(3,5-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		469.1
243	N-((2R,3S)-1-acetyl-2-(((cis-4-(2,3,5-trifluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		463.1
244	methyl (2R,3S)-3-((methylsulfonyl)amino)-2-(((cis-4-(2,3,5-trifluorophenyl)cyclohexyl)oxy)-methyl)piperidine-1-carboxylate		477.1
245	N-((2R,3S)-1-(cyclopropylcarbonyl)-2-(((cis-4-(2,3,5-trifluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		489.1
246	N-((2R,3S)-1-(cyclopropylcarbonyl)-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		454.2

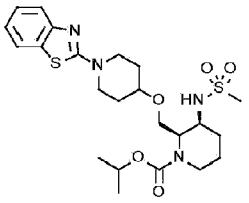
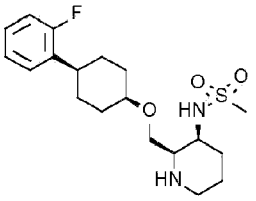
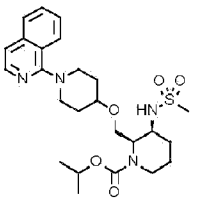
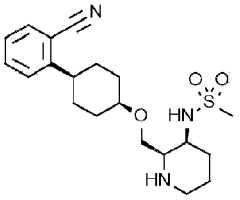
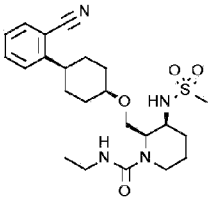
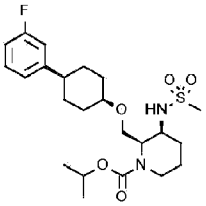
[Table 1-42]

Ex. No.	IUPAC name	Structure	MS
247	N-(cis-1-(cyclopropylcarbonyl)-2-(((1-phenylpiperidin-4-yl)oxy)methyl)piperidin-3-yl)methanesulfonamide		436.2
248	cis-N-ethyl-3-((methylsulfonyl)amino)-2-(((cis-3-(4-(trifluoromethyl)phenyl)-cyclobutyl)oxy)methyl)piperidine-1-carboxamide		478.2
249	cis-N-ethyl-3-((methylsulfonyl)amino)-2-(((cis-4-(2-(trifluoromethyl)phenyl)-cyclohexyl)oxy)methyl)piperidine-1-carboxamide		506.2
250	N-((2R,3S)-1-(cyclopropylcarbonyl)-2-(((cis-4-(2,3-difluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		471.2
251	N-(cis-1-(cyclopropylcarbonyl)-2-(((4-(pyridin-2-yl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		436.2
252	N-(cis-1-acetyl-2-(((cis-4-(3-cyanophenyl)cyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		434.1

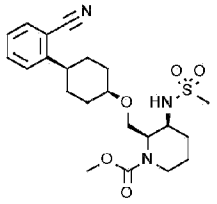
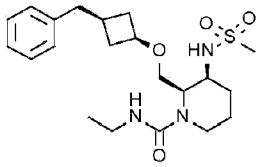
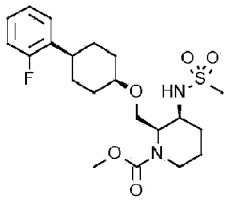
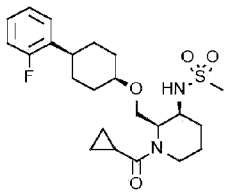
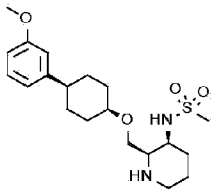
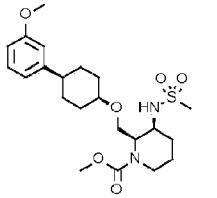
[Table 1-43]

Ex. No.	IUPAC name	Structure	MS
253	N-(cis-2-(((cis-4-(3-cyanophenyl)cyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		392.2
254	cis-2-(((cis-4-(3-cyanophenyl)cyclohexyl)oxy)methyl)-N-ethyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide		463.2
255	isopropyl cis-3-((methylsulfonyl)amino)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		456.2
256	isopropyl cis-3-((methylsulfonyl)amino)-2-(((1-(quinazolin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		506.2
257	methyl (2R,3S)-3-((methylsulfonyl)amino)-2-(((cis-4-(2,3,6-trifluorophenyl)cyclohexyl)oxy)-methyl)piperidine-1-carboxylate		477.1
258	N-((2R,3S)-1-(cyclopropylcarbonyl)-2-(((cis-4-(2,3,6-trifluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		489.1

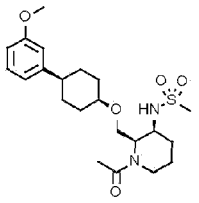
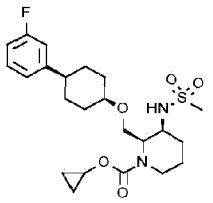
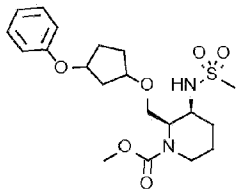
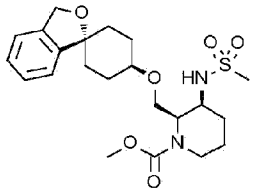
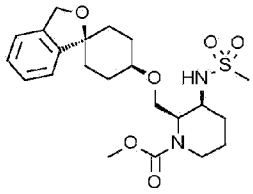
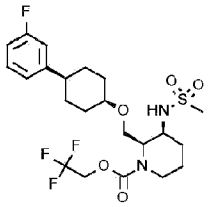
[Table 1-44]

Ex. No.	IUPAC name	Structure	MS
259	isopropyl cis-2-(((1-(1,3-benzothiazol-2-yl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		511.2
260	N-((2R,3S)-2-(((cis-4-(2-fluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		385.1
261	isopropyl cis-2-(((1-(isoquinolin-1-yl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		505.2
262	N-(cis-2-(((cis-4-(2-cyanophenyl)cyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		392.2
263	cis-2-(((cis-4-(2-cyanophenyl)cyclohexyl)oxy)methyl)-N-ethyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide		463.1
264	isopropyl (2R,3S)-2-(((cis-4-(3-fluorophenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		471.2

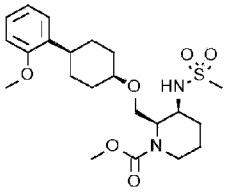
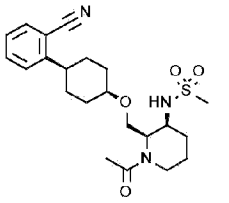
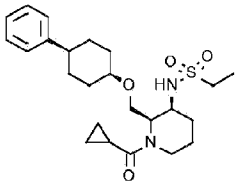
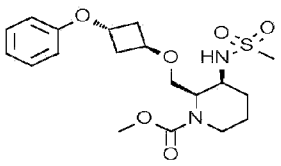
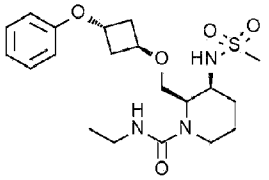
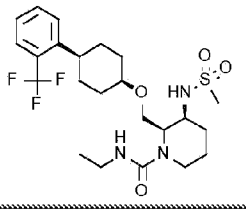
[Table 1-45]

Ex. No.	IUPAC name	Structure	MS
265	methyl cis-2-(((cis-4-(2-cyanophenyl)cyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		450.1
266	cis-2-(((cis-3-benzylcyclobutyl)oxy)methyl)-N-ethyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide		424.2
267	methyl (2R,3S)-2-(((cis-4-(2-fluorophenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		443.3
268	N-((2R,3S)-1-(cyclopropylcarbonyl)-2-(((cis-4-(2-fluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		453.2
269	N-(cis-2-(((cis-4-(3-methoxyphenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		397.2
270	methyl cis-2-(((cis-4-(3-methoxyphenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		455.2

