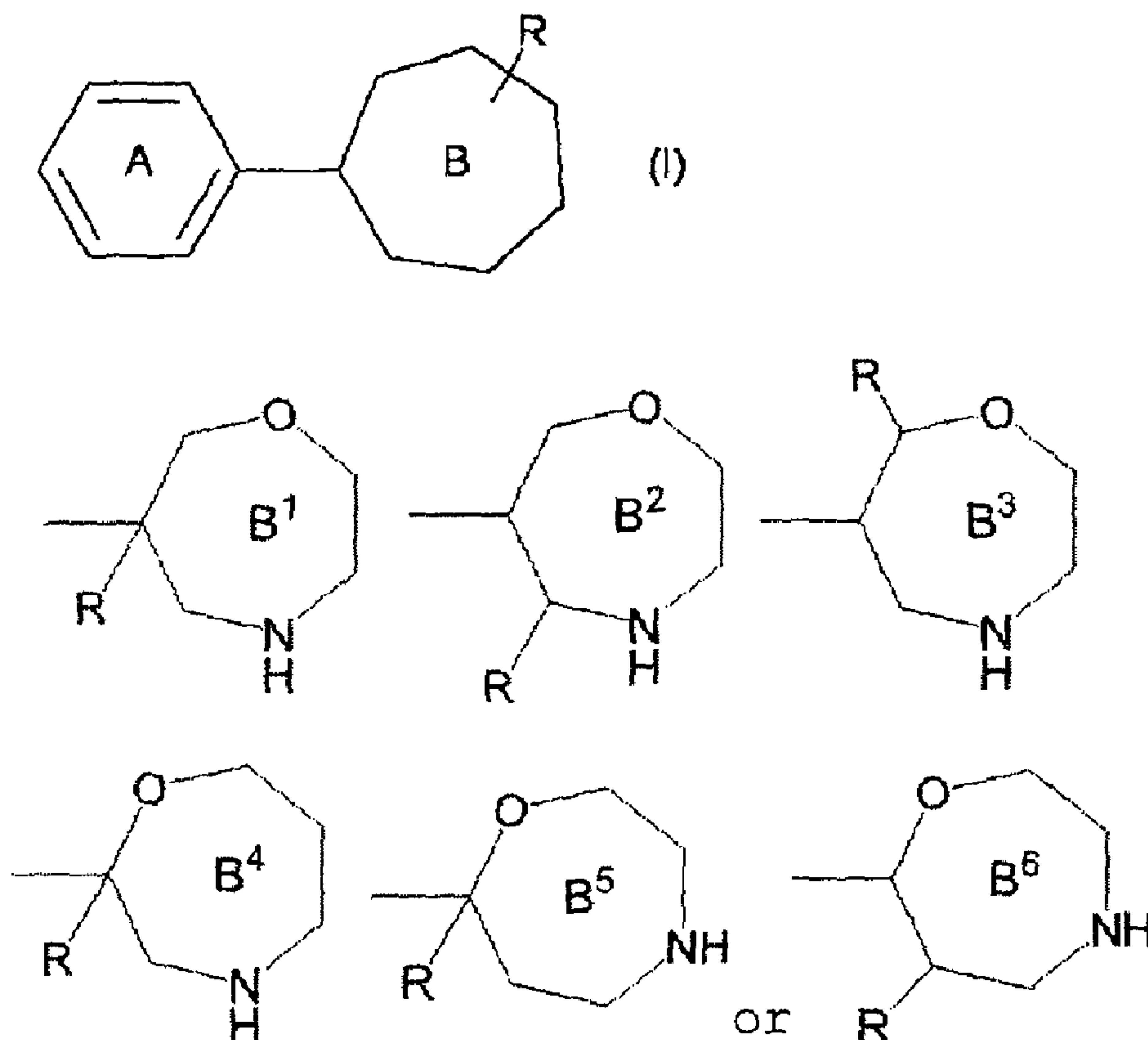




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C07D 413/14 (2006.01), *C07D 417/06* (2006.01),
C07D 417/14 (2006.01)
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FUJIMORI, IKUO, US;
NAKADA, YOSHIHISA, JP; ...

(54) Titre : DERIVES DE 1,4-OXAZEPANE
(54) Title: 1,4-OXAZEPANE DERIVATIVES



(57) Abrégé/Abstract:

Provided is a compound having a monoamine reuptake inhibitory activity, which is represented by the formula (I) wherein ring A is an optionally substituted 6-membered aromatic ring, ring B is the substituents on ring A are optionally bonded to form, together with ring A, an optionally substituted 9- or 10-membered aromatic fused ring, and other symbols are as defined in the specification, or a salt thereof.

(21) **2 813 911**

(13) **A1**

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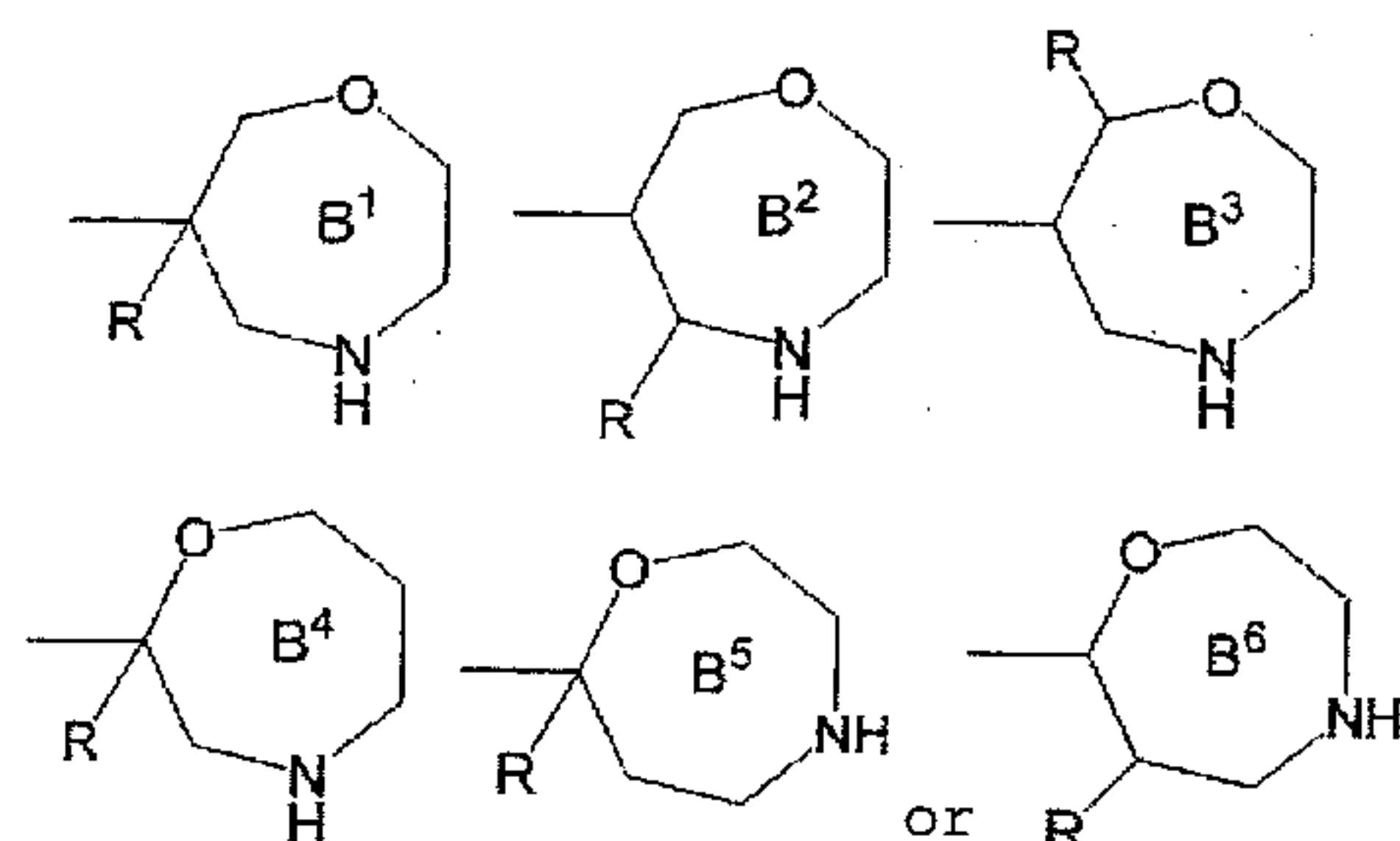
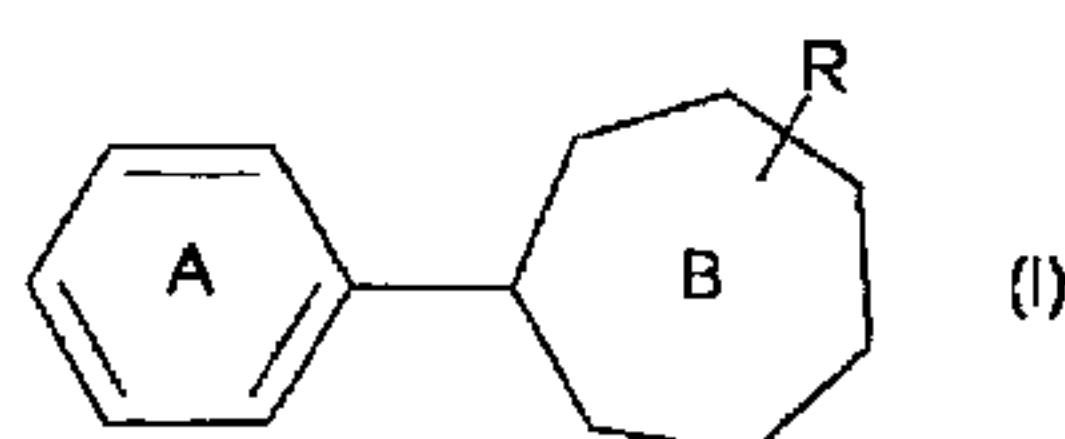
Ikuo [JP/US]; c/o Takeda San Diego, Inc., 10410 Science Center Drive, San Diego, California, 92121 (US). **NAKADA, Yoshihisa** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome, Fujisawa-shi, Kanagawa, 2510012 (JP). **YUKAWA, Tomoya** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome, Fujisawa-shi, Kanagawa, 2510012 (JP). **SAKAUCHI, Nobuki** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome, Fujisawa-shi, Kanagawa, 2510012 (JP). **OHBA, Yusuke** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome, Fujisawa-shi, Kanagawa, 2510012 (JP). **TSUKAMOTO, Tetsuya** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome, Fujisawa-shi, Kanagawa, 2510012 (JP).

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[Continued on next page]

(54) Title: 1,4-OXAZEPANE DERIVATIVES



(57) Abstract: Provided is a compound having a monoamine re-uptake inhibitory activity, which is represented by the formula (I) wherein ring A is an optionally substituted 6-membered aromatic ring, ring B is the substituents on ring A are optionally bonded to form, together with ring A, an optionally substituted 9- or 10-membered aromatic fused ring, and other symbols are as defined in the specification, or a salt thereof.

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SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS,

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CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 369

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 369

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

DESCRIPTION

1,4- OXAZEPANE DERIVATIVES

[TECHNICAL FIELD OF THE INVENTION]

[0001]

5 The present invention relates to heterocyclic compounds having a superior monoamine reuptake inhibitory activity, and useful as prophylactic or therapeutic drugs for depression, anxiety, attention deficit hyperactivity disorder, climacteric disorder, pain, stress urinary incontinence, mixed urinary
10 incontinence and the like.

[0002]

(Background of the Invention)

 Serotonin (5-HT), norepinephrine (NE) and dopamine (DA), which are monoamine neurotransmitters, are widely present in
15 the brain, and have various functions such as neurotransmission via receptors thereof and the like. These monoamines are released from the nerve terminal, and rapidly reuptaken from nerve gap by respective transporters (serotonin transporter: SERT, norepinephrine transporter: NET and
20 dopamine transporter: DAT), which terminates the neurotransmission. Compounds showing a monoamine reuptake inhibitory activity are known to be effective for various diseases including psychoneurotic diseases such as depression and the like, and widely used as therapeutic drugs. Compounds
25 that inhibit reuptake of 3 kinds of serotonin, norepinephrine and dopamine are called Triple Reuptake Inhibitors, and expected to provide therapeutic drugs for psychoneurotic diseases and the like.

[0003]

30 As a therapeutic drug for depression, tricyclic antidepressant (TCA) represented by imipramine, selective serotonin reuptake inhibitor (SSRI) represented by fluoxetine, selective serotonin-norepinephrine reuptake inhibitor (SNRI) represented by venlafaxine, norepinephrine-dopamine reuptake
35 inhibitors such as bupropion and the like, monoamine oxidase

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inhibitor and the like have been used. However, they are not entirely highly sufficient since they require several weeks before expression of the effect, and in terms of effectiveness, improving rate, side effects and the like (see
5 non-patent documents 1, 2).

[0004]

Moreover, TCA, SSRI and SNRI have been reported to be useful for improving the symptoms of psychoneurotic diseases such as depression as well as anxiety, attention deficit
10 hyperactivity disorder and the like, and neurodegenerative diseases such as Alzheimer's disease and the like; pain treatment of diabetic pain, muscle fibrosis and the like; or as therapeutic drugs for digestive tract diseases such as irritable bowel syndrome and the like.

15 [0005]

In addition, it has been reported that monoamine reuptake inhibitor is also effective as a therapeutic drug for lower urinary tract diseases such as overactive bladder, stress urinary incontinence and the like, particularly, stress
20 urinary incontinence. Stress urinary incontinence is a disease characterized by a symptom of urine leakage when intravesical pressure rises when the abdominal pressure rises transiently as a result of coughing, sneezing or light exercise. This disease is often found in female, and considered to be
25 developed because pelvic floor muscles are weakened due to childbirth and aging, and the urethral resistance decreases (see non-patent document 3). On the other hand, it has been clarified that a urethral continence reflex mechanism exists in which when intravesical pressure rises due to a transient
30 increase in the abdominal pressure, the pelvic floor muscles and the urethral sphincter muscle actively contract via a series of neural reflexes to maintain urethral continence (see non-patent documents 4-7). In recent years, it has been shown that serotonin and norepinephrine, which are monoamine
35 neurotransmitters, are involved in the urethral continence

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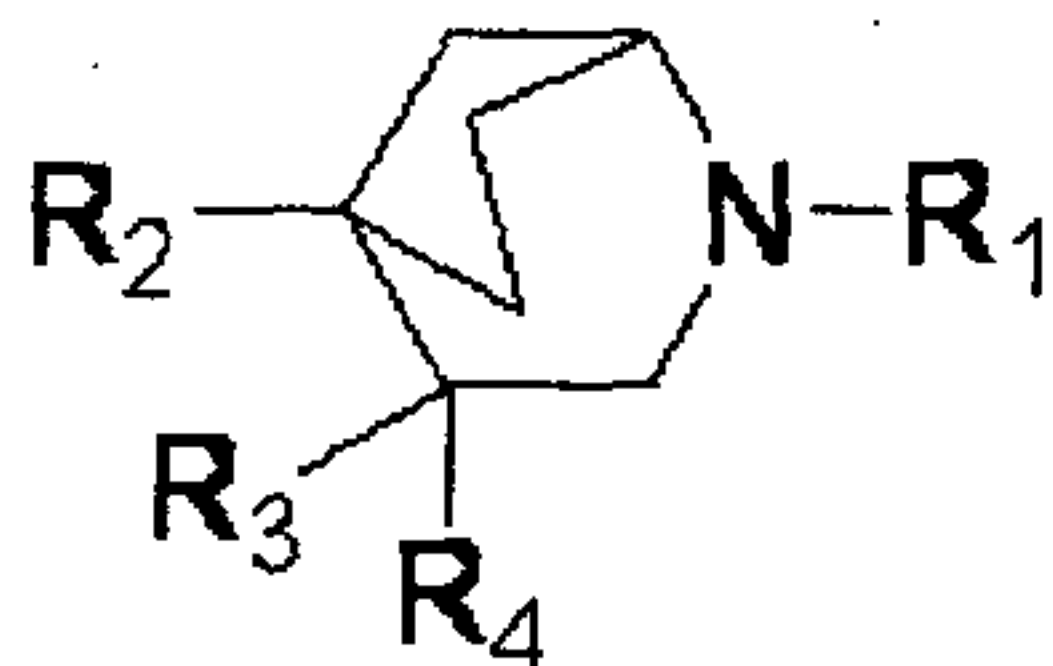
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reflex (see non-patent documents 6-8). Furthermore, it has been clarified that Duloxetine, which is a serotonin and norepinephrine reuptake inhibitor, Esreboxetine, which is a norepinephrine reuptake inhibitor, or the like can be used to provide a prophylactic or therapeutic effect on stress urinary incontinence, since they inhibit one of or both transporters and potentiate neurotransmission (see non-patent documents 9-11).

[0006]

Patent document 1 (WO2009/056520) describes, as azabicyclo[3.2.1]octane derivatives having a monoamine reuptake inhibitory action and useful as an antidepressant, a compound represented by the formula:

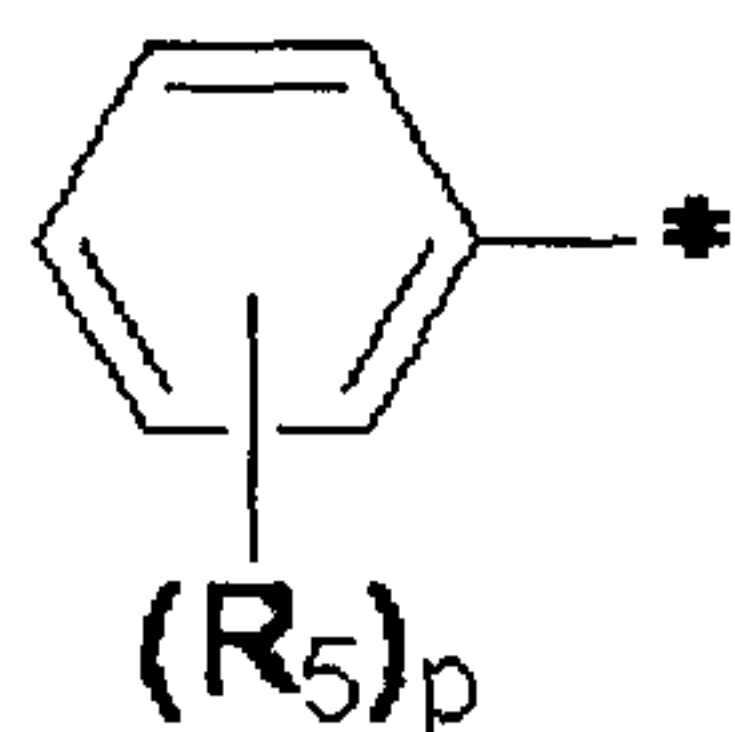
[0007]



[0008]

wherein R₂ is

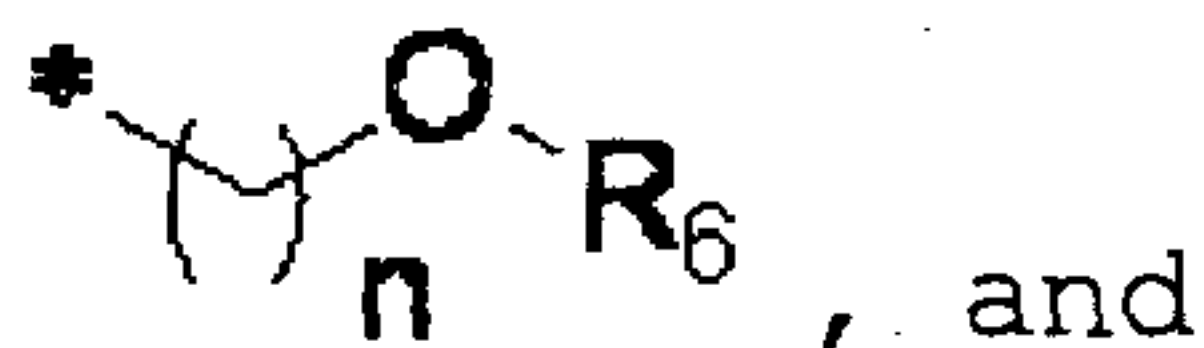
[0009]



[0010]

R₃ is

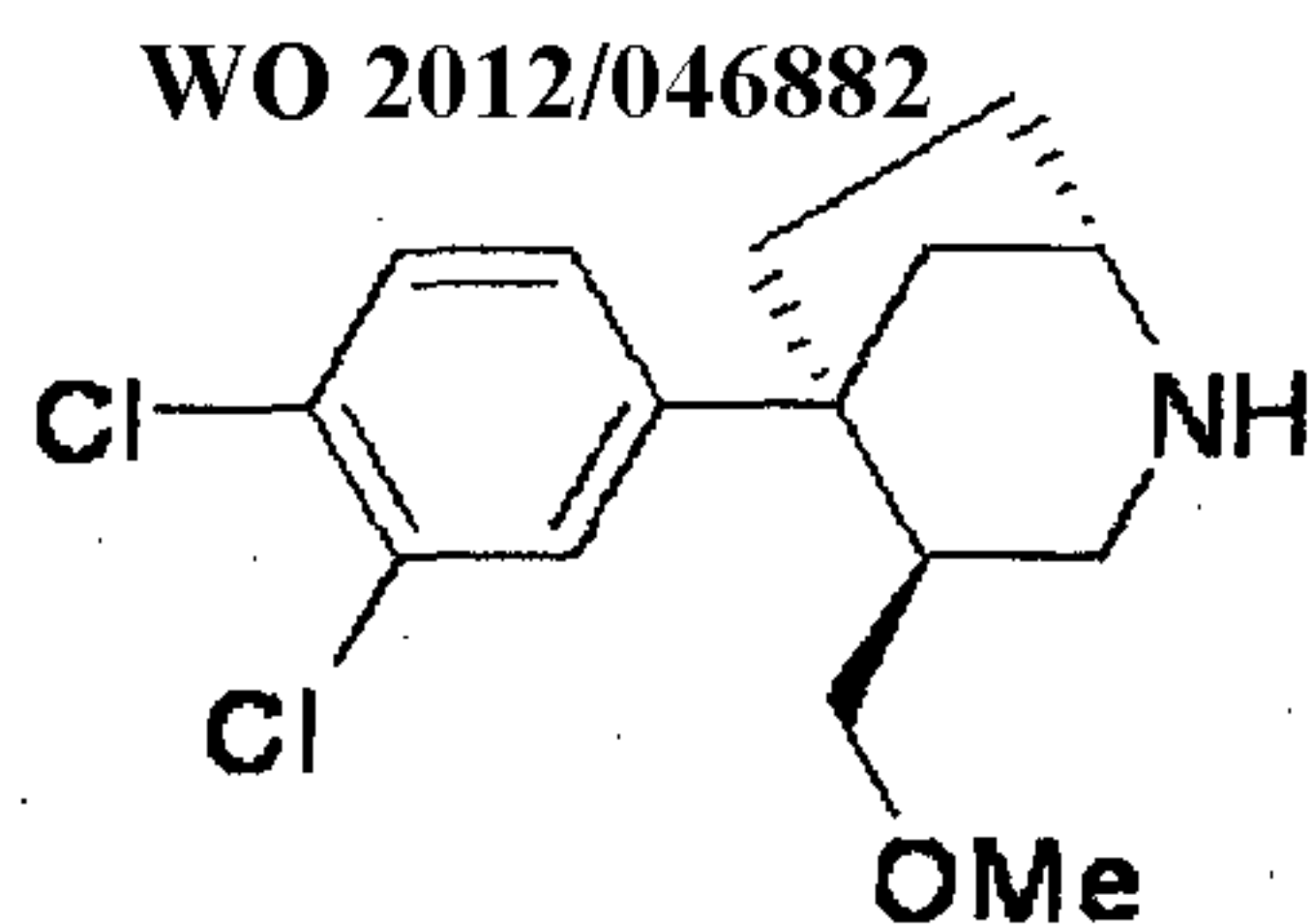
[0011]



[0012]

other symbols are as defined in patent document 1, and the following compound:

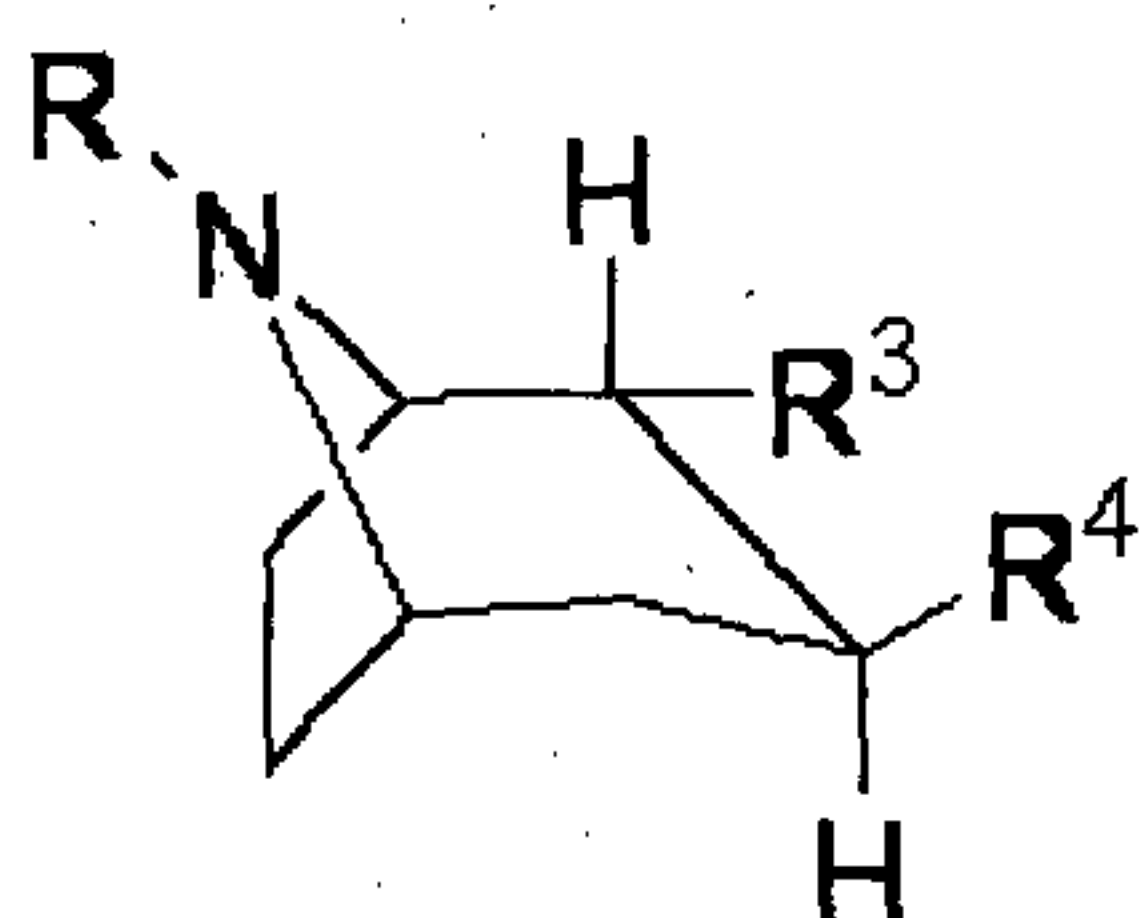
[0013]



[0014]

Patent document 2 (W097/30997) describes, as tropane derivatives having a monoamine reuptake inhibitory action and useful as therapeutic drugs for obesity and Parkinson's disease, a compound represented by the formula:

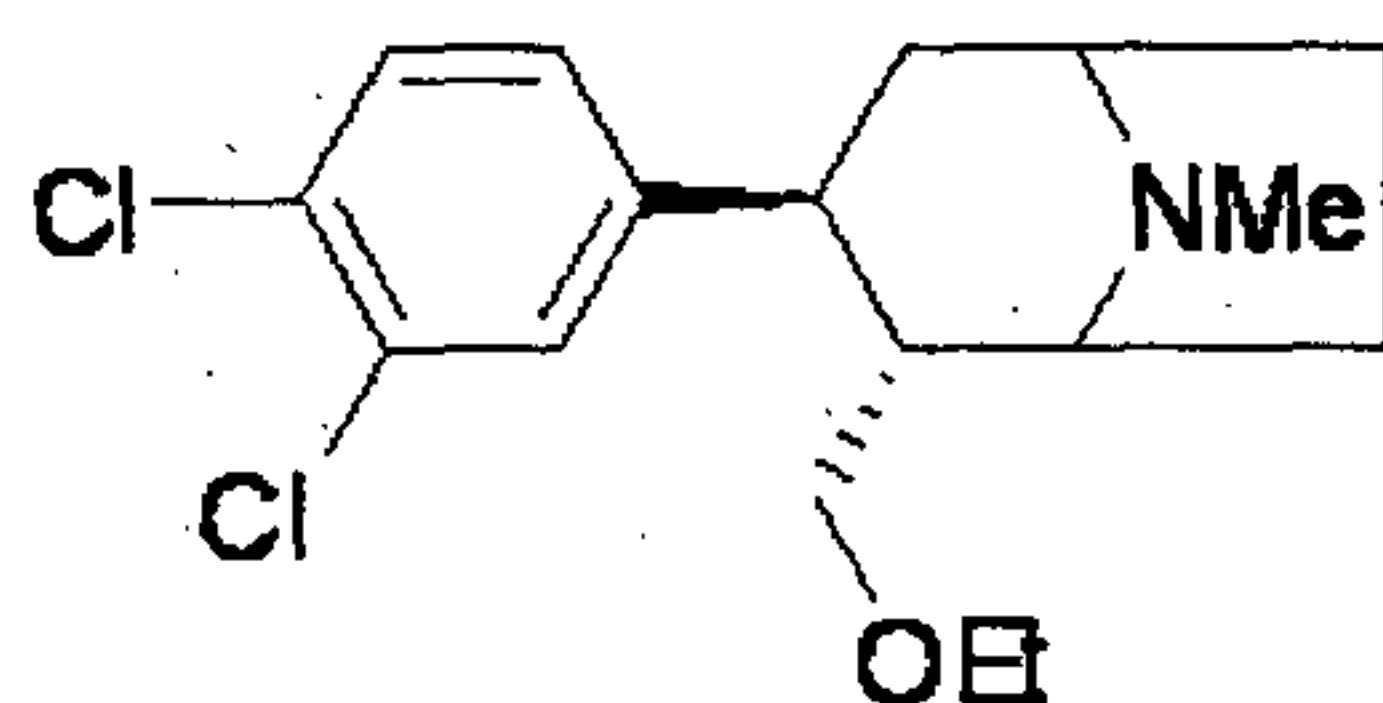
[0015]



10 [0016]

wherein each symbol is as defined in patent document 2, and the following compound:

[0017]

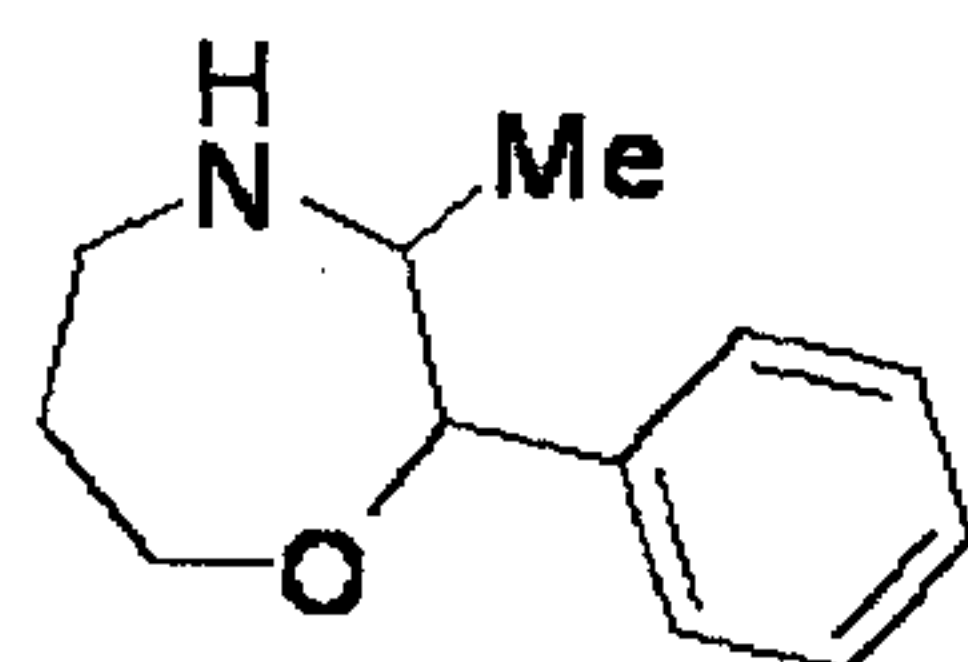


15 [0018]

Patent document 3 (US3018222) describes, as an oxazepine derivative useful as a central nervous system stimulant or anorectic agent, the following compound:

[0019]

20



[0020]