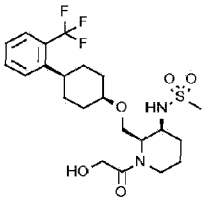
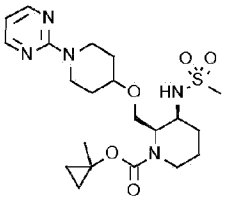
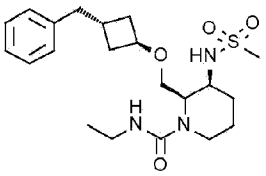
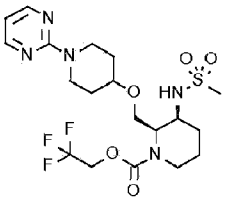
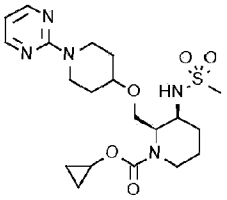
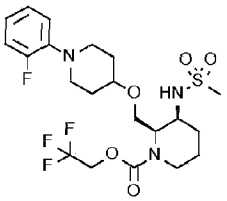
[Table 1-46]

Ex. No.	IUPAC name	Structure	MS
271	N-(cis-1-acetyl-2-(((cis-4-(3-methoxyphenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		439.2
272	cyclopropyl (2R,3S)-2-(((cis-4-(3-fluorophenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		469.2
273	methyl cis-3-((methylsulfonyl)amino)-2-(((3-phenoxycyclopentyl)oxy)methyl)-piperidine-1-carboxylate		427.1
274	methyl cis-3-((methylsulfonyl)amino)-2-(((1r,4'r)-3H-spiro[2-benzofuran-1,1'-cyclohexan]-4'-yloxy) methyl) piperidine-1-carboxylate		453.1
275	methyl cis-3-((methylsulfonyl)amino)-2-(((1s,4's)-3H-spiro[2-benzofuran-1,1'-cyclohexan]-4'-yloxy)methyl)piperidine-1-carboxylate		453.1
276	2,2,2-trifluoroethyl (2R,3S)-2-(((cis-4-(3-fluorophenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		509.2

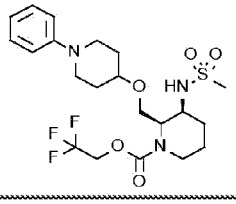
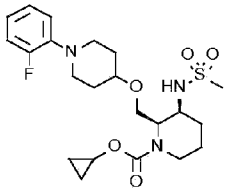
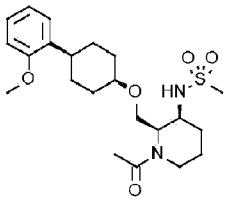
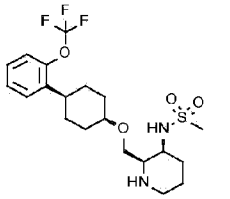
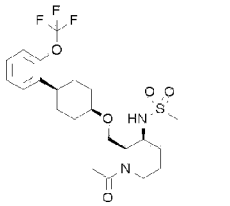
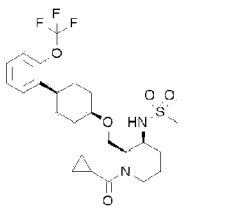
[Table 1-47]

Ex. No.	IUPAC name	Structure	MS
277	methyl (2R,3S)-2-(((cis-4-(2-methoxyphenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		455.2
278	N-(cis-1-acetyl-2-(((cis-4-(2-cyanophenyl)cyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		434.1
279	N-(cis-1-(cyclopropylcarbonyl)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)ethanesulfonamide		449.2
280	methyl cis-3-((methylsulfonyl)amino)-2-(((trans-3-phenoxycyclobutyl)oxy)methyl)-piperidine-1-carboxylate		411.1
281	cis-N-ethyl-3-((methylsulfonyl)amino)-2-(((trans-3-phenoxycyclobutyl)oxy)methyl)-piperidine-1-carboxamide		426.1
282	(2R,3S)-N-ethyl-3-((methylsulfonyl)amino)-2-(((cis-4-(2-(trifluoromethyl)phenyl)-cyclohexyl)oxy)methyl)piperidine-1-carboxamide		506.2

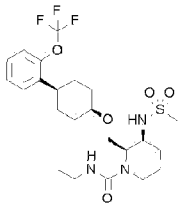
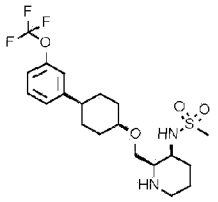
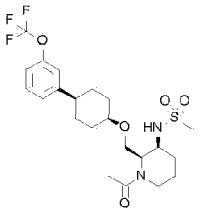
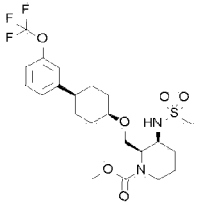
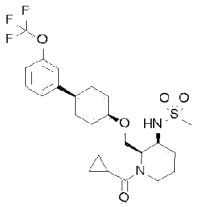
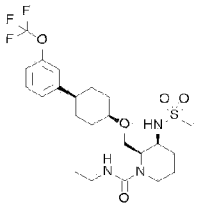
[Table 1-48]

Ex. No.	IUPAC name	Structure	MS
283	N-((2R,3S)-1-glycoloyl-2-(((cis-4-(2-(trifluoromethyl)phenyl)-cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		493.2
284	1-methylcyclopropyl cis-3-((methylsulfonyl)amino)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		468.2
285	cis-2-(((trans-3-benzylcyclobutyl)oxy)methyl)-N-ethyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide		424.2
286	2,2,2-trifluoroethyl cis-3-((methylsulfonyl)amino)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		496.1
287	cyclopropyl cis-3-((methylsulfonyl)amino)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		454.2
288	2,2,2-trifluoroethyl cis-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		512.2

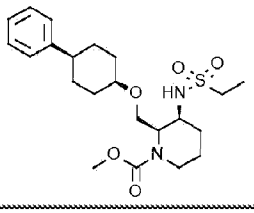
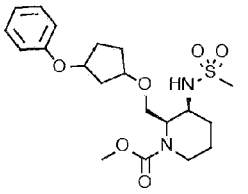
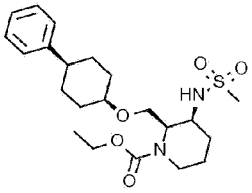
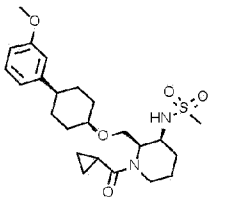
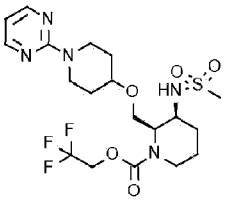
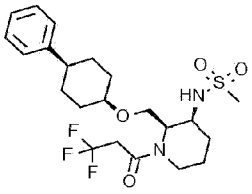
[Table 1-49]

Ex. No.	IUPAC name	Structure	MS
289	2,2,2-trifluoroethyl cis-3-((methylsulfonyl)amino)-2-(((1-phenylpiperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		494.2
290	cyclopropyl cis-2-(((1-(2-fluorophenyl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		470.2
291	N-((2R,3S)-1-acetyl-2-(((cis-4-(2-methoxyphenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		439.2
292	N-(cis-2-(((cis-4-(2-(trifluoromethoxy)phenyl)-cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		451.1
293	N-(cis-1-acetyl-2-(((cis-4-(2-(trifluoromethoxy)phenyl)-cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		493.2
294	N-(cis-1-(cyclopropylcarbonyl)-2-(((cis-4-(2-(trifluoromethoxy)phenyl)-cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		519.2

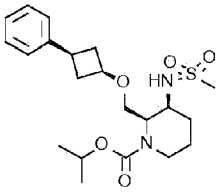
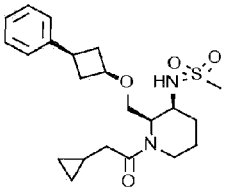
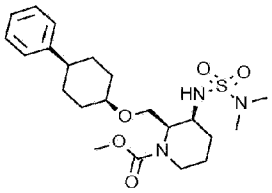
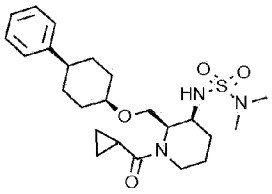
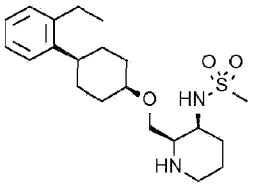
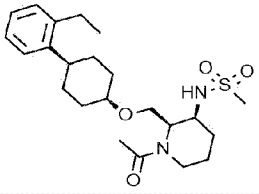
[Table 1-50]