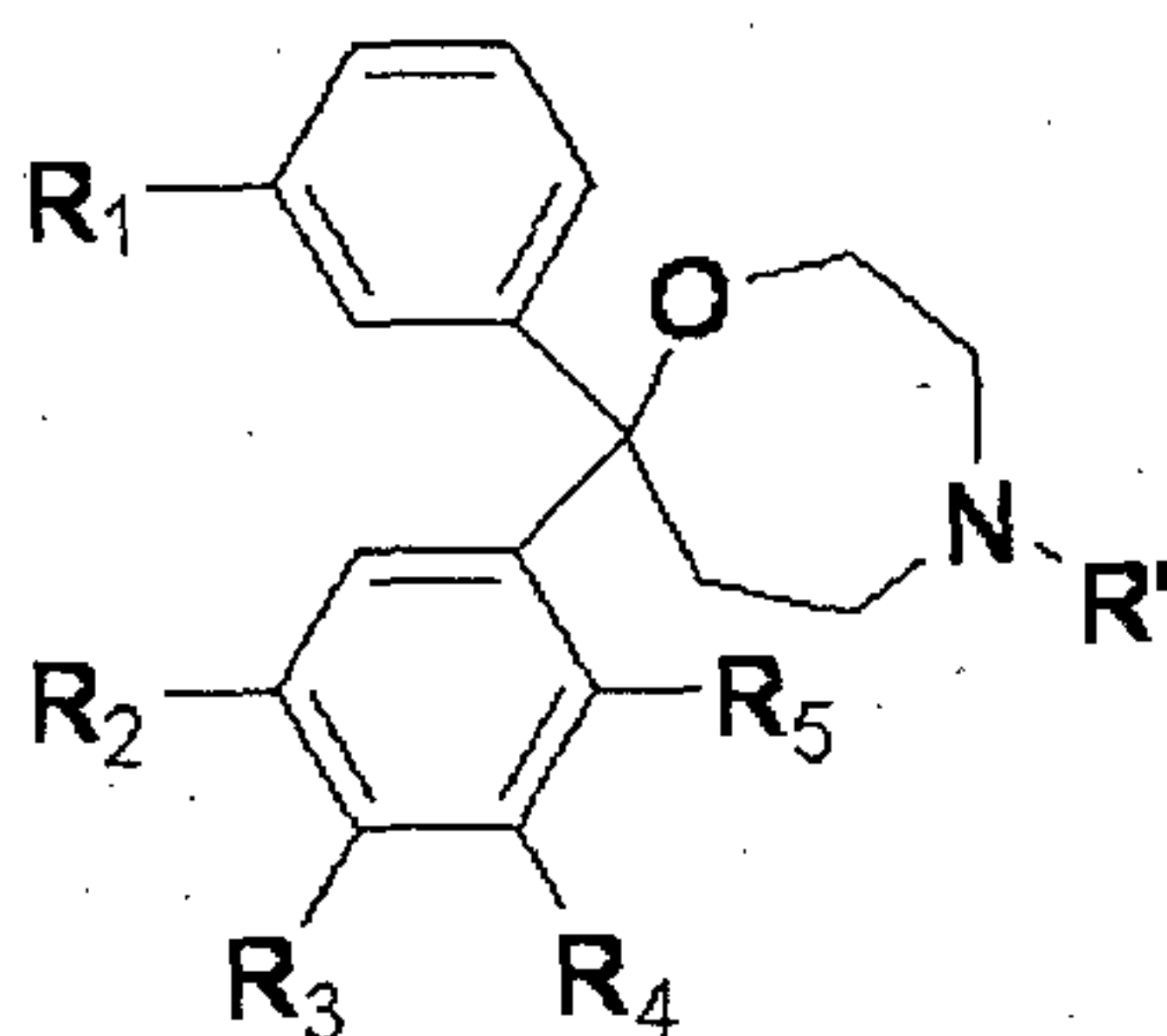
Patent document 4 (US4010166) describes, as 1,4-oxazepine derivatives useful as antidepressants, a compound represented

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by the formula:

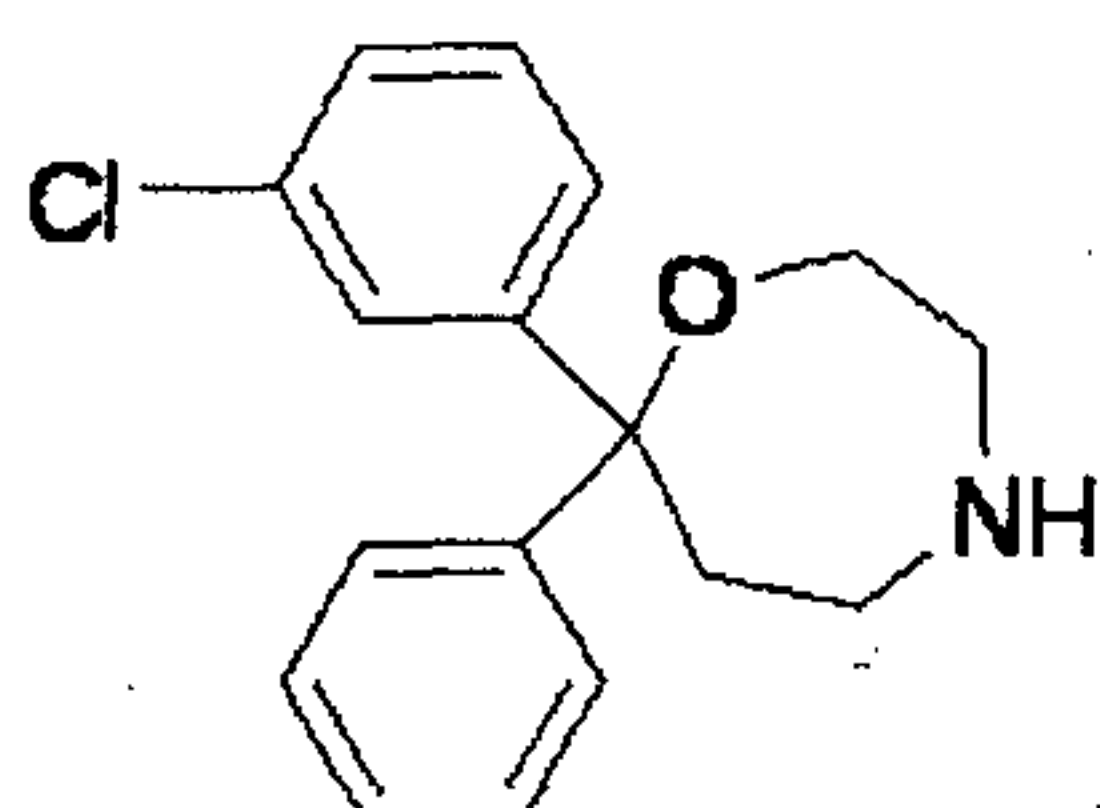
[0021]



[0022]

5 wherein each symbol is as defined in patent document 4, and the following compound:

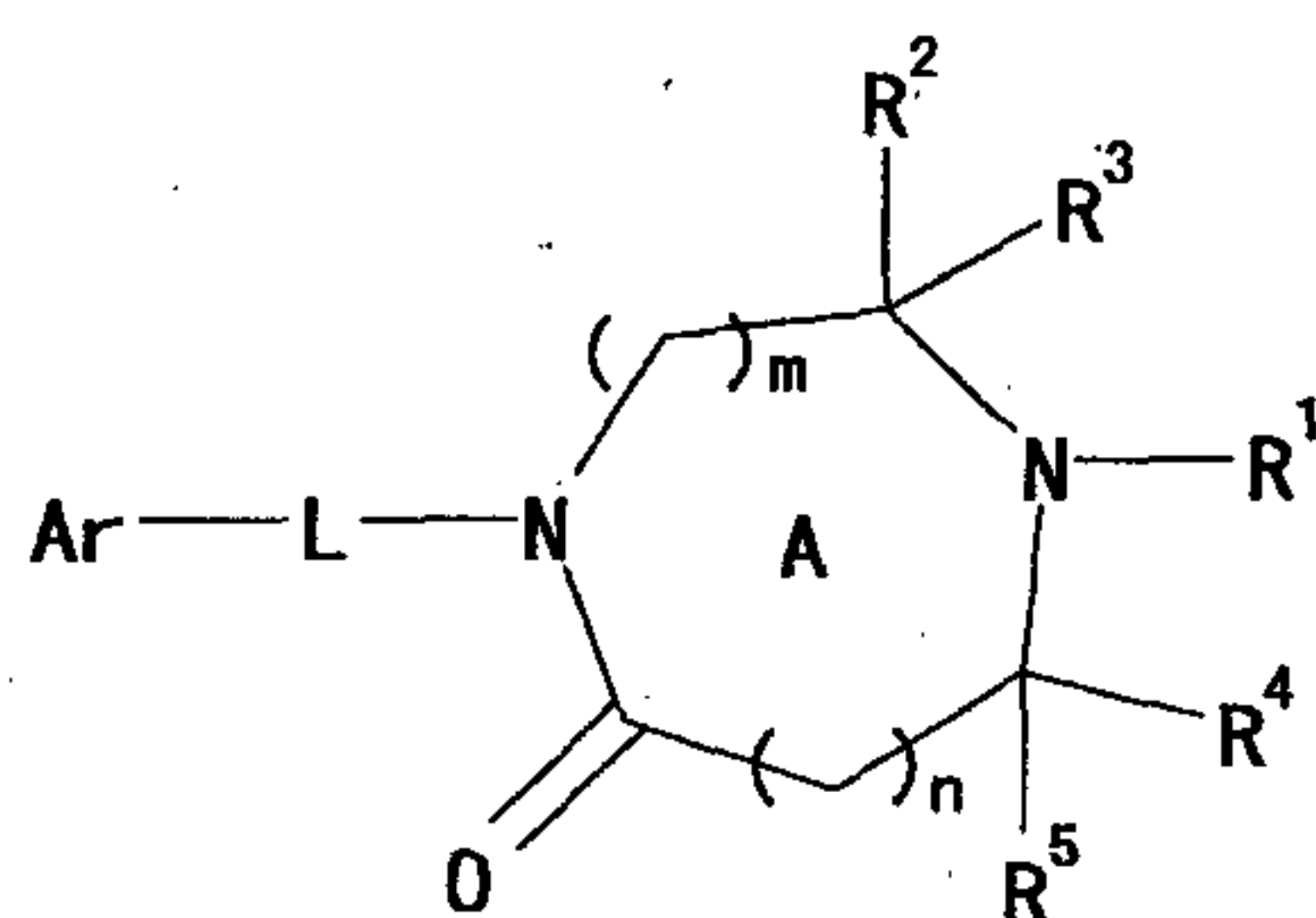
[0023]



[0024]

10 Patent document 5 (WO2009/119528) describes, as a homopiperazinone derivative having a monoamine reuptake inhibitory action and useful as an antidepressant, a compound represented by the formula:

[0025]



15

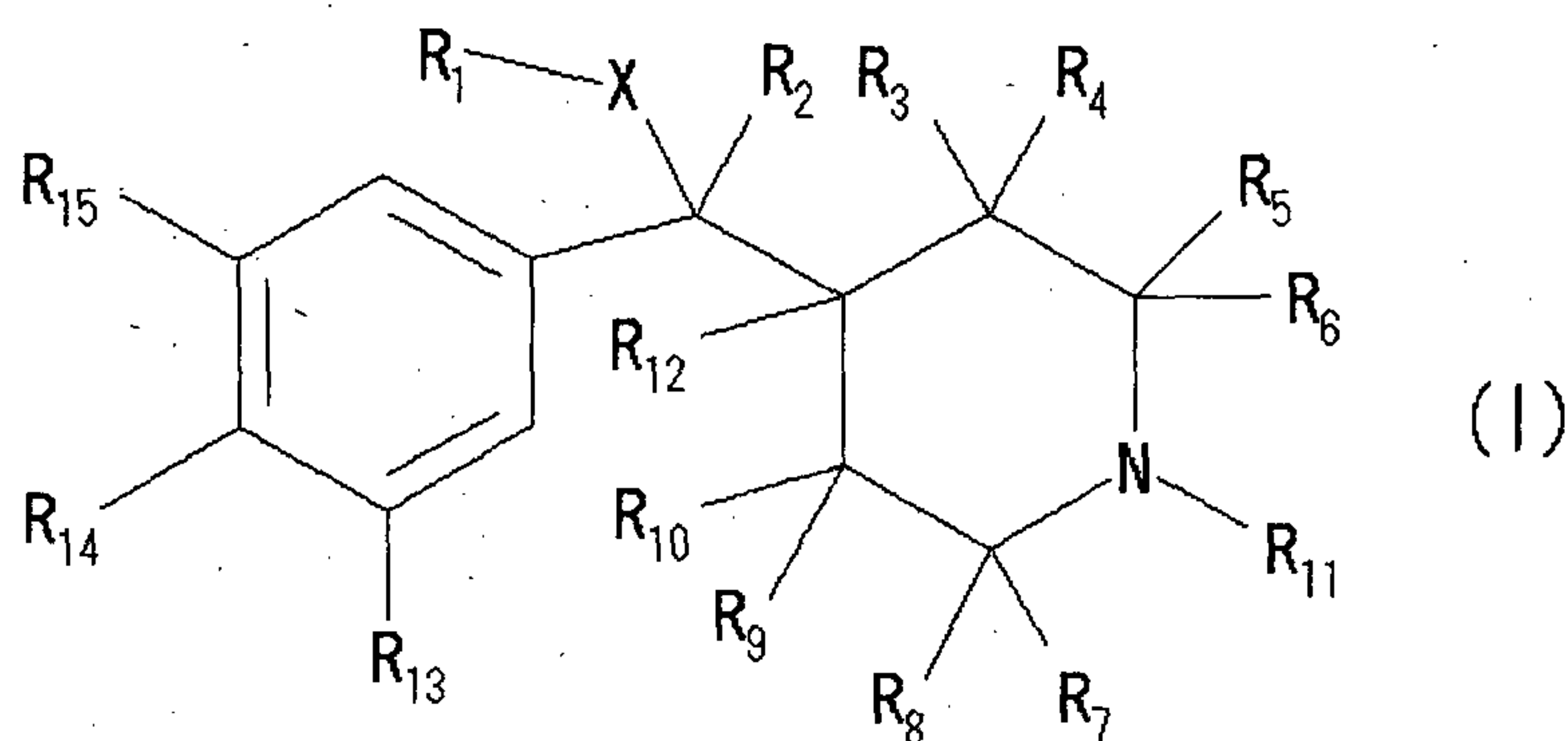
[0026]

wherein each symbol is as defined in patent document 5.

[0027]

Patent document 6 (WO2010/016554) describes, as a
20 piperidine derivative having a monoamine reuptake inhibitory action, a compound represented by the formula:

[0028]



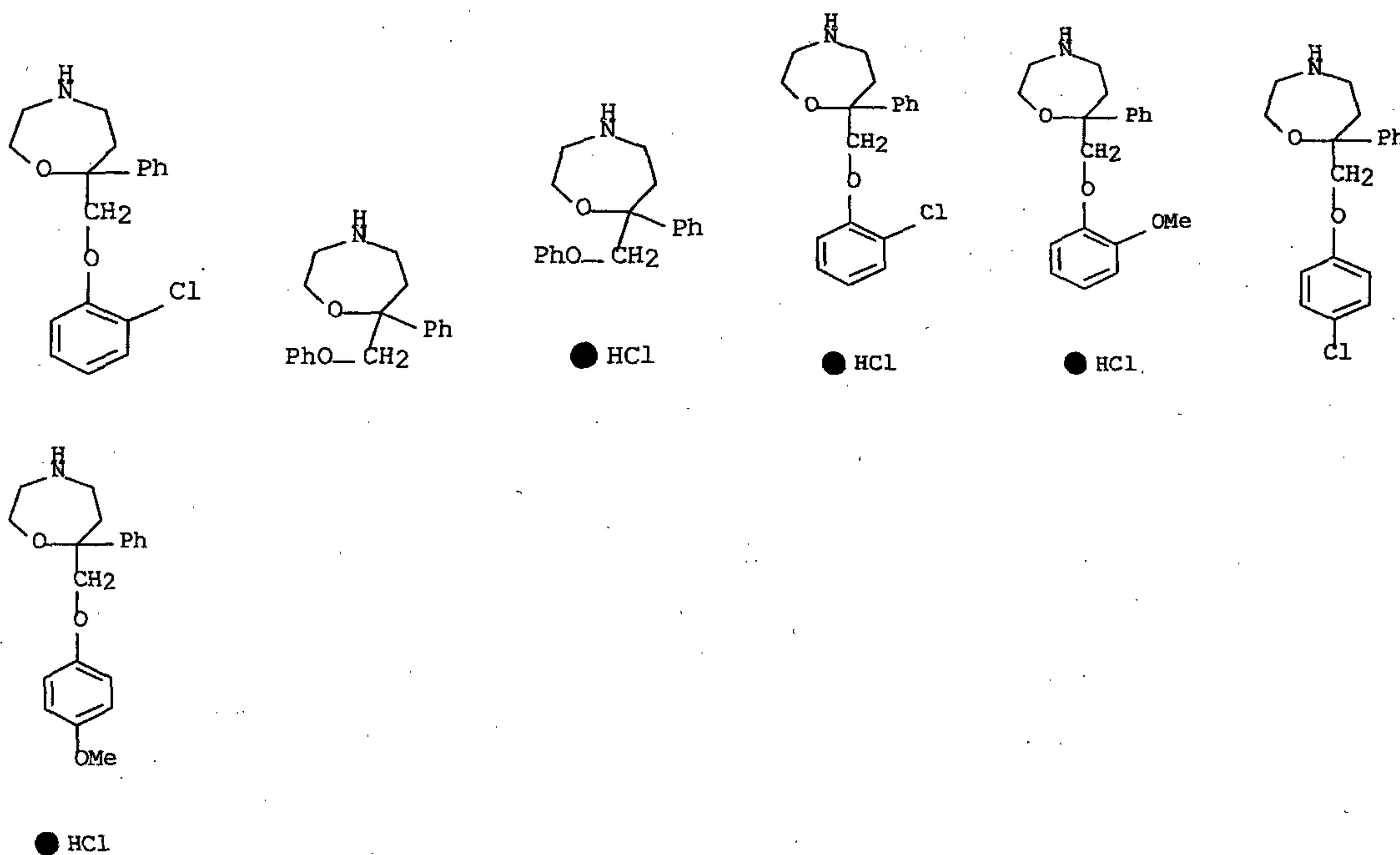
[0029]

wherein each symbol is as defined in patent document 6.

[0030]

5 In addition, as oxazepine compounds, patent document 7 (EP109622A1) describes the following compounds:

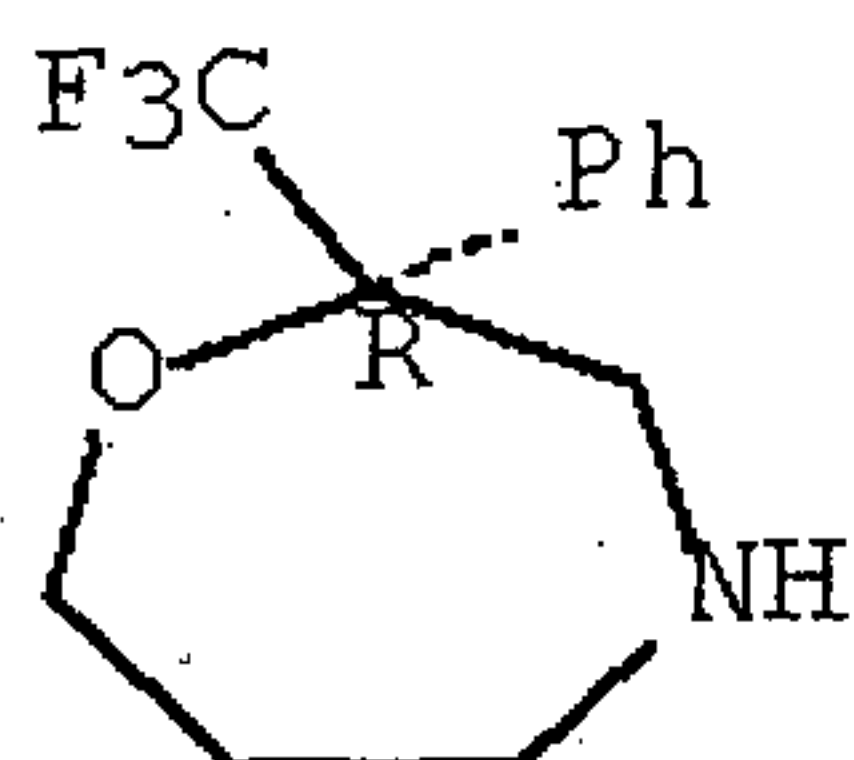
[0031]



[0032]

10 As an oxazepine compound, moreover, non-patent document 12 describes the following compound:

[0033]



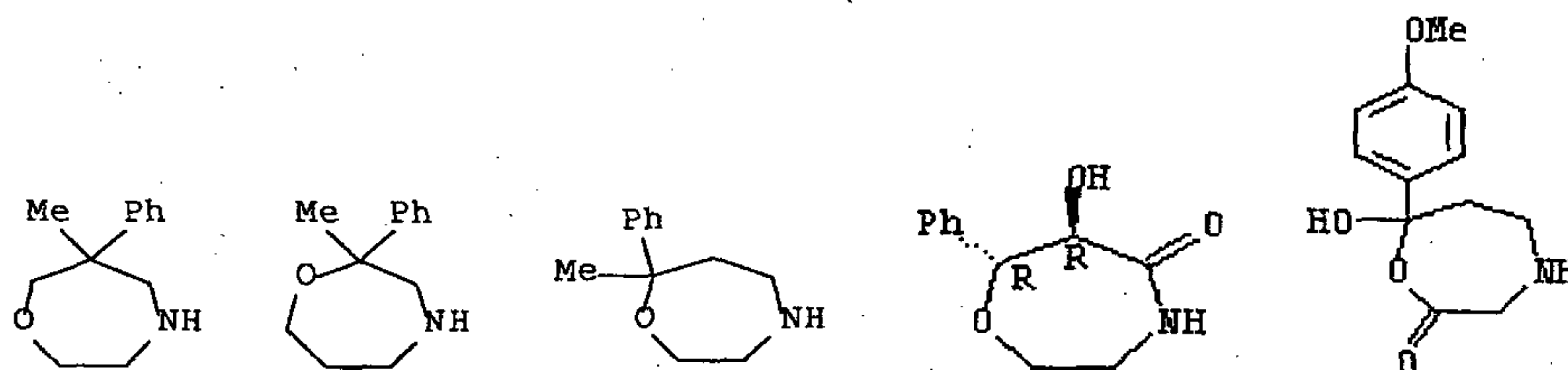
[0034]

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As oxazepine compounds, the following compounds are known:

[0035]



5 [Document List]

[patent documents]

[0036]

patent document 1: WO2009/056520

patent document 2: WO97/30997

10 patent document 3: US3018222

patent document 4: US4010166

patent document 5: WO2009/119528

patent document 6: WO2010/016554

patent document 7: EP109622A1

15 [non-patent documents]

[0037]

non-patent document 1: Annual Reports in Medicinal Chemistry, 2007, vol. 42, p.13-26

20 non-patent document 2: The Annals of Pharmacotherapy, 2002, vol. 36, No. 10, p.1577-1589

non-patent document 3: The Journal of Family Practice, 1982, vol. 14, p.935-936

25 non-patent document 4: American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 2003, vol. 285, p.R356-R365

non-patent document 5: American Journal of Physiology-Renal Physiology, 2004, vol. 287, p.F434-F441

non-patent document 6: American Journal of Physiology-Renal Physiology, 2007, vol. 293, p.F920-F926

30 non-patent document 7: International Journal of Gynecology and Obstetrics, 2004, vol. 86, p.S38-S52

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non-patent document 8: American Journal of Physiology-Renal Physiology, 2007, vol. 292, p.F639-F646

non-patent document 9: BJU International, 2004, vol. 93, p.311-318

5 non-patent document 10: BJU International, 2008, vol. 102, p.214-218

non-patent document 11: Annual Meeting of American Urological Association, 2008, Abst 1667

non-patent document 12: European Journal of Organic Chemistry, 10 2009, No. 22, p.3726-3731

[SUMMARY OF THE INVENTION]

Problems to be Solved by the Invention

[0038]

It has been desired to develop a compound having a
15 monoamine (serotonin, norepinephrine, dopamine etc.) reuptake inhibitory activity, useful as a prophylactic or therapeutic drug for depression, anxiety, attention deficit hyperactivity disorder, climacteric disorder, pain, stress urinary incontinence, mixed urinary incontinence and the like, and
20 having superior properties in the efficacy, duration of action, specificity, lower toxicity and the like.

[0039]

The present invention aims to provide a compound having a chemical structure different from the structures of known
25 compounds including the aforementioned compounds, as well as a monoamine reuptake inhibitory activity and the like, and a novel prophylactic or therapeutic drug for depression, anxiety, attention deficit hyperactivity disorder, climacteric disorder, pain, stress urinary incontinence, mixed urinary
30 incontinence and the like.

Means of Solving the Problems

[0040]

The present inventors have conducted intensive studies in an attempt to solve the aforementioned problems and found that
35 a compound represented by the following formula (I) has a

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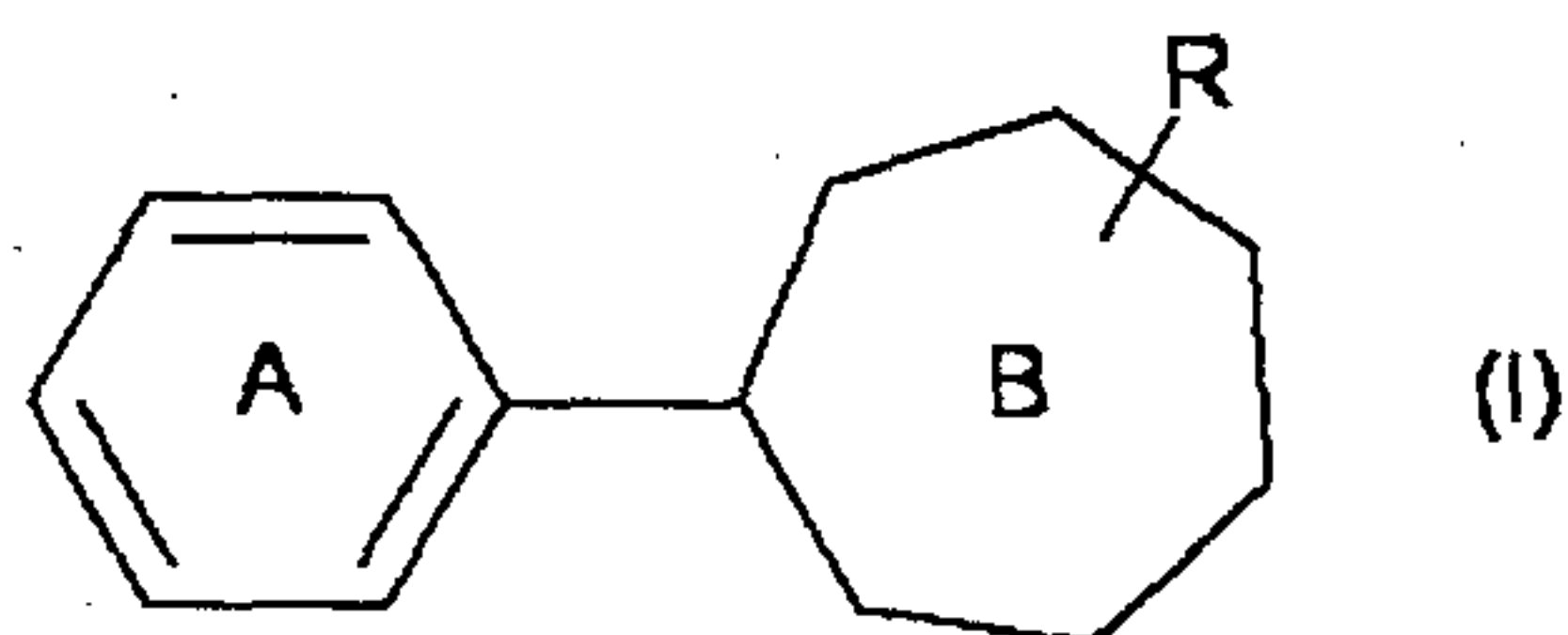
superior monoamine (serotonin, norepinephrine, dopamine etc.) reuptake inhibitory activity, which resulted in the completion of the present invention.

[0041]

5 Accordingly, the present invention relates to:

[1] a compound represented by the formula (I)

[0042]

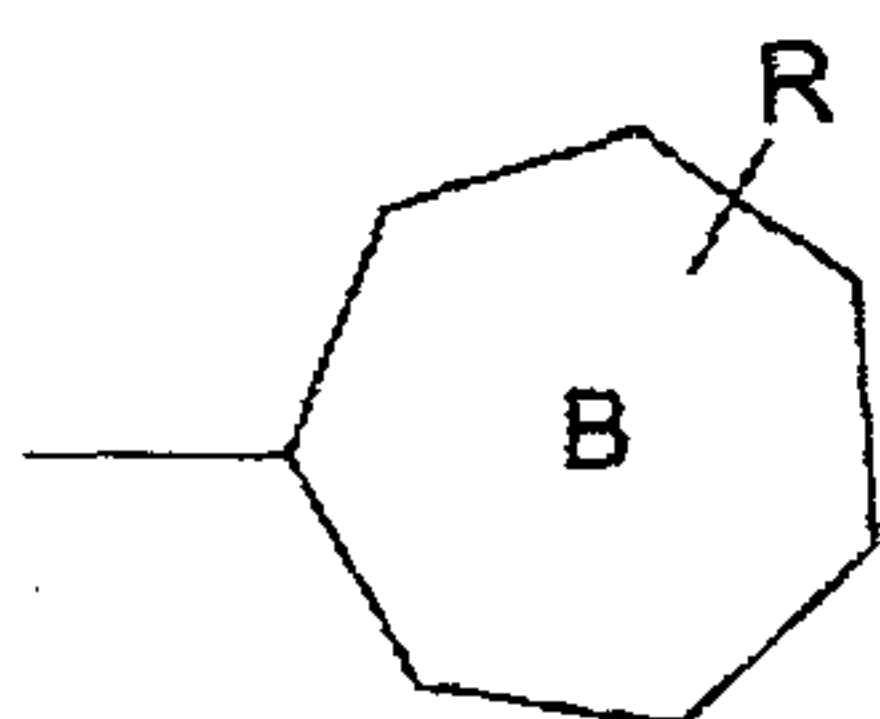


[0043]

10 wherein

ring A is an optionally substituted 6-membered aromatic ring, and a group represented by

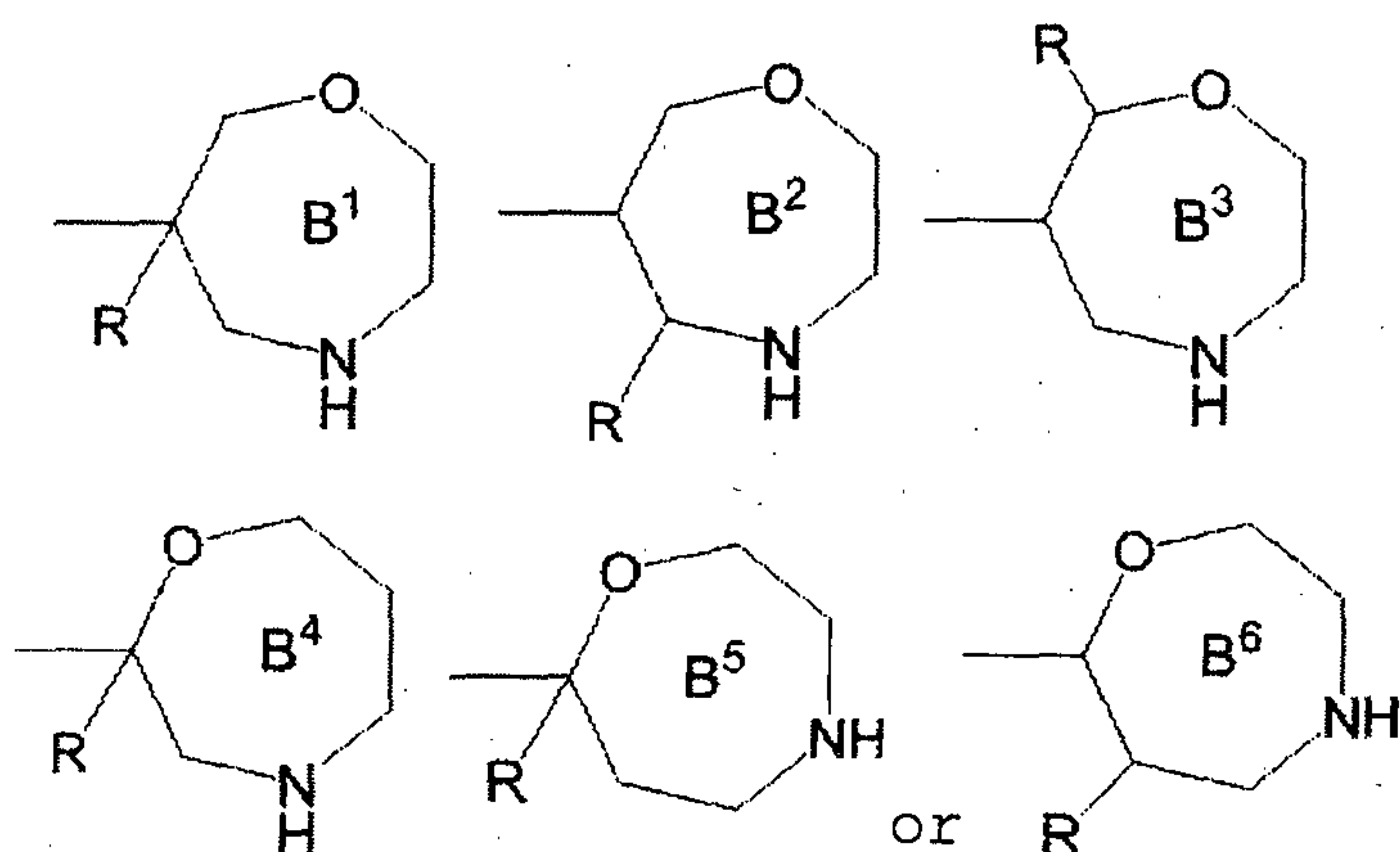
[0044]