Ex. No.	IUPAC name	Structure	MS
295	cis-N-ethyl-3-((methylsulfonyl)amino)-2-(((cis-4-(2-(trifluoromethoxy)phenyl)-cyclohexyl)oxy)methyl)piperidine-1-carboxamide		522.2
296	N-(cis-2-(((cis-4-(3-(trifluoromethoxy)phenyl)-cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		451.1
297	N-(cis-1-acetyl-2-(((cis-4-(3-(trifluoromethoxy)phenyl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		493.2
298	methyl cis-3-((methylsulfonyl)amino)-2-(((cis-4-(3-(trifluoromethoxy)phenyl)-cyclohexyl)oxy)methyl)piperidine-1-carboxylate		507.2
299	N-(cis-1-(cyclopropylcarbonyl)-2-(((cis-4-(3-(trifluoromethoxy)phenyl)-cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		519.1
300	cis-N-ethyl-3-((methylsulfonyl)amino)-2-(((cis-4-(3-(trifluoromethoxy)phenyl)-cyclohexyl)oxy)methyl)piperidine-1-carboxamide		522.2

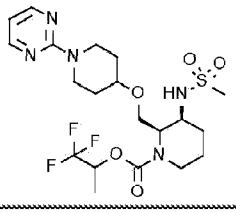
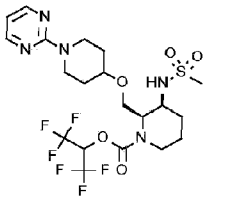
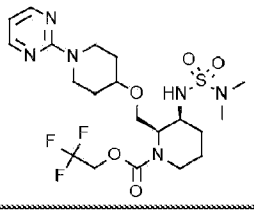
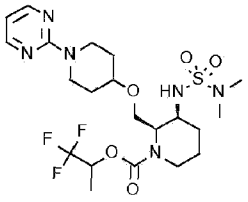
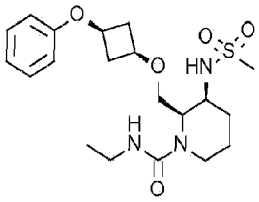
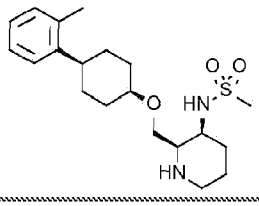
[Table 1-51]

Ex. No.	IUPAC name	Structure	MS
301	methyl cis-3-((ethylsulfonyl)amino)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidine-1-carboxylate		439.2
302	methyl cis-3-((methylsulfonyl)amino)-2-(((3-phenoxycyclopentyl)oxy)methyl)-piperidine-1-carboxylate		427.2
303	ethyl (2R,3S)-3-((methylsulfonyl)amino)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidine-1-carboxylate		439.2
304	N-((2R,3S)-1-(cyclopropylcarbonyl)-2-(((cis-4-(3-methoxyphenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		465.2
305	2,2,2-trifluoroethyl (2R,3S)-3-((methylsulfonyl)amino)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		496.2
306	N-((2R,3S)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-1-(3,3,3-trifluoropropanoyl)piperidin-3-yl)methanesulfonamide		477.2

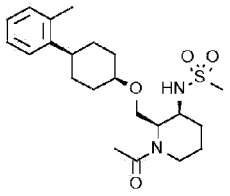
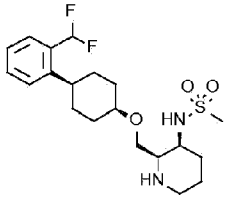
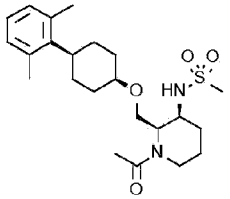
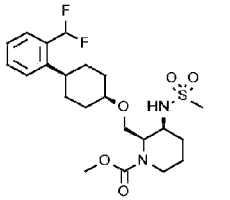
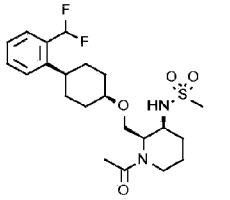
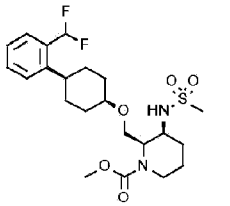
[Table 1-52]

Ex. No.	IUPAC name	Structure	MS
307	isopropyl cis-3-((methylsulfonyl)amino)-2-(((cis-3-phenylcyclobutyl)oxy)methyl)-piperidine-1-carboxylate		425.2
308	N-(cis-1-(cyclopropylacetyl)-2-(((cis-3-phenylcyclobutyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		421.2
309	methyl (2R,3S)-3-((dimethylsulfamoyl)amino)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidine-1-carboxylate		454.2
310	N'-((2R,3S)-1-(cyclopropylcarbonyl)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)-N,N-dimethylsulfuric diamide		464.2
311	N-(cis-2-(((cis-4-(2-ethylphenyl)cyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		395.3
312	N-((2R,3S)-1-acetyl-2-(((cis-4-(2-ethylphenyl)cyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		437.2

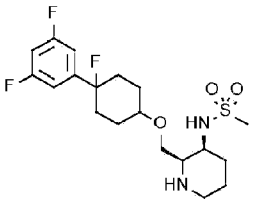
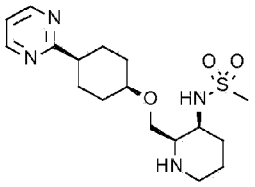
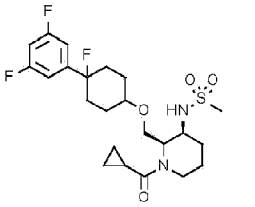
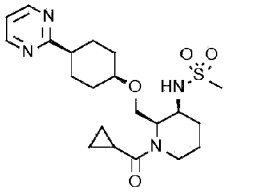
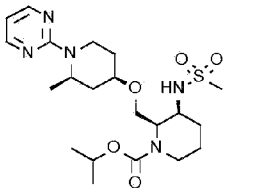
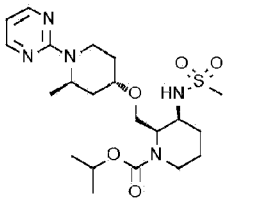
[Table 1-53]

Ex. No.	IUPAC name	Structure	MS
313	1,1,1-trifluoropropan-2-yl cis-3-((methylsulfonyl)amino)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		510.1
314	1,1,1,3,3,3-hexafluoropropan-2-yl cis-3-((methylsulfonyl)amino)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		564.1
315	2,2,2-trifluoroethyl cis-3-((dimethylsulfamoyl)amino)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		525.2
316	1,1,1-trifluoropropan-2-yl cis-3-((dimethylsulfamoyl)amino)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		539.2
317	cis-N-ethyl-3-((methylsulfonyl)amino)-2-(((cis-3-phenoxycyclobutyl)oxy)methyl)-piperidine-1-carboxamide		426.1
318	N-((2R,3S)-2-(((cis-4-(2-methylphenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		381.2

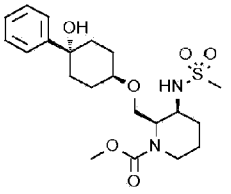
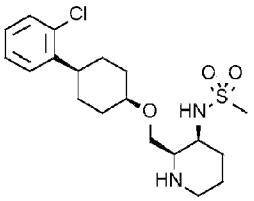
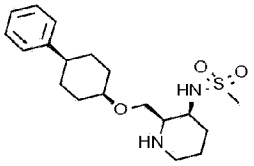
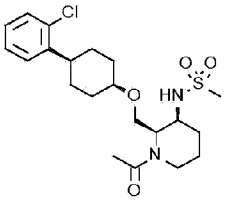
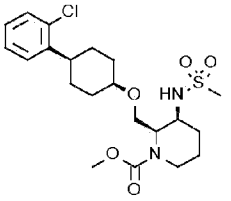
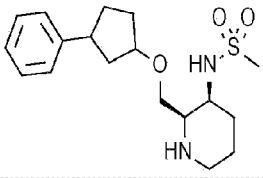
[Table 1-54]