15 [0045]

is

[0046]



[0047]

20 wherein rings B¹ - B⁶ are optionally further substituted, provided a hydrogen atom bonded to a nitrogen atom constituting rings B¹ - B⁶ is not substituted, and R is a hydroxy group, a cyano group, an optionally substituted

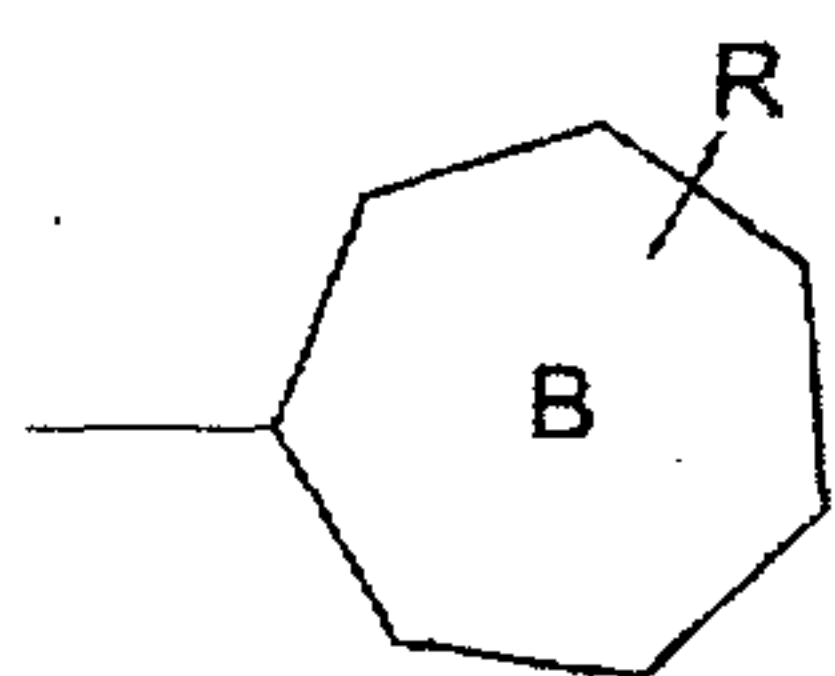
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carboxy group, an optionally substituted amino group, an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₁₋₆ alkoxy group, an optionally substituted C₁₋₆ alkyl-carbonyl group, an optionally substituted carbamoyl group, an optionally substituted C₆₋₁₂ aryloxy group, an optionally substituted aromatic heterocyclyl-oxy group, an optionally substituted aromatic heterocyclic group, or an optionally substituted nonaromatic heterocyclic group, wherein substituents on ring A are optionally bonded to form, together with ring A, optionally substituted 9- or 10-membered aromatic fused ring, provided that

(1) a compound, wherein a partial structure of the formula (I):

15 [0048]

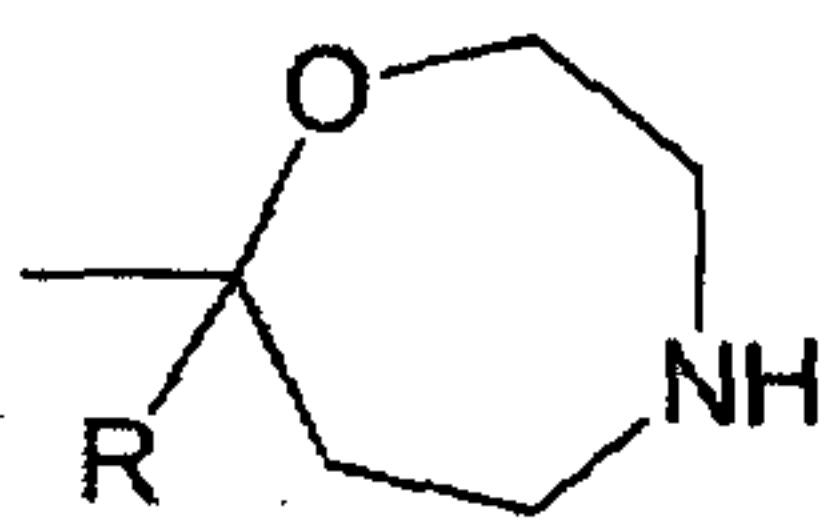


[0049]

is

[0050]

20



[0051]

ring A is a benzene ring, and

R is R^x-CH₂- (R^x is a phenoxy group optionally substituted by substituent(s) selected from a halogen atom and a methoxy group),

(2) 2-methyl-2-phenyl-1,4-oxazepane,

(3) 6-methyl-6-phenyl-1,4-oxazepane,

(4) (2R)-2-phenyl-2-(trifluoromethyl)-1,4-oxazepane,

30 (5) 7-methyl-7-phenyl-1,4-oxazepane,

(6) (6R,7R)-6-hydroxy-7-phenyl-1,4-oxazepan-5-one, and

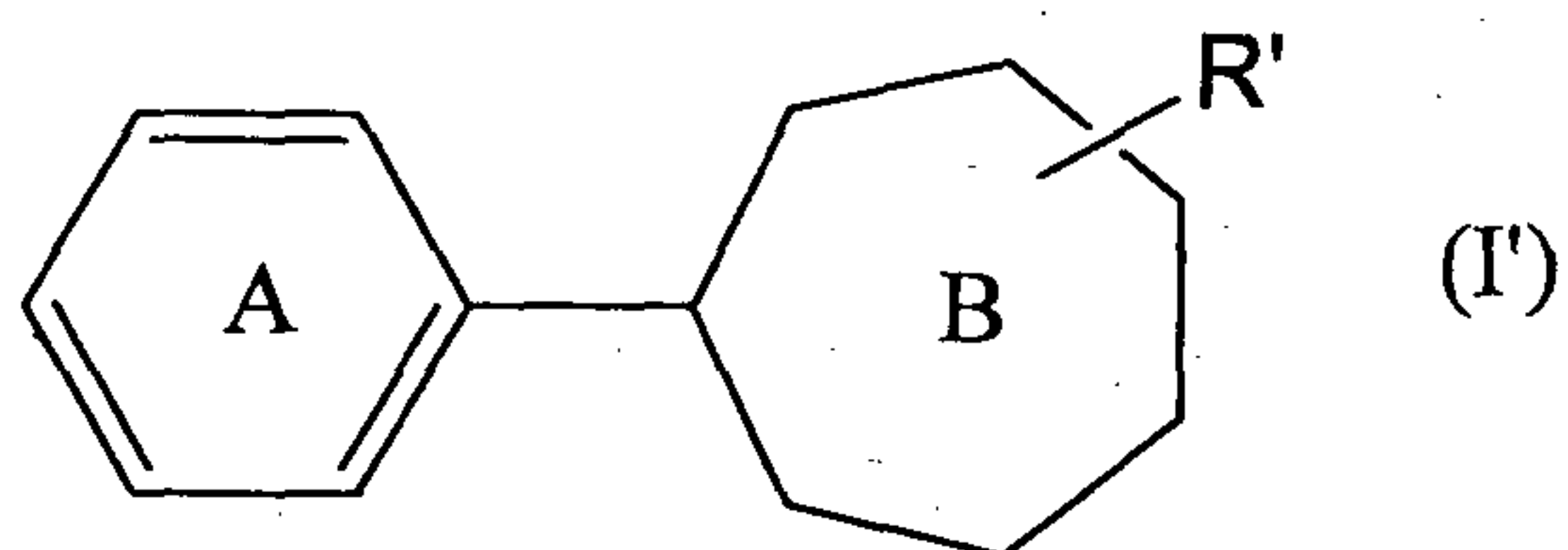
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(7) 7-hydroxy-7-(4-methoxyphenyl)-1,4-oxazepan-2-one are excluded, or a salt thereof,

[2] a compound represented by the formula (I')

[0052]



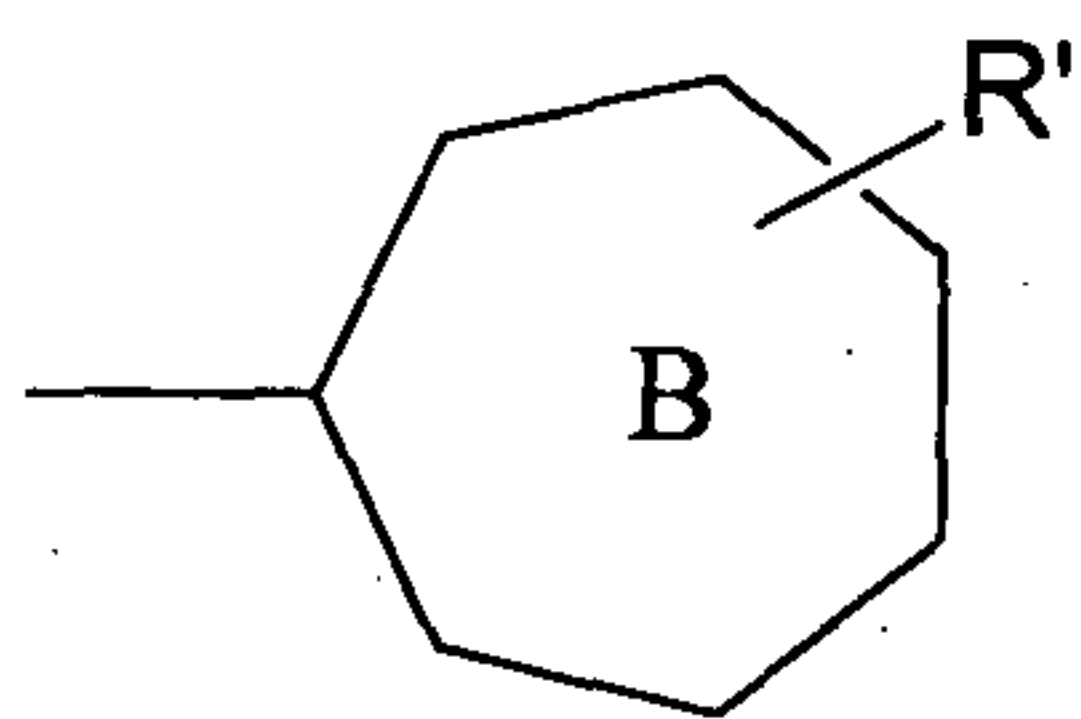
[0053]

wherein

ring A is an optionally substituted 6-membered aromatic ring, and

10 a group represented by

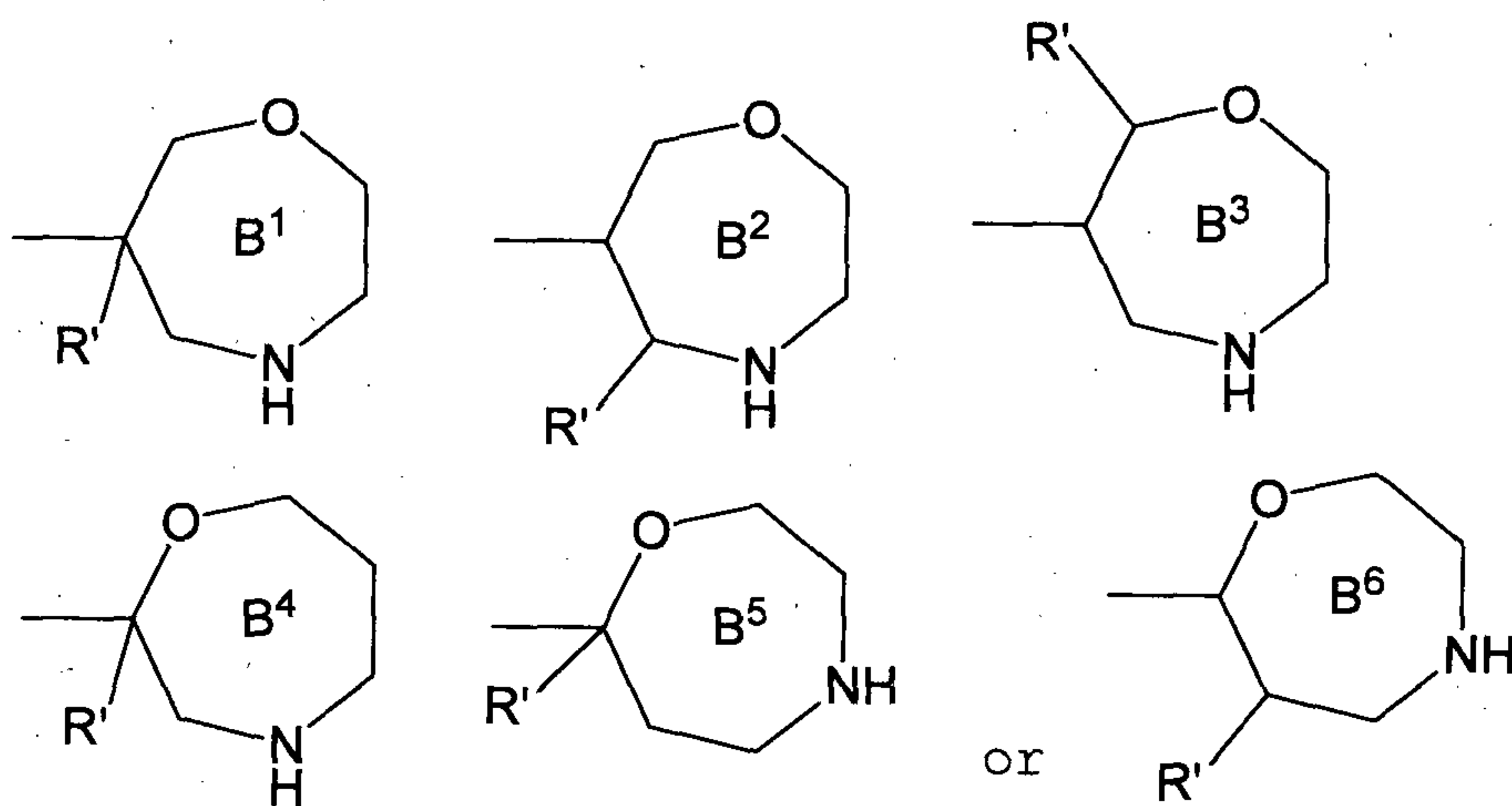
[0054]



[0055]

is

15 [0056]



[0057]

wherein rings B¹ - B⁶ are optionally further substituted, provided a hydrogen atom bonded to a nitrogen atom

20 constituting rings B¹ - B⁶ is not substituted, and R' is a hydroxy group, a cyano group, an optionally substituted

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carboxy group, an optionally substituted amino group, an optionally substituted C₁₋₆ alkyl group, an optionally substituted C₁₋₆ alkoxy group, or an optionally substituted carbamoyl group,

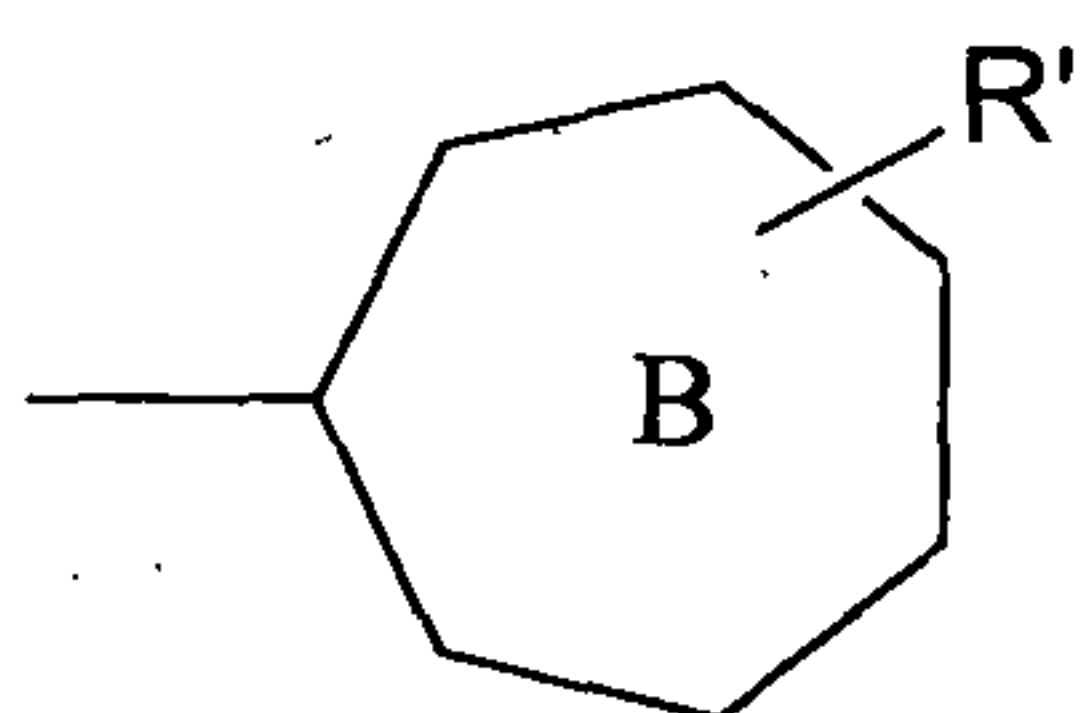
5 wherein substituents on ring A are optionally bonded to form, together with ring A, optionally substituted 9- or 10-membered aromatic fused ring,

provided that

(1) a compound, wherein a partial structure of the formula

10 (I):

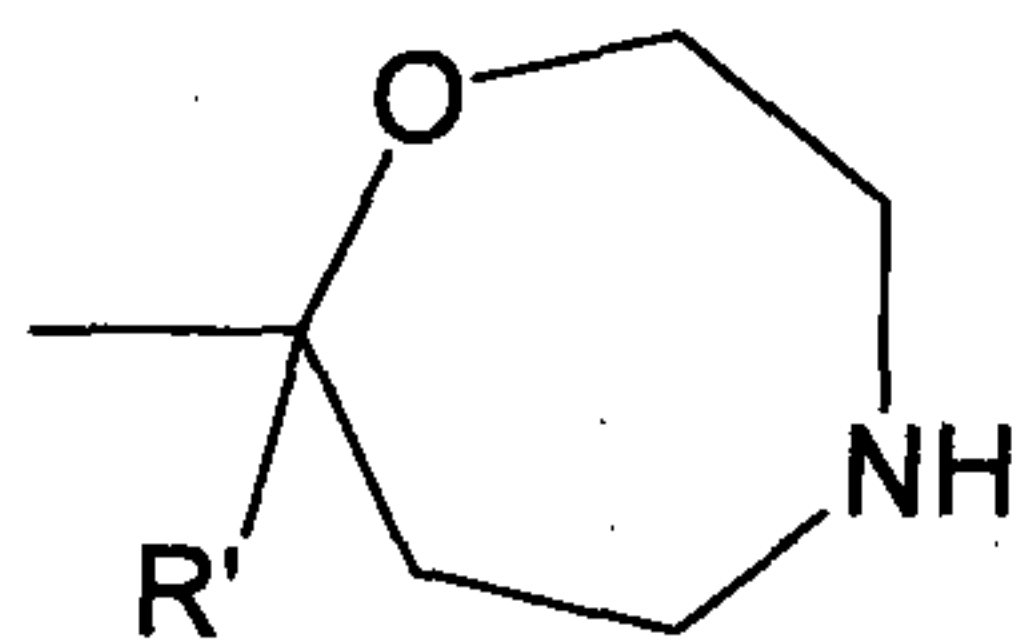
[0058]



[0059]

is

15 [0060]



[0061]

ring A is a benzene ring, and

20 R' is R^x-CH₂- (R^x is a phenoxy group optionally substituted by substituent(s) selected from a halogen atom and a methoxy group),

(2) 2-methyl-2-phenyl-1,4-oxazepane,

(3) 6-methyl-6-phenyl-1,4-oxazepane,

(4) (2R)-2-phenyl-2-(trifluoromethyl)-1,4-oxazepane,

25 (5) 7-methyl-7-phenyl-1,4-oxazepane,

(6) (6R,7R)-6-hydroxy-7-phenyl-1,4-oxazepan-5-one, and

(7) 7-hydroxy-7-(4-methoxyphenyl)-1,4-oxazepan-2-one are excluded, or a salt thereof,

[3] the compound of [2], wherein ring A is an optionally

substituted benzene ring, or a salt thereof,

[4] the compound of [2] or [3], wherein R' is

(1) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group,

(2) a sulfamoylamino group, or

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

(a) a hydroxy group,

(b) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group,

(c) a sulfamoylamino group,

10 (d) a C₁₋₆ alkoxy-C₁₋₆ alkyl-carbonylamino group,

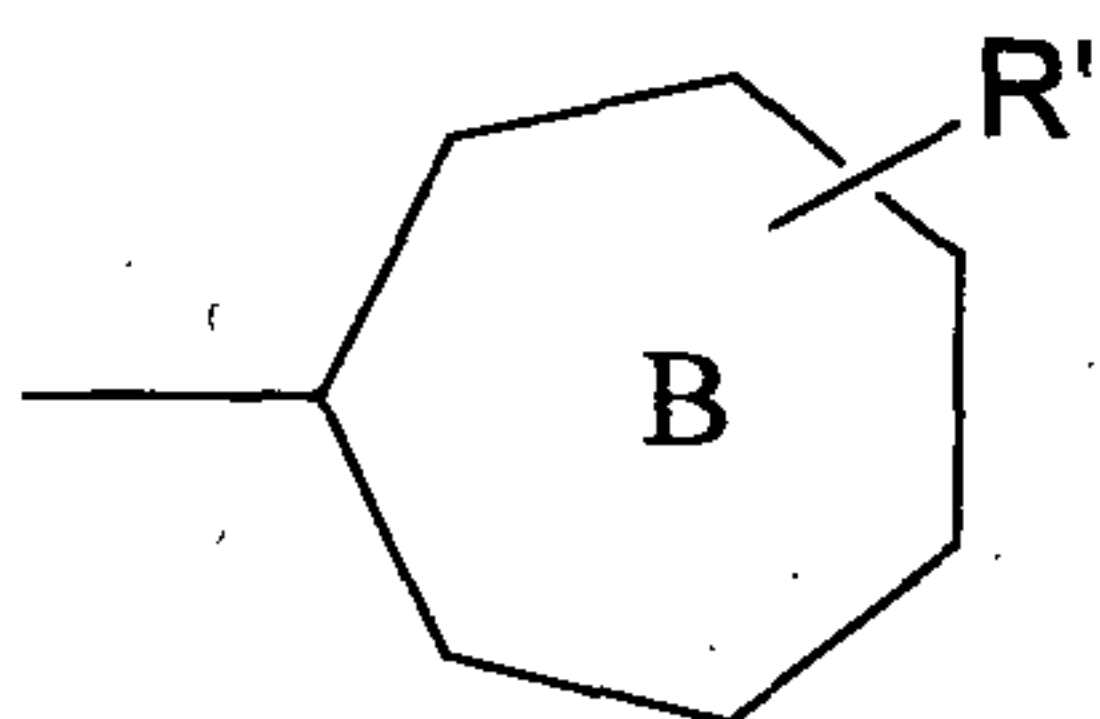
(e) a C₁₋₆ alkylsulfonfylamino group, and

(f) 2-oxopyridin-1(2H)-yl optionally substituted by 1 to 3 substituents selected from a carboxy group and 5-oxo-4,5-dihydro-1,2,4-oxadiazolyl,

15 or a salt thereof,

[5] the compound of any of [2] to [4], wherein the group represented by

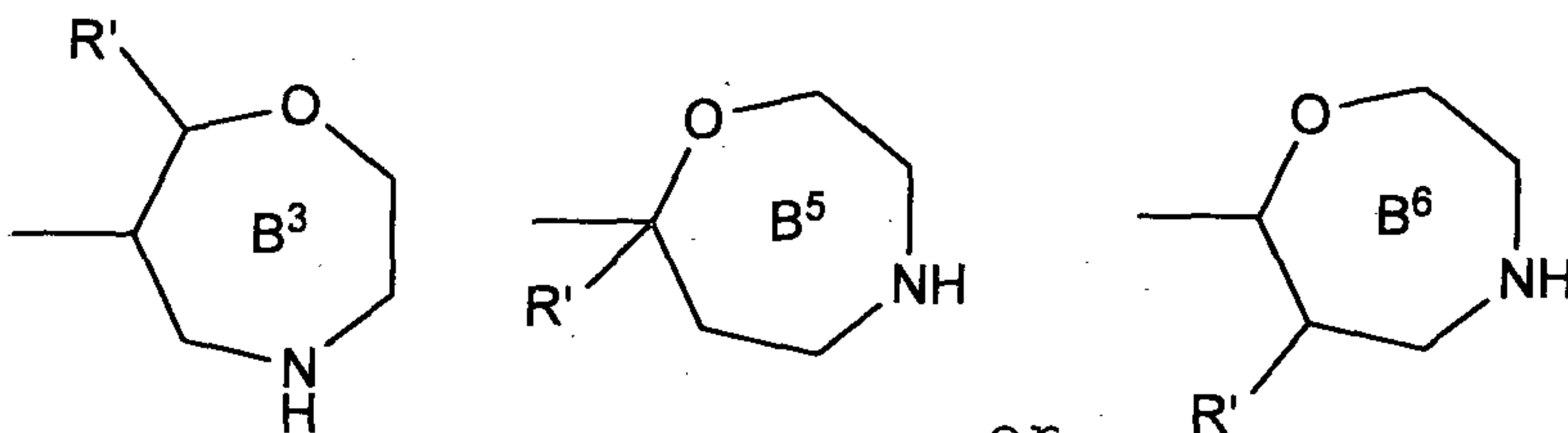
[0062]



20 [0063]

is

[0064]



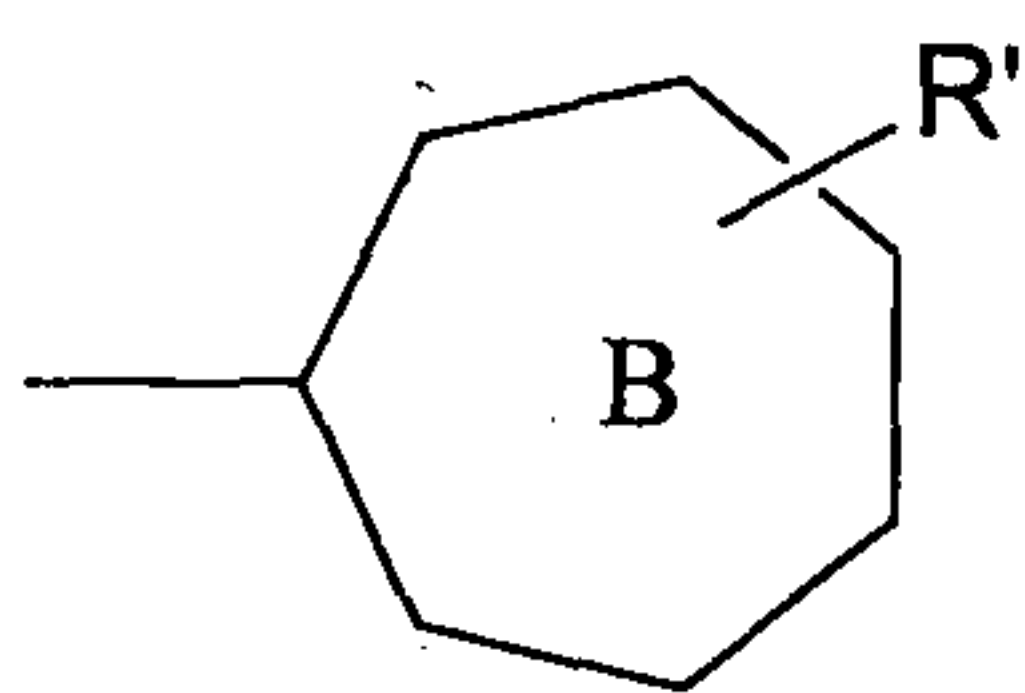
[0065]

25 wherein each symbol is as defined in [2],
or a salt thereof,

[6] the compound of [2], wherein the ring A is a benzene ring substituted by 2 substituents selected from a fluorine atom

and a chlorine atom, the group represented by

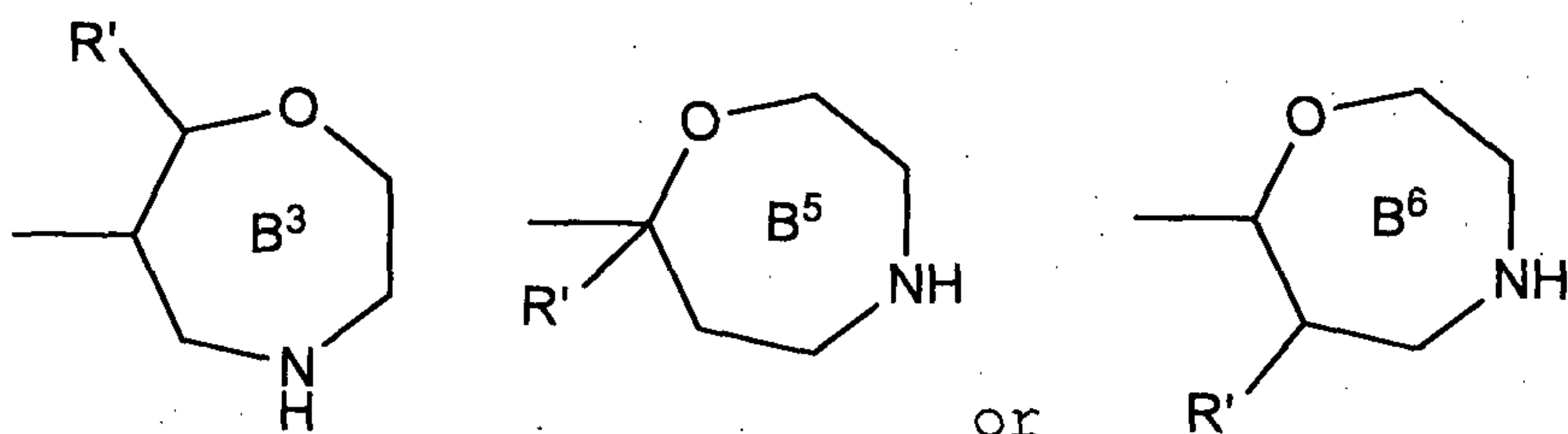
[0066]



[0067]

5 is

[0068]



[0069]

wherein

10 R' is

- (1) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group,
- (2) a sulfamoylamino group, or
- (3) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from

- 15 (a) a hydroxy group,
- (b) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group,
- (c) a sulfamoylamino group,
- (d) a C₁₋₆ alkoxy-C₁₋₆ alkyl-carbonylamino group,
- (e) a C₁₋₆ alkylsulfonfylamino group, and
- 20 (f) 2-oxopyridin-1(2H)-yl optionally substituted by 1 to 3 substituents selected from a carboxy group and 5-oxo-4,5-dihydro-1,2,4-oxadiazolyl,

and other symbols are as defined in [2], or a salt thereof,

[7] N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-2-methoxyacetamide, or a salt thereof,

[8] N-[(6R,7S)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]acetamide, or a salt thereof,

[9] N-{[(6S,7R)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-

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yl)methyl}-2-[(²H₃)methyloxy]acetamide, or a salt thereof,

[10] 1-{[(6S,7R)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-yl)methyl}-2-oxo-1,2-dihydropyridine-3-carboxylic acid, or a salt thereof,

5 [11] (1S)-1-[(6R,7R)-6-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]ethane-1,2-diol, or a salt thereof,

[12] [(7S)-7-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]methanol, or a salt thereof,

[13] a medicament comprising the compound of [1] or [2] or a
10 salt thereof,

[14] the medicament of [13], which is a monoamine reuptake inhibitor,

[15] the medicament of [13], which is a prophylactic or therapeutic drug for depression, anxiety, attention deficit
15 hyperactivity disorder, climacteric disorder, pain, stress urinary incontinence or mixed urinary incontinence,

[16] a method for the prophylaxis or treatment of depression, anxiety, attention deficit hyperactivity disorder, climacteric disorder, pain, stress urinary incontinence or mixed urinary
20 incontinence in a mammal, comprising administering an effective amount of the compound of [1] or [2] or a salt thereof to said mammal,

[17] use of the compound of [1] or [2] or a salt thereof for the production of a prophylactic or therapeutic drug for
25 depression, anxiety, attention deficit hyperactivity disorder, climacteric disorder, pain, stress urinary incontinence or mixed urinary incontinence,

[18] the compound of [1] or [2] or a salt thereof for the prophylaxis or treatment of depression, anxiety, attention
30 deficit hyperactivity disorder, climacteric disorder, pain, stress urinary incontinence or mixed urinary incontinence, and the like.