Ex. No.	IUPAC name	Structure	MS
319	N-((2R,3S)-1-acetyl-2-(((cis-4-(2-methylphenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		423.2
320	N-((2R,3S)-2-(((cis-4-(2-(difluoromethyl)phenyl)cyclohexyl)-oxy)methyl)piperidin-3-yl)methanesulfonamide		417.1
321	N-(cis-1-acetyl-2-(((cis-4-(2,6-dimethylphenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		437.2
322	methyl cis-2-(((cis-4-(2-(difluoromethyl)phenyl)cyclohexyl)-oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		473.1
323	N-((2R,3S)-1-acetyl-2-(((cis-4-(2-(difluoromethyl)phenyl)cyclohexyl)-oxy)methyl)piperidin-3-yl)methanesulfonamide		459.2
324	methyl (2R,3S)-2-(((cis-4-(2-(difluoromethyl)phenyl)cyclohexyl)-oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		473.1

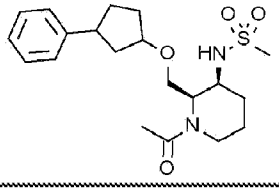
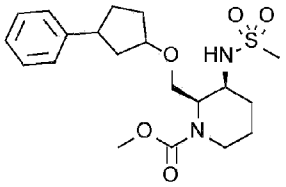
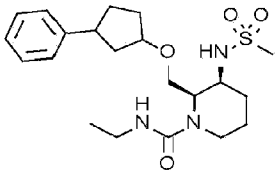
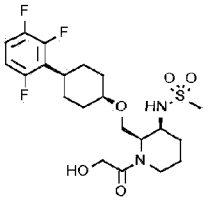
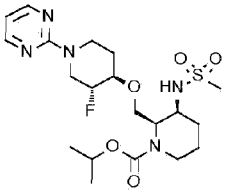
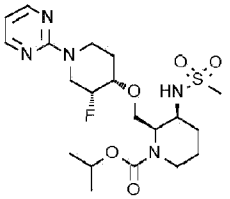
[Table 1-55]

Ex. No.	IUPAC name	Structure	MS
325	N-(cis-2-(((4-(3,5-difluorophenyl)-4-fluorocyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		421.2
326	N-(cis-2-(((cis-4-(pyrimidin-2-yl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		369.1
327	N-(cis-1-(cyclopropylcarbonyl)-2-(((4-(3,5-difluorophenyl)-4-fluorocyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		489.2
328	N-(cis-1-(cyclopropylcarbonyl)-2-(((cis-4-(pyrimidin-2-yl)cyclohexyl)oxy)methyl)piperidin-3-yl)methanesulfonamide		437.2
329	isopropyl cis-2-(((cis-2-methyl-1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		470.2
330	isopropyl cis-2-(((trans-2-methyl-1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		470.2

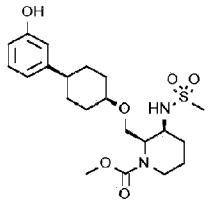
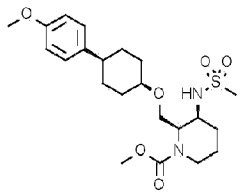
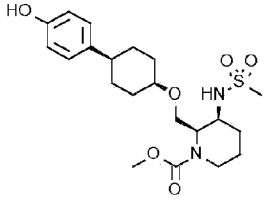
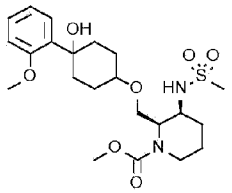
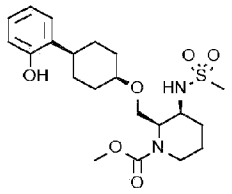
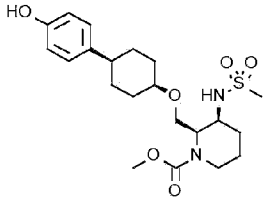
[Table 1-56]

Ex. No.	IUPAC name	Structure	MS
331	methyl cis-2-(((trans-4-hydroxy-4-phenylcyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		439.1
332	N-(cis-2-(((cis-4-(2-chlorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		401.1
333	N-((2R,3S)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide (s)-mandelate		367.2
334	N-(cis-1-acetyl-2-(((cis-4-(2-chlorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		443.2
335	methyl cis-2-(((cis-4-(2-chlorophenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		459.2
336	N-(cis-2-(((3-phenylcyclopentyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		353.2

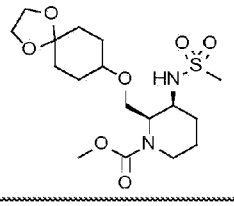
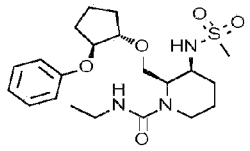
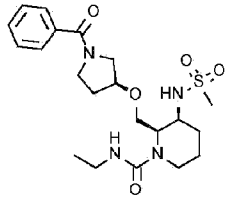
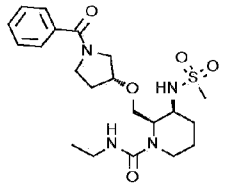
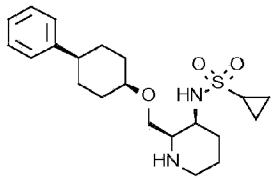
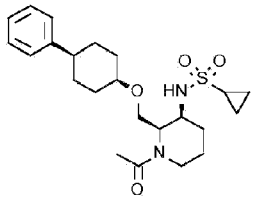
[Table 1-57]

Ex. No.	IUPAC name	Structure	MS
337	N-(cis-1-acetyl-2-(((3-phenylcyclopentyl)oxy)methyl)-piperidin-3-yl)methanesulfonamide		395.3
338	methyl cis-3-((methylsulfonyl)amino)-2-(((3-phenylcyclopentyl)oxy)methyl)-piperidine-1-carboxylate		411.2
339	cis-N-ethyl-3-((methylsulfonyl)amino)-2-(((3-phenylcyclopentyl)oxy)methyl)-piperidine-1-carboxamide		424.1
340	N-((2R,3S)-1-glycoloyl-2-(((cis-4-(2,3,6-trifluorophenyl)cyclohexyl)oxy)-methyl)piperidin-3-yl)methanesulfonamide		479.2
341	isopropyl cis-2-(((trans-3-fluoro-1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		474.2
342	isopropyl cis-2-(((cis-3-fluoro-1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		474.2

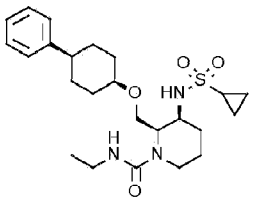
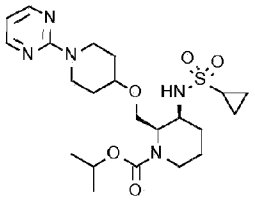
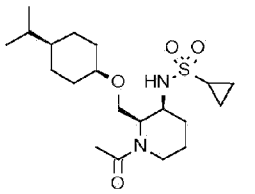
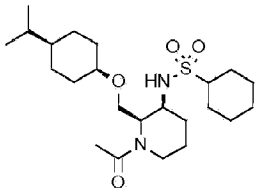
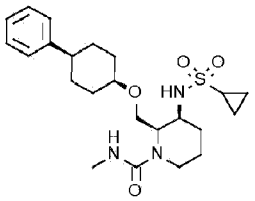
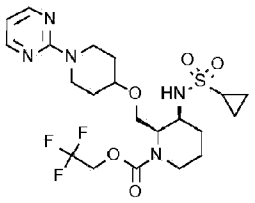
[Table 1-58]

Ex. No.	IUPAC name	Structure	MS
343	methyl cis-2-(((cis-4-(3-hydroxyphenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		441.2
344	methyl cis-2-(((cis-4-(4-methoxyphenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		455.2
345	methyl cis-2-(((cis-4-(4-hydroxyphenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		439.0
346	methyl cis-2-(((4-hydroxy-4-(2-methoxyphenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		469.1
347	methyl cis-2-(((cis-4-(2-hydroxyphenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		439.2
348	methyl (2R,3S)-2-(((cis-4-(4-hydroxyphenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		439.1

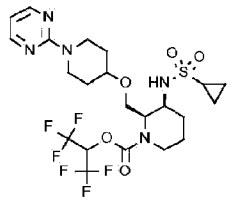
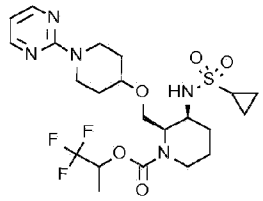
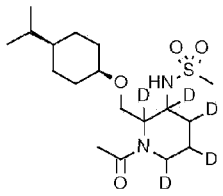
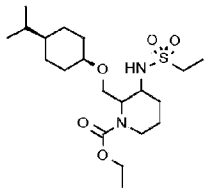
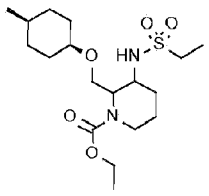
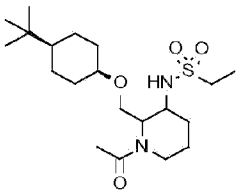
[Table 1-59]