Effect of the Invention

[0070]

35 Since the compound of the present invention has a

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superior monoamine (serotonin, norepinephrine, dopamine etc.) reuptake inhibitory activity, it is useful as a prophylactic or therapeutic drug for, for example, depression, anxiety, attention deficit hyperactivity disorder, climacteric disorder, pain, stress urinary incontinence, mixed urinary incontinence and the like.

[Description of Embodiments]

[0071]

(DETAILED DESCRIPTION OF THE INVENTION)

10 The present invention is explained in detail in the following.

[0072]

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

[0073]

 In the present specification, examples of the "C₁₋₆ alkyl group" and "C₁₋₆ alkyl" in a substituent include a linear or branched chain C₁₋₆ alkyl group, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, 1-methylpropyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1,2-dimethylpropyl, hexyl, 2-methylpentyl, 3-methylpentyl, 1,2-dimethylbutyl, 1,2,2-trimethylpropyl and the like.

[0074]

25 In the present specification, examples of the "C₁₋₆ alkoxy group" and "C₁₋₆ alkoxy" in a substituent include linear or branched chain C₁₋₆ alkoxy group, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, 1-methylpropoxy, pentyloxy, isopentyloxy, neopentyloxy, tert-pentyloxy, 1,2-dimethylpropoxy, hexyloxy, 2-methylpentyloxy, 3-methylpentyloxy, 1,2-dimethylbutoxy, 1,2,2-trimethylpropoxy and the like.

[0075]

 In the present specification, examples of the "C₃₋₆ cycloalkyl group" and "C₃₋₆ cycloalkyl" in a substituent include

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cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.
[0076]

In the present specification, examples of the "C₃₋₆ cycloalkyloxy group" include cyclopropyloxy, cyclobutyloxy,
5 cyclopentyloxy, cyclohexyloxy and the like.
[0077]

In the present specification, examples of the "C₆₋₁₂ aryl group" and "C₆₋₁₂ aryl" in a substituent include phenyl, naphthyl (1-naphthyl, 2-naphthyl) and the like.
10 [0078]

In the present specification, examples of the "C₇₋₁₂ aralkyl group" and "C₇₋₁₂ aralkyl" in a substituent include benzyl, 2-phenylethyl, 1-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 1-naphthylmethyl, 2-naphthylmethyl and the like.
15 [0079]

In the present specification, examples of the "aromatic heterocyclic group" and "aromatic heterocyclyl-" in a substituent include a 4- to 7-membered (preferably 5- or 6-membered) monocyclic aromatic heterocyclic group containing,
20 as a ring constituting atom besides carbon atom, 1 - 4 hetero atoms selected from an oxygen atom, a sulfur atom (said sulfur atom is optionally oxidized) and a nitrogen atom, and a condensed aromatic heterocyclic group. Examples of the condensed aromatic heterocyclic group include groups wherein
25 these 4- to 7-membered monocyclic aromatic heterocyclic groups are condensed with 1 or 2 selected from a 5- or 6-membered aromatic heterocycle (e.g., pyrrole, imidazole, pyrazole, pyrazine, pyridine, pyrimidine) containing 1 or 2 nitrogen atoms, a 5-membered aromatic heterocycle (e.g., thiophene)
30 containing one sulfur atom, and a benzene ring and the like, and the like.

Preferable examples of the "aromatic heterocyclic group" and "aromatic heterocyclyl-" in a substituent include monocyclic aromatic heterocyclic groups such as furyl (e.g.,
35 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl),

pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrazinyl (e.g., 2-pyrazinyl), pyrrolyl (e.g., 2-pyrrolyl, 3-pyrrolyl),
 5 imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-
 10 oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (e.g., 1,2,5-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-3-yl), thiadiazolyl (e.g., 1,2,3-thiadiazol-4-yl, 1,3,4-thiadiazol-2-yl), triazolyl (e.g., 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-
 15 1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g., tetrazol-1-yl, tetrazol-5-yl), triazinyl (e.g., 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,2,4-triazin-6-yl) and the like;

condensed aromatic heterocyclic groups such as quinolyl (e.g.,
 20 2-quinolyl, 3-quinolyl, 4-quinolyl, 6-quinolyl), isoquinolyl (e.g., 3-isoquinolyl), quinazolyl (e.g., 2-quinazolyl, 4-quinazolyl), quinoxalyl (e.g., 2-quinoxalyl, 6-quinoxalyl), benzofuranyl (e.g., 2-benzofuranyl, 3-benzofuranyl, 4-benzofuranyl, 5-benzofuranyl, 6-benzofuranyl, 7-benzofuranyl),
 25 benzothienyl (e.g., 2-benzothienyl, 3-benzothienyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzisoxazolyl (e.g., 7-benzisoxazolyl), benzothiazolyl (e.g., 2-benzothiazolyl, 6-benzothiazolyl), benzimidazolyl (e.g., benzimidazol-1-yl, benzimidazol-2-yl, benzimidazol-5-yl), benzotriazolyl (e.g.,
 30 1H-1,2,3-benzotriazol-1-yl, 1H-1,2,3-benzotriazol-5-yl), indolyl (e.g., indol-1-yl, indol-2-yl, indol-3-yl, indol-5-yl), indazolyl (e.g., 2H-indazol-3-yl, 1H-indazol-1-yl), pyrrolopyrazinyl (e.g., 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyrazin-6-yl), imidazopyridinyl (e.g., 1H-
 35 imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 2H-

imidazo[1,2-a]pyridin-3-yl), imidazopyrazinyl (e.g., 1H-imidazo[4,5-b]pyrazin-2-yl), pyrazolopyridinyl (e.g., 1H-pyrazolo[4,3-c]pyridin-3-yl), thienopyrazolyl (e.g., 1H-thieno[2,3-c]pyrazol-5-yl), pyrazolotriazinyl (e.g.,
5 pyrazolo[5,1-c][1,2,4]triazin-3-yl), triazolopyrimidinyl (e.g., [1,2,4]triazolo[1,5-a]pyrimidin-2-yl), phthalazinyl and the like;
and the like.

[0080]

10 In the present specification, examples of the "nonaromatic heterocyclic group" and "nonaromatic heterocycl-yl-" in a substituent include a 4- to 7-membered (preferably 5- or 6-membered) monocyclic nonaromatic heterocyclic group containing, as a ring constituting atom
15 besides carbon atom, 1 - 4 hetero atoms selected from an oxygen atom, a sulfur atom (said sulfur atom is optionally oxidized) and a nitrogen atom, and a condensed nonaromatic heterocyclic group. Examples of the condensed nonaromatic heterocyclic group include groups wherein these 4- to 7-
20 membered monocyclic nonaromatic heterocyclic groups are condensed with 1 or 2 selected from a 5- or 6-membered aromatic or nonaromatic heterocycle (e.g., pyrrole, imidazole, pyrazole, pyrazine, pyridine, pyrimidine) containing 1 or 2 nitrogen atoms, a 5-membered aromatic or nonaromatic
25 heterocycle (e.g., thiophene) containing one sulfur atom, and a benzene ring and the like, and the like. The monocyclic nonaromatic heterocyclic group and condensed nonaromatic heterocyclic group may be crosslinked.

Preferable examples of the "nonaromatic heterocyclic
30 group" and "nonaromatic heterocycl-yl-" in a substituent include,
monocyclic nonaromatic heterocyclic groups such as azetidiny (e.g., 2-azetidiny), pyrrolidiny (e.g., 2-pyrrolidiny, 3-pyrrolidiny), piperidyl (e.g., 2-piperidyl, 3-piperidyl, 4-
35 piperidyl), homopiperidiny (e.g., 2-homopiperidyl, 3-

homopiperidyl, 4-homopiperidyl), tetrahydropyridyl (e.g., 1,2,3,6-tetrahydropyridin-2-yl), dihydropyridyl (e.g., 2,3-dihydropyridin-4-yl, 1,2-dihydropyridin-1-yl, 1,2-dihydropyridin-3-yl), morpholinyl (e.g., 2-morpholinyl),
5 thiomorpholinyl (e.g., 2-thiomorpholinyl), 1,1-dioxide-thiomorpholinyl (e.g., 1,1-dioxide-thiomorpholin-2-yl), piperazinyl (e.g., 2-piperazinyl), hexamethyleneiminyl (e.g., 2-hexamethyleneiminyl), oxazolidinyl (e.g., 2-oxazolidinyl), thiazolidinyl (e.g., 2-thiazolidinyl), imidazolidinyl (e.g.,
10 2-imidazolidinyl), oxazolinyl (e.g., 2-oxazolinyl), thiazolinyl (e.g., 2-thiazolinyl), imidazolinyl (e.g., 2-imidazolinyl), dioxolyl (e.g., 1,3-dioxol-4-yl), dioxolanyl (e.g., 1,3-dioxolan-4-yl), dihydrooxadiazolyl (e.g., 4,5-dihydro-1,2,4-oxadiazol-3-yl, 2,3-dihydro-1,3,4-oxadiazol-5-
15 yl), pyranyl (e.g., 2-pyranyl, 4-pyranyl), tetrahydropyranyl (e.g., 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl), thiopyranyl (e.g., 4-thiopyranyl), tetrahydrothiopyranyl (e.g., 2-tetrahydrothiopyranyl, 3-tetrahydrothiopyranyl, 4-tetrahydrothiopyranyl), 1-oxide-tetrahydrothiopyranyl (e.g., 1-oxide-tetrahydrothiopyran-4-
20 yl), 1,1-dioxide-tetrahydrothiopyranyl (e.g., 1,1-dioxide-tetrahydrothiopyran-4-yl), tetrahydrofuryl (e.g., tetrahydrofuran-3-yl, tetrahydrofuran-2-yl), pyrazolidinyl (e.g., 3-pyrazolidinyl), pyrazolinyl (e.g., 3-pyrazolinyl),
25 tetrahydropyrimidinyl (e.g., 2-tetrahydropyrimidinyl), hexahydropyrimidinyl (e.g., 2-hexahydropyrimidinyl), dihydrotriazolyl (e.g., 2,3-dihydro-1H-1,2,3-triazol-4-yl, 4,5-dihydro-1H-1,2,4-triazol-3-yl), tetrahydrotriazolyl (e.g., 2,3,4,5-tetrahydro-1H-1,2,3-triazol-4-yl), thiazinyl (e.g.,
30 1,4-thiazin-2-yl), 1,1-dioxide-thiazinanyl (e.g., 1,1-dioxide-1,2-thiazinan-3-yl), dihydropyridazinyl (e.g., 1,6-dihydropyridazin-3-yl, 2,3-dihydropyridazin-3-yl), tetrahydropyridazinyl (e.g., 1,4,5,6-tetrahydropyridazin-3-yl), dihydrothioxazinyl (e.g., 2,3-dihydro-1,4-thioxazin-3-
35 yl), dihydrothiazinyl (e.g., 3,4-dihydro-2H-1,4-thiazin-5-yl),

dioxanyl (e.g., 1,4-dioxan-2-yl) and the like;
 condensed nonaromatic heterocyclic groups such as
 dihydroindolyl (e.g., 2,3-dihydro-1H-indol-2-yl),
 dihydroisoindolyl (e.g., 2,3-dihydro-1H-isoindol-1-yl, 1,3-
 5 dihydro-2H-isoindol-2-yl), dihydrobenzofuranyl (e.g., 2,3-
 dihydro-1-benzofuran-5-yl), dihydrobenzodioxinyl (e.g., 2,3-
 dihydro-1,4-benzodioxinyl), dihydrobenzodioxepinyl (e.g., 3,4-
 dihydro-2H-1,5-benzodioxepin-7-yl), tetrahydrobenzofuranyl
 (e.g., 4,5,6,7-tetrahydro-1-benzofuran-3-yl), chromenyl (e.g.,
 10 4H-chromen-2-yl, 2H-chromen-3-yl, 2H-chromen-7-yl),
 dihydroquinolinyl (e.g., 1,2-dihydroquinolin-4-yl, 3,4-
 dihydroquinolin-2(1H)-yl), tetrahydroquinolinyl (e.g.,
 1,2,3,4-tetrahydroquinolin-4-yl), dihydroisoquinolinyl (e.g.,
 1,2-dihydroisoquinolin-4-yl), tetrahydroisoquinolinyl (e.g.,
 15 1,2,3,4-tetrahydroisoquinolin-4-yl, 1,2,3,4-
 tetrahydroisoquinolin-1-yl), dihydrophthalazinyl (e.g., 3,4-
 dihydrophthalazin-1-yl, 1,4-dihydrophthalazin-4-yl),
 tetrahydrobenzoazepinyl (e.g., 2,3,4,5-tetrahydro-1H-
 benzo[c]azepin-1-yl), benzodioxolyl (e.g., 1,3-benzodioxol-5-
 20 yl), benzothiazine (e.g., 3,4-dihydro-2H-1,4-benzothiazin-2-
 yl) and the like ;
 and the like.

[0081]

In the present specification, examples of the "cyclic
 25 amino" of the "cyclic amino group" and substituent include
 cyclic amino groups such as 1-azetidiny, 1-pyrrolidinyl,
 piperidino, homopiperidino, thiomorpholino, 1,1-dioxide-
 thiomorpholino, morpholino, 1-piperazinyl, 1-imidazolidinyl,
 1-pyrrolyl, 1-imidazolyl, 1-dihydropyridazinyl (e.g., 2,3-
 30 dihydropyridazin-2-yl), 1-hexahydropyrimidinyl,
 tetrahydropyridyl (e.g., 1,2,3,6-tetrahydropyridin-1-yl), 1-
 hexamethyleneiminyl, 3-oxazolidinyl, 3-thiazolidinyl, 1-
 imidazolinyl, 1-pyrazolidinyl, 1-pyrazolinyl, 1-
 tetrahydropyrimidinyl, dihydrotriazolyl (e.g., 2,3-dihydro-1H-
 35 1,2,3-triazol-1-yl, 4,5-dihydro-1H-1,2,4-triazol-1-yl),

tetrahydrotriazolyl (e.g., 2,3,4,5-tetrahydro-1H-1,2,3-triazol-1-yl), 1,1-dioxide-thiazinanyl (e.g., 1,1-dioxide-1,2-thiazinan-2-yl), dihydropyridazinyl (e.g., 1,6-dihydropyridazin-1-yl, 2,3-dihydropyridazin-2-yl), 1-
 5 dihydroindolyl (e.g., 2,3-dihydro-1H-indol-1-yl), 1-dihydroquinolinyl (e.g., 1,2-dihydroquinolin-1-yl, 3,4-dihydroquinolin-1(2H)-yl), 1-tetrahydroquinolinyl (e.g., 1,2,3,4-tetrahydroquinolin-1-yl), 2-dihydroisoquinolinyl (e.g., 1,2-dihydroisoquinolin-2-yl), 2-tetrahydroisoquinolinyl
 10 (e.g., 1,2,3,4-tetrahydroisoquinolin-2-yl), 2-dihydroisoindolyl (e.g., 1,3-dihydro-2H-isoindol-2-yl), 3-dihydroquinazolinyl (e.g., 3,4-dihydroquinazolin-3-yl), 3-tetrahydroquinazolinyl (e.g., 1,2,3,4-tetrahydroquinazolin-3-yl), 3-tetrahydropyrido[3,2-d]pyrimidinyl (e.g., 1,2,3,4-
 15 tetrahydropyrido[3,2-d]pyrimidin-3-yl), 3-tetrahydropteridinyl (e.g., 1,2,3,4-tetrahydropteridin-3-yl), 8-oxa-3-azabicyclo[3.2.1]octan-3-yl and the like.

[0082]

Examples of the "6-membered aromatic ring" of the
 20 "optionally substituted 6-membered aromatic ring" for ring A include benzene ring, 6-membered aromatic heterocycle containing 1 to 3 nitrogen atoms (e.g., pyridine, pyrazine, pyrimidine, pyridazine, triazine) and the like.