Ex. No.	IUPAC name	Structure	MS
349	methyl cis-2-((1,4-dioxaspiro[4.5]dec-8-yloxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxylate		405.1
350	cis-N-ethyl-3-((methylsulfonyl)amino)-2-((((1S,2S)-2-phenoxycyclopentyl)oxy)methyl)-piperidine-1-carboxamide		438.0
351	cis-2-((((3S)-1-benzoylpyrrolidin-3-yl)oxy)methyl)-N-ethyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide		453.3
352	cis-2-((((3R)-1-benzoylpyrrolidin-3-yl)oxy)methyl)-N-ethyl-3-((methylsulfonyl)amino)piperidine-1-carboxamide		451.0
353	N-(cis-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)cyclopropanesulfonamide		393.2
354	N-(cis-1-acetyl-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-3-yl)cyclopropanesulfonamide		435.1

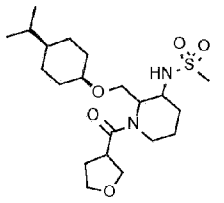
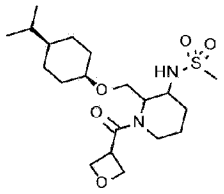
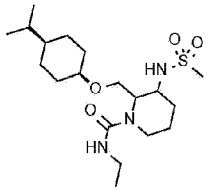
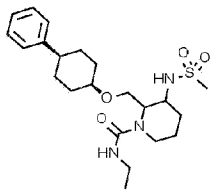
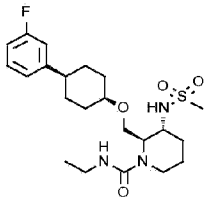
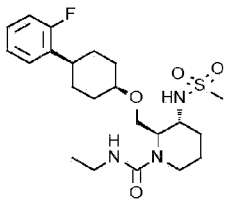
[Table 1-60]

Ex. No.	IUPAC name	Structure	MS
355	cis-3-((cyclopropylsulfonyl)amino)-N-ethyl-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidine-1-carboxamide		464.1
356	isopropyl cis-3-((cyclopropylsulfonyl)amino)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		482.2
357	N-(cis-1-acetyl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)cyclopropanesulfonamide		401.1
358	N-(cis-1-acetyl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidin-3-yl)cyclohexanesulfonamide		443.2
359	cis-3-((cyclopropylsulfonyl)amino)-N-methyl-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidine-1-carboxamide		450.1
360	2,2,2-trifluoroethyl cis-3-((cyclopropylsulfonyl)amino)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		522.2

[Table 1-61]

Ex. No.	IUPAC name	Structure	MS
361	1,1,1,3,3,3-hexafluoropropan-2-yl cis-3-((cyclopropylsulfonyl)amino)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		590.2
362	1,1,1-trifluoropropan-2-yl cis-3-((cyclopropylsulfonyl)amino)-2-(((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)methyl)piperidine-1-carboxylate		536.3
363	N-(1-acetyl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-(2,3,4,5,6-d5)piperidin-3-yl)methanesulfonamide		380.2
364	ethyl 3-((ethylsulfonyl)amino)-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-piperidine-1-carboxylate		417.2
365	ethyl 3-((ethylsulfonyl)amino)-2-(((cis-4-methylcyclohexyl)oxy)methyl)-piperidine-1-carboxylate		391.2
366	N-(1-acetyl-2-(((cis-4-tert-butylcyclohexyl)oxy)methyl)-piperidin-3-yl)ethanesulfonamide		403.1

[Table 1-62]

Ex. No.	IUPAC name	Structure	MS
367	N-(2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-(tetrahydrofuran-3-ylcarbonyl)piperidin-3-yl)methanesulfonamide		431.2
368	N-(2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-1-(oxetan-3-ylcarbonyl)piperidin-3-yl)methanesulfonamide		417.1
369	N-ethyl-2-(((cis-4-isopropylcyclohexyl)oxy)methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide		404.2
370	N-ethyl-3-((methylsulfonyl)amino)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidine-1-carboxamide		438.2
371	trans-N-ethyl-2-(((cis-4-(3-fluorophenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide		456.0
372	trans-N-ethyl-2-(((cis-4-(2-fluorophenyl)cyclohexyl)oxy)-methyl)-3-((methylsulfonyl)amino)piperidine-1-carboxamide		456.1

Experimental Example 1: Obtainment of cell stably expressing human orexin type 2 receptor

[0251] To obtain a cell clone stably expressing human orexin type 2 receptor, human orexin

type 2 receptor cDNA was inserted 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.

Experimental Example 2-1: Measurement of orexin type 2 receptor agonist activity

[0252] Chinese hamster ovary (CHO) dhfr-cells forcibly expressing human orexin type 2 receptor (hOX2R) were seeded in each well of Black clear bottom plate (384 wells) (Becton, Dickinson and Company) by 10,000 cells, and cultured for 16 hr in an MEM-alpha (Nikken-Bio Co., Ltd.) medium containing 100 U/ml penicillin, 100 ug/ml streptomycin, 0.5 g/ml G418 (all above Invitrogen), and 10% fetal calf serum (Thermo), under the conditions of 37°C, 5% CO_2. After removal of the medium, 30 µL of assay buffer 1 (0.1% bovine serum albumin (Wako Pure Chemical Industries, Ltd.), 1.25 mM probenecid, 10% B2-Quencher, 2.5 µg/mL Fluo-4AM, 10 mM HEPES (DOJINDO)) was added, and the cells were incubated for 60 min under the conditions of 37°C, 5% CO_2. A test compound was dissolved in dimethyl sulfoxide to 10 mM, and then diluted with assay buffer 2 (20 mM HEPES, Hanks' balanced salt solution (Invitrogen), 0.1% bovine serum albumin). For the reaction, a test compound solution (10 µL) was added using Fluorescent Imaging Plate Reader TETRA (FLIPR TETRA; manufactured by Molecular Devices), a fluorescence value (excitation wavelength 488 nm, measurement wavelength 570 nm) of each well was measured every one second for 1 min, and the agonist activity was determined using the area of the fluorescence value as an indicator of intracellular Ca^{2+} concentration. The agonist activity of the test compound was calculated assuming that the fluorescence value of the well added with only the dilution buffer was 0% and the fluorescence value of the well added with 10 nM human orexin B (PEPTIDE INSTITUTE, INC.) buffer was 100%. The agonist activity values EC_{50} and Emax of each compound are shown below. As used herein, Emax indicates the value at 30 uM concentration when orexin B is converted to a full agonist (maximum value of agonist activity: 100%). As is clear from the results, the compound of the present invention was shown to have an agonist activity on hOX2R.

[Table 2-1]

Ex. No.	EC_{50} (nM)	Emax (%)
2	1.9	99
3	540	96
4	44	106
5	2.2	98
7	250	100
8	5.6	96
10	220	113
11	2.0	114

Ex. No.	EC_{50} (nM)	Emax (%)
13	130	115
14	6.6	105
15	280	105
16	0.84	99
18	520	96
19	12	102
20	3.4	100
21	200	108
22	5.3	98
23	1200	90
24	21	102
25	7.9	94
27	310	108
28	2.7	96
29	17	104
30	0.11	113
31	0.66	95
32	15	102
33	68	98
35	93	99
36	880	74
37	880	97
39	940	93
40	720	91
42	210	97
43	1100	93
44	1300	96
45	330	100
47	60	101
53	980	96
54	4100	88
55	140	97
60	140	101
62	2300	93

Ex. No.	EC_{50} (nM)	Emax (%)
65	1300	95
66	3800	87
67	910	93
70	97	98
71	4300	83
72	89	96
73	560	92
74	750	89
75	220	88
76	300	103
77	1000	91
78	63	91
79	330	85
80	660	98
84	840	98
87	4900	82
90	2800	74
91	39	89
92	370	92
93	2300	84
95	4300	89
96	26	95
97	4.5	108
98	2.9	107
99	13	112
100	2.2	112
101	2.3	115
102	1.2	101
103	170	98
104	22	100
106	4800	89
107	120	75
109	480	102
111	13	97

Ex. No.	EC_{50} (nM)	Emax (%)
112	420	94
113	59	93
114	3500	79
115	770	97
117	0.12	91
118	4.6	105
119	30	107
120	61	96

[Table 2-2]

Ex. No.	EC_{50} (nM)	Emax (%)
121	8.8	111
123	390	120
126	2600	85
128	2400	88
129	39	96
130	460	96
133	1000	97
136	0.22	102
137	240	101
138	22	94
139	31	103
140	390	92
141	460	95
142	4000	96
143	590	96
144	1.0	104
145	810	106
146	2.5	100
147	10	100
148	0.053	103
149	25	100
150	30	99
151	490	107
152	290	96

Ex. No.	EC_{50} (nM)	Emax (%)
154	2400	94
155	1700	95
156	350	95
157	140	91
158	1600	83
159	140	96
165	3800	80
167	2400	83
176	45	98
177	190	96
179	0.31	100
180	17	106
181	240	89
182	2.3	92
183	40	94
184	9.3	93
185	21	98
186	3300	86
187	370	93
188	23	97
189	78	88
191	2.9	107
192	150	108
193	300	88
194	2400	81
195	250	102
196	30	104
197	100	90
198	56	92
200	2.2	95
201	2000	92
202	19	97
204	710	102
207	26	110

Ex. No.	EC_{50} (nM)	Emax (%)
208	940	93
209	1900	89
210	3600	86
211	1100	94
212	2200	89
213	0.44	102
214	1.5	105
215	2.5	105
216	210	105
217	13	110
219	3000	91
221	1600	96
222	2100	102
223	1100	110
224	1700	90
225	1000	98
226	2200	86
227	2400	102
228	2100	89
229	1500	85
230	2600	80
233	5000	83
236	1800	86
237	490	90
238	2100	91
239	280	102

[Table 2-3]

Ex. No.	EC_{50} (nM)	Emax (%)
240	24	107
241	1.2	97
242	0.88	99
243	17	97
244	2.6	97
246	2.0	97

Ex. No.	EC_{50} (nM)	Emax (%)
246	130	113
247	960	102
249	0.61	99
250	1.7	105
251	240	98
252	2900	93
254	88	105
255	8.1	102
257	2.6	97
258	0.72	101
260	550	99
262	2500	94
263	57	88
264	21	91
265	2300	94
266	3700	95
267	3.4	94
268	1.5	103
269	3000	95
270	80	102
271	650	104
272	28	96
274	260	118
275	3100	87
276	110	95
277	2.9	95
219	5.2	97
281	3300	81
282	0.55	93
283	8.9	95
284	260	95
286	130	93
287	150	99
290	3300	79

Ex. No.	EC_{50} (nM)	Emax (%)
299	26	98
293	540	78
294	130	95
295	42	93
297	2100	76
298	280	92
299	95	90
300	9.7	94
301	21	105
303	15	102
304	23	105
305	53	106
306	13	101
307	1600	98
308	590	109
309	3.1	106
310	2.2	101
311	3200	98
312	32	98
313	270	95
315	170	103
316	330	91
318	1100	99
319	29	106
320	2000	74
321	2200	37
322	25	71
323	96	95
324	8.0	95
325	5000	75
327	2600	86
328	7100	72
329	22	93
331	1500	98

Ex. No.	EC_{50} (nM)	Emax (%)
332	610	93
333	340	87
334	27	93
335	6.1	101
33.1	2400	88
338	490	83
339	11	101
340	2.5	109
341	13	103
342	30	104

Experimental Example 2-2: Measurement of orexin type 2 receptor agonist activity

[0253] 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 5% CO_2 incubator at 37°C. After removal of the medium in the cell plate, assay buffer A containing a calcium indicator (HBSS (Life Technologies), 20 mM HEPES (Life Technologies), 0.1% BSA (Wako Pure Chemical Industries, Ltd.), 2.5 μg/mL Fluo-4 AM (DOJINDO Chemical), 0.08% 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% CO_2 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 10 μL/well, and the fluorescence value was measured by FDSSμCELL (Hamamatsu Photonics K.K.) every one see for 1 min, and thereafter every two see 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 test compound was 0% inhibition, and variation in the fluorescence value when OX-A was added at the final concentration of 10 nM was 100% inhibition.

[Table 2-4]

Ex. No.	EC_{50} (nM)	Emax (%)
343	150	109
344	290	109
345	21	105
347	260	94
348	9.5	92
350	1600	116
353	1300	100

Ex. No.	EC_{50} (nM)	Emax (%)
354	51	104
355	0.44	108
356	21	98
357	84	101
359	1.1	97
360	210	98
362	390	95

Experimental Example 3: Measurement of locomotor activity in mice

[0254] Increased locomotor activity is one of the indexes of arousal action together with increase in wakefulness time, increase in body temperature, enhancement of cardiovascular system parameters. In this Experimental Example, the arousal action effective for the treatment of narcolepsy was evaluated by measuring the locomotor activity of mouse. Male C57BL/6J mice (6-10 weeks old, Japan CLEA) were used for the measurement of locomotor activity (8 mice each group), infrared rays were irradiated from the top part of the cage, and a locomotor activity measuring device (MDC system - Neurosciences Idea) capable of quantifying the number of times the mice pass through the irradiated rays was used. To be specific, the mice were placed in the cage of the device and acclimatized for 4 hours or longer, and a test compound was intraperitoneally administered (dose: 30 mg/kg body weight). The locomotor activity was measured for 2 hr after the administration. In the test compound group, a solution obtained by dissolving the test compound in a solvent (composition: 10% DMSO, 10% Cremophor EL (trade name), 20% polyethylene glycol 400 (20% PEG400, 60% H_20)) was administered to mice. On the other hand, in the control group, only the aforementioned solvent not containing the test compound was administered to mice.

[0255] The results are shown in Table 3 below.

Table 3

test compound	control group	Example 2	Example 5	Example 340
locomotor activity (counts) (mean ±S.E.M., n=8)	372.00 ± 24.23	817.00 ± 67.88	1175.25 ± 61.97	979.25 ± 109.96

[0256] As is clear from Table 3, the compound of the present invention enhanced the locomotor activity of mice.

[0257] That is, the compound of the present invention has a waking-up effect and was shown

to be effective for the treatment of narcolepsy.

Formulation Example 1 (production of capsule)

[0258]

1)	compound of Example 1	30 mg
2)	crystalline cellulose	10 mg
3)	lactose	19 mg
4)	magnesium stearate	1 mg
total		60 mg

1), 2), 3) and 4) are mixed and filled in a gelatin capsule.

Formulation Example 2 (production of tablet)

[0259]

1)	compound of Example 1	30 g
2)	lactose	50 g
3)	cornstarch	15 g
4)	calcium carboxymethylcellulose	44 g
5)	magnesium stearate	1 g
1000 tablets		140 g in total

[0260] The total amount of 1), 2), 3) and 30 g of 4) are kneaded 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]

[0261] The compound of the present invention has an orexin type 2 receptor agonist activity, and is useful as a prophylactic or therapeutic agent for narcolepsy.

REFERENCES CITED IN THE DESCRIPTION

Cited references

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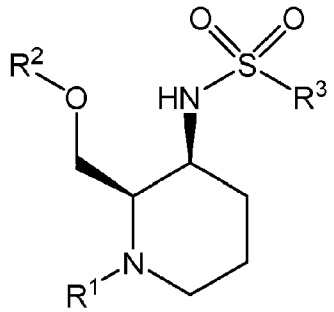
Patentkrav

1. Medikament, der omfatter en forbindelse, der er angivet med formlen:



(II)

hvor

R^1 er

(1) et hydrogenatom,

(2) en C_{1-6}-alkyl-carbonylgruppe, der eventuelt er substitueret med 1 til 7 substituenter, som er valgt blandt (i) et halogenatom, (ii) en cyanogruppe, (iii) en hydroxygruppe, (iv) en C_{3-10}-cycloalkylgruppe, (v) en C_{1-6}-alkoxygruppe, (vi) en C_{6-14}-arylgruppe, (vii) en C_{6-14}-aryloxygruppe, (viii) en pyrazolylgruppe, en thiazolylgruppe, en pyrimidinylgruppe eller en pyridazinylgruppe, der hver især eventuelt er substitueret med en oxogruppe, (ix) en pyrazolyloxygruppe, der eventuelt er substitueret med 1 til 3 C_{1-6}-alkylgrupper, (x) en C_{1-6}-alkyl-carbonylgruppe, (xi) en C_{1-6}-alkoxy-carbonylgruppe, (xii) en C_{1-6}-alkyl-carbonyloxygruppe, (xiii) en C_{1-6}-alkylsulfonylgruppe, (xiv) en mono- eller di-C_{1-6}-alkylaminogruppe, (xv) en C_{1-6}-alkyl-carbonylaminogruppe og (xvi) en (C_{1-6}-alkyl) (C_{1-6}-alkyl-carbonyl)-aminogruppe,

(3) en C_{3-10}-cycloalkyl-carbonylgruppe, der eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt et halogenatom, en cyanogruppe, en hydroxygruppe, en oxogruppe og en C_{1-6}-alkylgruppe,

(4) en C_{1-6}-alkoxy-carbonylgruppe, der eventuelt er substitueret med 1 til 6 substituenter, som er valgt blandt deuterium, et halogenatom og en C_{6-14}-arylgruppe,

(5) en C_{3-10}-cycloalkyloxy-carbonylgruppe, der eventuelt er substitueret med 1 til 3 substituenter, som er valgt fra en C_{1-6}-alkylgruppe,

(6) en C_{6-14}-aryl-carbonylgruppe, der eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt et halogenatom og en C_{6-14}-arylgruppe,

(7) en C_{6-14}-aryloxy-carbonylgruppe,

(8) en furylcarbonylgruppe, en thienylcarbonylgruppe, en pyrazolylcarbonylgruppe, en isoxazolylcarbonylgruppe eller en pyridylcarbonylgruppe, der hver især eventuelt er substitueret med 1 til 3 substituenter, som er valgt fra en C_{1-6}-alkylgruppe,

(9) en azetidinylcarbonylgruppe, en oxetanylcarbonylgruppe, en pyrrolidinylcarbonylgruppe, en tetrahydrofuranylcarbonylgruppe, en tetrahydropyranylcarbonylgruppe eller en morpholinylcarbonylgruppe, der hver især eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt en oxogruppe, en C_{1-6}-alkyl-carbonylgruppe, en C_{1-6}-alkoxy-carbonylgruppe og en C_{1-6}-alkylsulfonylgruppe,

(10) en mono- eller di-C_{1-6}-alkyl-carbamoylgruppe, der eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt et halogenatom, en cyanogruppe, en hydroxygruppe og en C_{1-6}-alkoxygruppe,

(11) en mono- eller di-C_{3-10}-cycloalkyl-carbamoylgruppe,

(12) en mono- eller di-C_{6-14}-aryl-carbamoylgruppe,

(13) en C_{1-6}-alkylsulfonylgruppe,

(14) en C_{3-10}-cycloalkylsulfonylgruppe,

(15) en C_{6-14}-arylsulfonylgruppe, der eventuelt er substitueret med 1 til 3 halogenatomer,

(16) en thienylsulfonylgruppe, en pyrazolylsulfonylgruppe, en imidazolylsulfonylgruppe, en pyridylsulfonylgruppe eller en dihydrochromenylsulfonylgruppe, der hver især eventuelt er substitueret med 1 til 3 substituenter, som er valgt fra en C_{1-6}-alkylgruppe,

(17) en mono- eller di-C_{1-6}-alkyl-sulfamoylgruppe eller

(18) en C_{1-6}-alkyl-carbonyl-carbonylgruppe;

R^2 er en C_{3-6}-cycloalkylgruppe, en pyrrolidinylgruppe, en piperidinylgruppe eller en dioxanylgruppe, der hver især eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt

(1) deuterium,

(2) et halogenatom,

(3) en hydroxygruppe,

(4) en C_{1-6}-alkylgruppe, der eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt et halogenatom og en C_{6-14}-arylgruppe,

(5) en C_{3-10}-cycloalkylgruppe,

(6) en C_{1-6}-alkoxygruppe, der eventuelt er substitueret med en C_{3-10}-cycloalkylgruppe,

(7) en C_{6-14}-arylgruppe, der eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt et halogenatom, en cyanogruppe, en C_{1-6}-alkylgruppe, der eventuelt er substitueret med 1 til 3 halogenatomer, en C_{1-6}-alkoxygruppe, der eventuelt er substitueret med 1 til 3 halogenatomer, og en hydroxygruppe,

(8) en C_{6-14}-aryloxygruppe,

(9) en tri-C_{1-6}-alkylsilyloxygruppe,

(10) en pyrazolylgruppe, en thiazolylgruppe, en pyridylgruppe, en pyrimidinylgruppe, en quinazolinylgruppe, en benzothiazolylgruppe eller en isoquinolinylgruppe, der hver især eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt et halogenatom, en C_{1-6}-alkylgruppe og en C_{1-6}-alkoxygruppe, og

(11) en C_{6-14}-aryl-carbonylgruppe; og

R^3 er en C_{1-6}-alkylgruppe eller en mono- eller di-C_{1-6}-alkylaminogruppe eller et salt deraf.

2. Medikament ifølge krav 1, hvor R^1 er

(1) et hydrogenatom,

(2) en C_{1-6}-alkyl-carbonylgruppe, der eventuelt er substitueret med en hydroxygruppe,

(3) en cyclopropancarbonylgruppe,

(4) en C_{1-6}-alkoxy-carbonylgruppe eller

(5) en mono- eller di-C_{1-6}-alkyl-carbamoylgruppe;

R^2 er

(A) en cyclohexylgruppe, der eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt

(1) en C_{1-6}-alkylgruppe og

(2) en phenylgruppe, der eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt et halogenatom, en C_{1-6}-alkylgruppe, der eventuelt er substitueret med 1 til 3 halogenatomer, og en C_{1-6}-alkoxygruppe, eller

(B) en piperidinylgruppe, der eventuelt er substitueret med 1 til 3 pyrimidinylgrupper; og

R^3 er en C_{1-6}-alkylgruppe eller en di-C_{1-6}-alkylaminogruppe eller et salt deraf.

3. Medikament ifølge krav 1, hvor R^1 er

(1) en C_{1-6}-alkyl-carbonylgruppe, der eventuelt er substitueret med en hydroxygruppe,

(2) en C_{1-6}-alkoxy-carbonylgruppe eller

(3) en mono- eller di-C_{1-6}-alkyl-carbamoylgruppe;

R^2 er en cyclohexylgruppe, der eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt

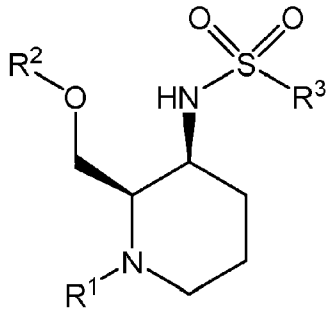
(1) en C_{1-6}-alkylgruppe og

(2) en phenylgruppe, der eventuelt er substitueret med 1 til 3 halogenatomer; og R^3 er en C_{1-6}-alkylgruppe eller et salt deraf.

4. Medikament ifølge krav 1, hvor forbindelsen er methyl-(2R,3S)-3-((methylsulfonyl)amino)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-1-carboxylat eller et salt deraf.

5. Medikament ifølge et hvilket som helst af kravene 1 til krav 4 til anvendelse som en orexin-type 2-receptor-agonist.

6. Forbindelse, der er angivet med formlen:



(II)

hvor

R^1 er

(1) et hydrogenatom,

(2) en C_{1-6}-alkyl-carbonylgruppe, der eventuelt er substitueret med 1 til 7 substituenter, som er valgt blandt (i) et halogenatom, (ii) en cyanogruppe, (iii) en hydroxygruppe, (iv) en C_{3-10}-cycloalkylgruppe, (v) en C_{1-6}-alkoxygruppe, (vi) en C_{6-14}-arylgruppe, (vii) en C_{6-14}-aryloxygruppe, (viii) en pyrazolylgruppe, en thiazolylgruppe, en pyrimidinylgruppe eller en pyridazinylgruppe, der hver især

eventuelt er substitueret med en oxogruppe, (ix) en pyrazolyloxygruppe, der eventuelt er substitueret med 1 til 3 C_{1-6}-alkylgrupper, (x) en C_{1-6}-alkyl-carbonylgruppe, (xi) en C_{1-6}-alkoxy-carbonylgruppe, (xii) en C_{1-6}-alkyl-carbonyloxygruppe, (xiii) en C_{1-6}-alkylsulfonylgruppe, (xiv) en mono- eller di-C_{1-6}-alkylaminogruppe, (xv) en C_{1-6}-alkyl-carbonylaminogruppe og (xvi) en (C_{1-6}-alkyl) (C_{1-6}-alkyl-carbonyl)-aminogruppe,

(3) en C_{3-10}-cycloalkyl-carbonylgruppe, der eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt et halogenatom, en cyanogruppe, en hydroxygruppe, en oxogruppe og en C_{1-6}-alkylgruppe,

(4) en C_{1-6}-alkoxy-carbonylgruppe, der eventuelt er substitueret med 1 til 6 substituenter, som er valgt blandt deuterium, et halogenatom og en C_{6-14}-arylgruppe,

(5) en C_{3-10}-cycloalkyloxy-carbonylgruppe, der eventuelt er substitueret med 1 til 3 substituenter, som er valgt fra en C_{1-6}-alkylgruppe,

(6) en C_{6-14}-aryl-carbonylgruppe, der eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt et halogenatom og en C_{6-14}-arylgruppe,

(7) en C_{6-14}-aryloxy-carbonylgruppe,

(8) en furylcarbonylgruppe, en thienylcarbonylgruppe, en pyrazolylcarbonylgruppe, en isoxazolylcarbonylgruppe eller en pyridylcarbonylgruppe, der hver især eventuelt er substitueret med 1 til 3 substituenter, som er valgt fra en C_{1-6}-alkylgruppe,

(9) en azetidinylcarbonylgruppe, en oxetanylcarbonylgruppe, en pyrrolidinylcarbonylgruppe, en tetrahydrofuranylcarbonylgruppe, en tetrahydropyranylcarbonylgruppe eller en morpholinylcarbonylgruppe, der hver især eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt en oxogruppe, en C_{1-6}-alkyl-carbonylgruppe, en C_{1-6}-alkoxy-carbonylgruppe og en C_{1-6}-alkylsulfonylgruppe,

(10) en mono- eller di-C_{1-6}-alkyl-carbamoylgruppe, der eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt et halogenatom, en cyanogruppe, en hydroxygruppe og en C_{1-6}-alkoxygruppe,

(11) en mono- eller di-C_{3-10}-cycloalkyl-carbamoylgruppe,

(12) en mono- eller di-C_{6-14}-aryl-carbamoylgruppe,

(13) en C_{1-6}-alkylsulfonylgruppe,

(14) en C_{3-10}-cycloalkylsulfonylgruppe,

(15) en C_{6-14}-arylsulfonylgruppe, der eventuelt er substitueret med 1 til 3 halogenatomer,

(16) en thienylsulfonylgruppe, en pyrazolylsulfonylgruppe, en imidazolylsulfonylgruppe, en pyridylsulfonylgruppe eller en dihydrochromenylsulfonylgruppe, der hver især eventuelt er substitueret med 1 til 3 substituenter, som er valgt fra en C_{1-6}-alkylgruppe,

(17) en mono- eller di-C_{1-6}-alkyl-sulfamoylgruppe eller

(18) en C_{1-6}-alkyl-carbonyl-carbonylgruppe;

R^2 er en C_{3-6}-cycloalkylgruppe, en pyrrolidinylgruppe, en piperidinylgruppe eller en dioxanylgruppe, der hver især eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt

(1) deuterium,

(2) et halogenatom,

(3) en hydroxygruppe,

(4) en C_{1-6}-alkylgruppe, der eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt et halogenatom og en C_{6-14}-arylgruppe,

(5) en C_{3-10}-cycloalkylgruppe,

(6) en C_{1-6}-alkoxygruppe, der eventuelt er substitueret med en C_{3-10}-cycloalkylgruppe,

(7) en C_{6-14}-arylgruppe, der eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt et halogenatom, en cyanogruppe, en C_{1-6}-alkylgruppe, der eventuelt er substitueret med 1 til 3 halogenatomer, en C_{1-6}-alkoxygruppe, der eventuelt er substitueret med 1 til 3 halogenatomer, og en hydroxygruppe,

(8) en C_{6-14}-aryloxygruppe,

(9) en tri-C_{1-6}-alkylsilyloxygruppe,

(10) en pyrazolylgruppe, en thiazolylgruppe, en pyridylgruppe, en pyrimidinylgruppe, en quinazolinylgruppe, en benzothiazolylgruppe eller en isoquinolinylgruppe, der hver især eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt et halogenatom, en C_{1-6}-alkylgruppe og en C_{1-6}-alkoxygruppe, og

(11) en C_{6-14}-aryl-carbonylgruppe; og

R^3 er en C_{1-6}-alkylgruppe eller en mono- eller di-C_{1-6}-alkylaminogruppe,

eller et salt deraf;

til anvendelse ved terapi.

7. Forbindelse til anvendelse ifølge krav 6, hvor R^1 er

(1) et hydrogenatom,

(2) en C_{1-6}-alkyl-carbonylgruppe, der eventuelt er substitueret med en hydroxygruppe,
(3) en cyclopropancarbonylgruppe,
(4) en C_{1-6}-alkoxy-carbonylgruppe eller
(5) en mono- eller di-C_{1-6}-alkyl-carbamoylgruppe;
R^2 er
(A) en cyclohexylgruppe, der eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt
(1) en C_{1-6}-alkylgruppe og
(2) en phenylgruppe, der eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt et halogenatom, en C_{1-6}-alkylgruppe, der eventuelt er substitueret med 1 til 3 halogenatomer, og en C_{1-6}-alkoxygruppe, eller
(B) en piperidinylgruppe, der eventuelt er substitueret med 1 til 3 pyrimidinylgrupper; og
R^3 er en C_{1-6}-alkylgruppe eller en di-C_{1-6}-alkylaminogruppe eller et salt deraf.

8. Forbindelse til anvendelse ifølge krav 6, hvor R^1 er
(1) en C_{1-6}-alkyl-carbonylgruppe, der eventuelt er substitueret med en hydroxygruppe,
(2) en C_{1-6}-alkoxy-carbonylgruppe eller
(3) en mono- eller di-C_{1-6}-alkyl-carbamoylgruppe;
R^2 er en cyclohexylgruppe, der eventuelt er substitueret med 1 til 3 substituenter, som er valgt blandt
(1) en C_{1-6}-alkylgruppe og
(2) en phenylgruppe, der eventuelt er substitueret med 1 til 3 halogenatomer; og
R^3 er en C_{1-6}-alkylgruppe eller et salt deraf.

9. Forbindelse til anvendelse ifølge krav 6, hvor forbindelsen er methyl-(2R,3S)-3-((methylsulfonyl)amino)-2-(((cis-4-phenylcyclohexyl)oxy)methyl)-piperidin-1-carboxylat eller et salt deraf.

10. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 6 til 9, hvor terapien omfatter behandling af en sygdom eller lidelse, der er associeret med en orexin-type 2-receptor.

11. Forbindelse til anvendelse ifølge krav 10, hvor sygdommen eller lidelsen er valgt fra gruppen bestående af narkolepsi, idiopatisk hypersomni, hypersomni, søvnapnøsyndrom, narkolepsisyndrom ledsaget af narkolepsilignende symptomer, hypersomnisyndrom ledsaget af hypersomni i løbet af dagen, Alzheimers, adipositas, insulinresistenssyndrom, hjertesvigt, sygdomme relateret til knogletab, sepsis, bevidsthedsforstyrrelse såsom koma og lignende og bivirkninger og komplikationer på grund af anæstesi eller til anvendelse som en anæstesiantagonist.

12. Forbindelse til anvendelse ifølge krav 11, hvor sygdommen eller lidelsen er valgt fra gruppen bestående af narkolepsi, idiopatisk hypersomni, hypersomni eller søvnapnøsyndrom.

13. Forbindelse til anvendelse ifølge krav 12, hvor sygdommen eller lidelsen er narkolepsi.

DRAWINGS

Drawing

FIG 1