[0083]

25 Examples of the substituent that the "6-membered aromatic ring" optionally has include substituents selected from
 (1) a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom),
 (2) a cyano group,
 30 (3) a hydroxy group,
 (4) a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms,
 (5) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atoms. The number of the substituents is 1 to 5, preferably 1
 35 to 3, more preferably 1 or 2.

Examples of the "9 or 10-membered aromatic fused ring" of the "optionally substituted 9 or 10-membered aromatic fused ring" formed, together with ring A, by the substituents on
5 ring A bonded to each other include naphthalene, benzofuran, indazole and the like. Examples of the substituent that the "9 or 10-membered aromatic fused ring" optionally has include those similar to the substituents that the 6-membered aromatic ring for ring A optionally has. The number of the substituents
10 is 1 to 5, preferably 1 to 3, more preferably 1 or 2.

[0085]

Ring A is preferably an optionally substituted benzene ring. As the "optionally substituted benzene ring", a benzene ring substituted by 1 to 3 (preferably 2) substituents
15 selected from a halogen atom, a C₁₋₆ alkyl group and a C₁₋₆ alkoxy group is preferable, and a benzene ring substituted by 2 halogen atoms is particularly preferable.

[0086]

In another embodiment, ring A is preferably an optionally
20 substituted benzene ring, more preferably, a benzene ring optionally substituted 1 to 3 (preferably 2) substituents selected from a halogen atom, a C₁₋₆ alkyl group and a C₁₋₆ alkoxy group, more preferably, a benzene ring optionally substituted 1 to 3 (preferably 1 or 2) halogen atoms
25 (preferably, a fluorine atom, a chlorine atom).

[0087]

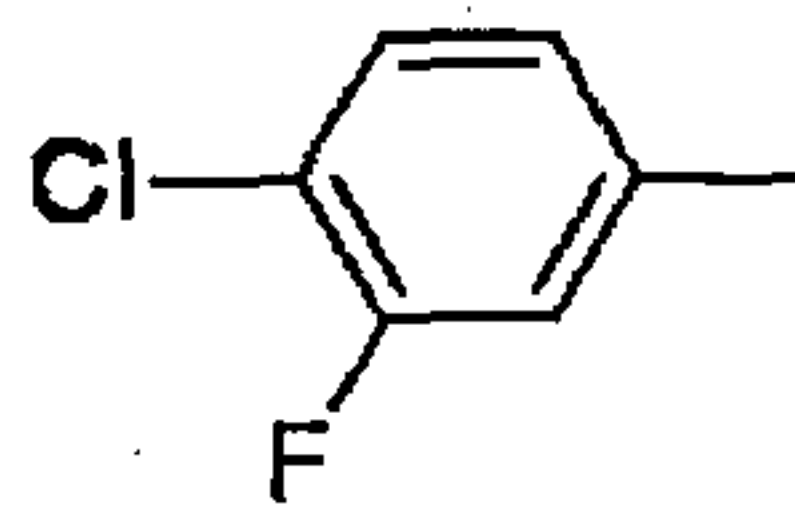
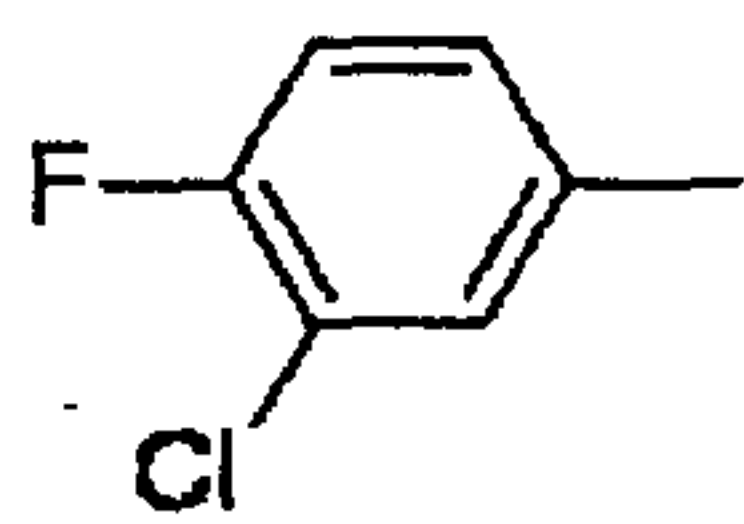
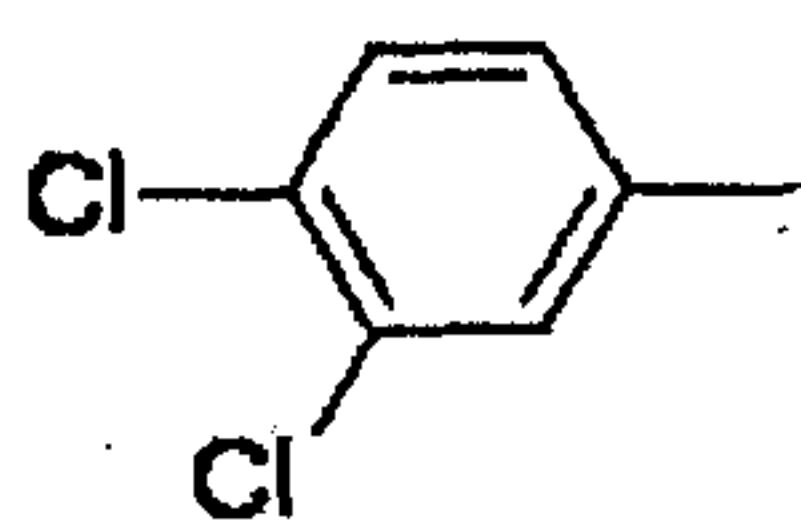
In another embodiment, ring A is preferably an optionally substituted benzene ring, more preferably, a benzene ring optionally substituted by 1 to 3 (preferably 2) substituents
30 selected from a halogen atom (preferably, a fluorine atom, a chlorine atom) and a C₁₋₆ alkyl group (preferably, methyl), more preferably, a benzene ring substituted by 2 substituents selected from a fluorine atom and a chlorine atom.

[0088]

35 Preferable examples of ring A include

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[0089]

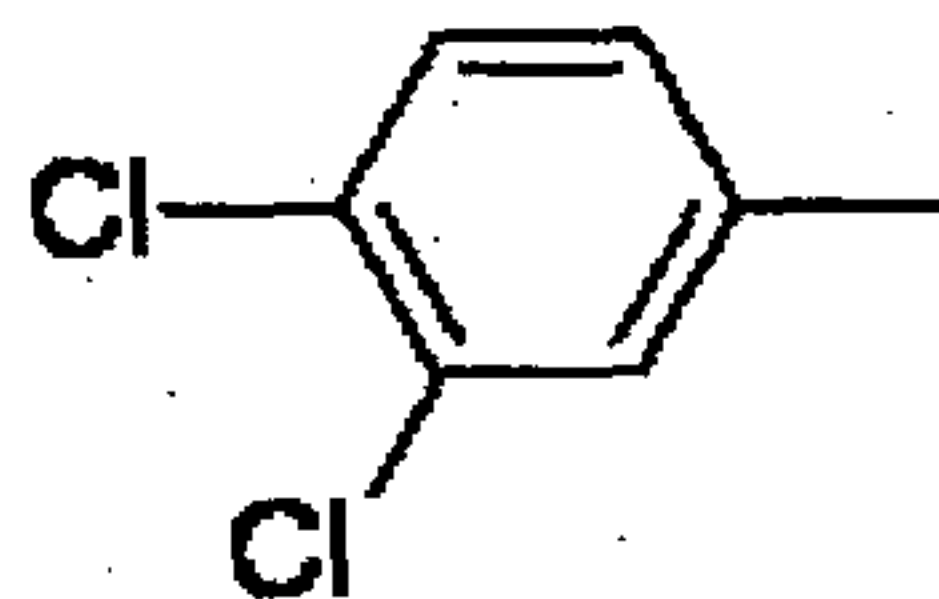
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[0090]

and the like. Particularly preferred is

5 [0091]

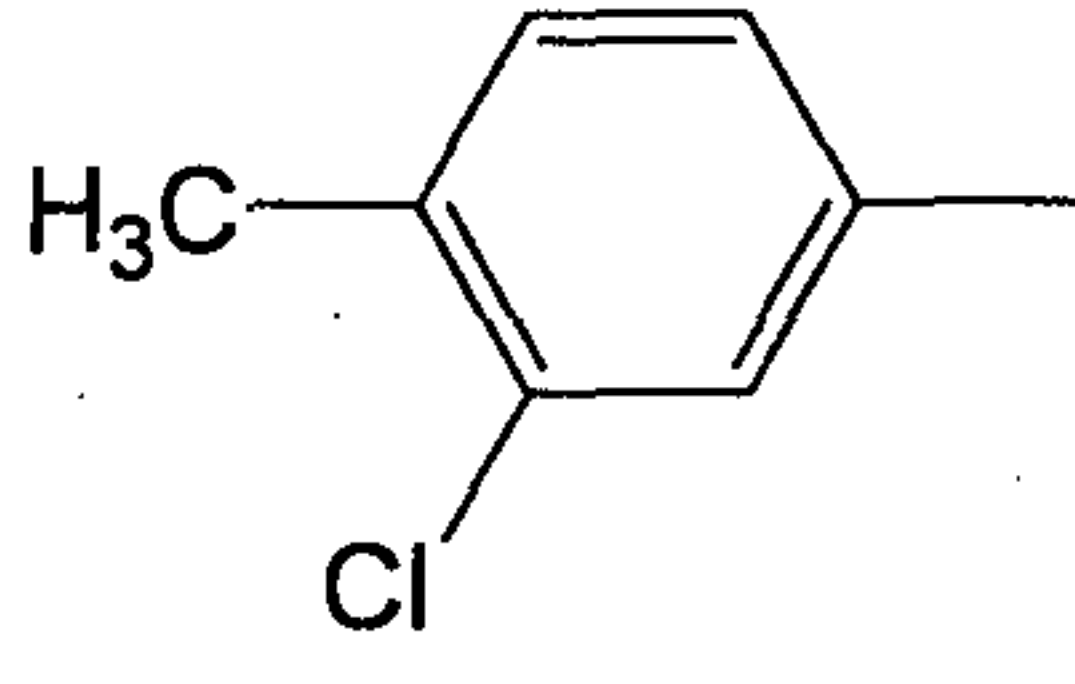
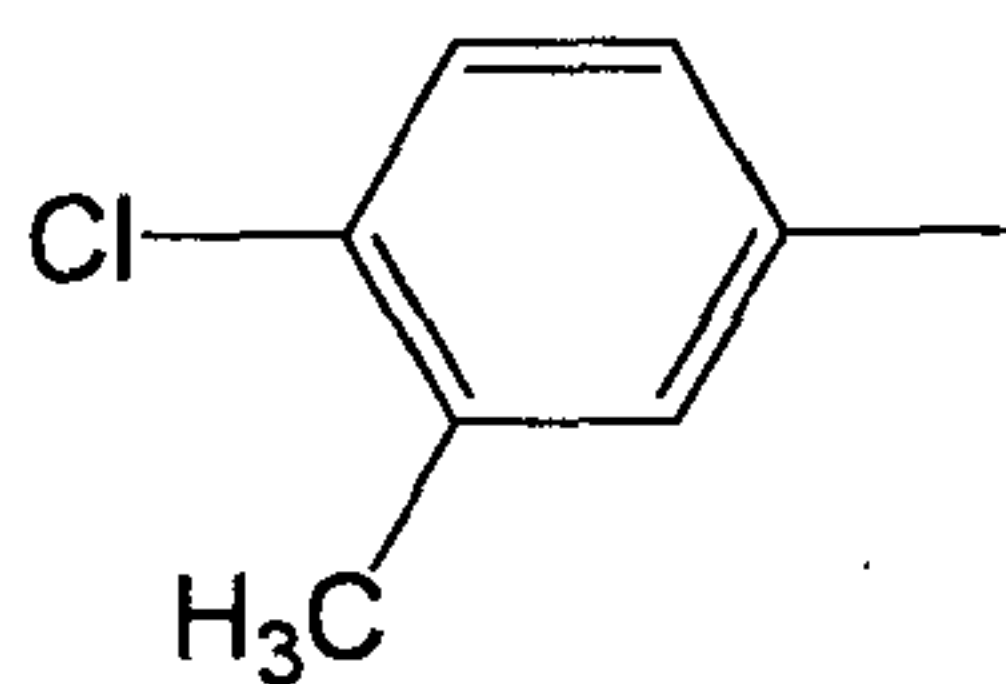
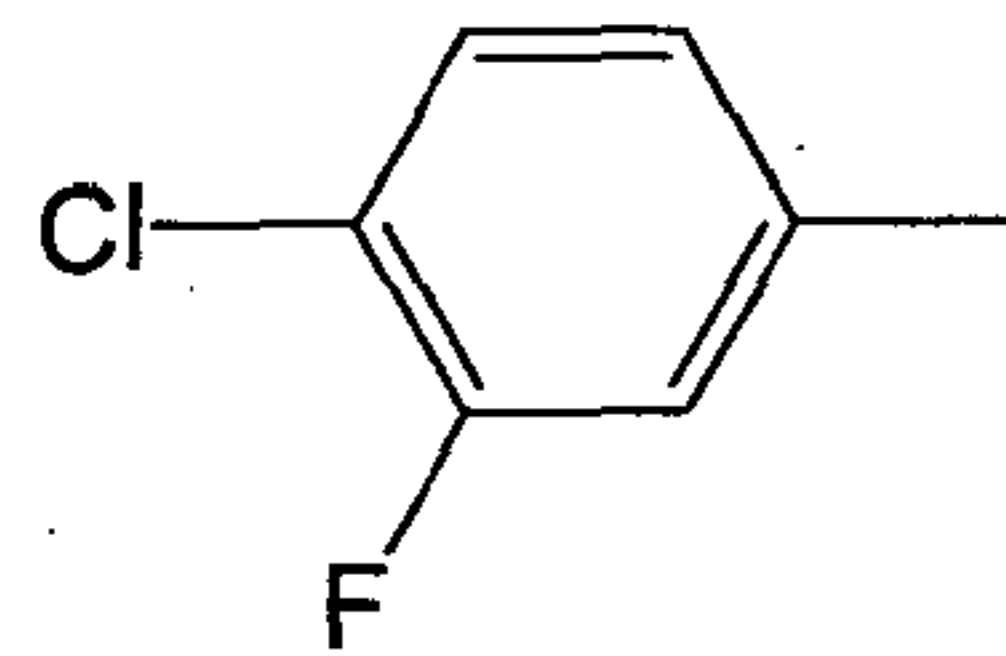
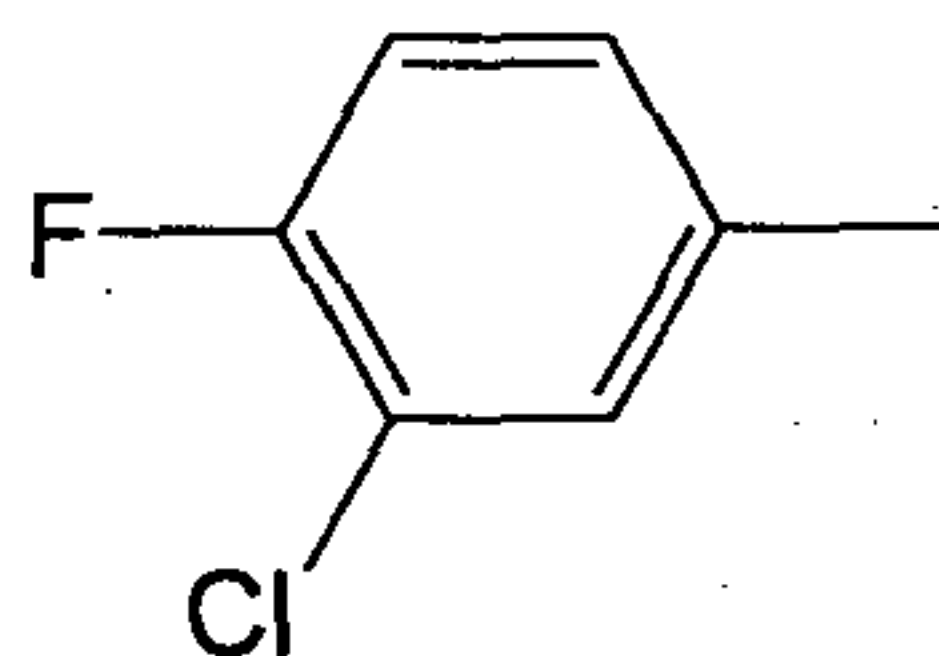
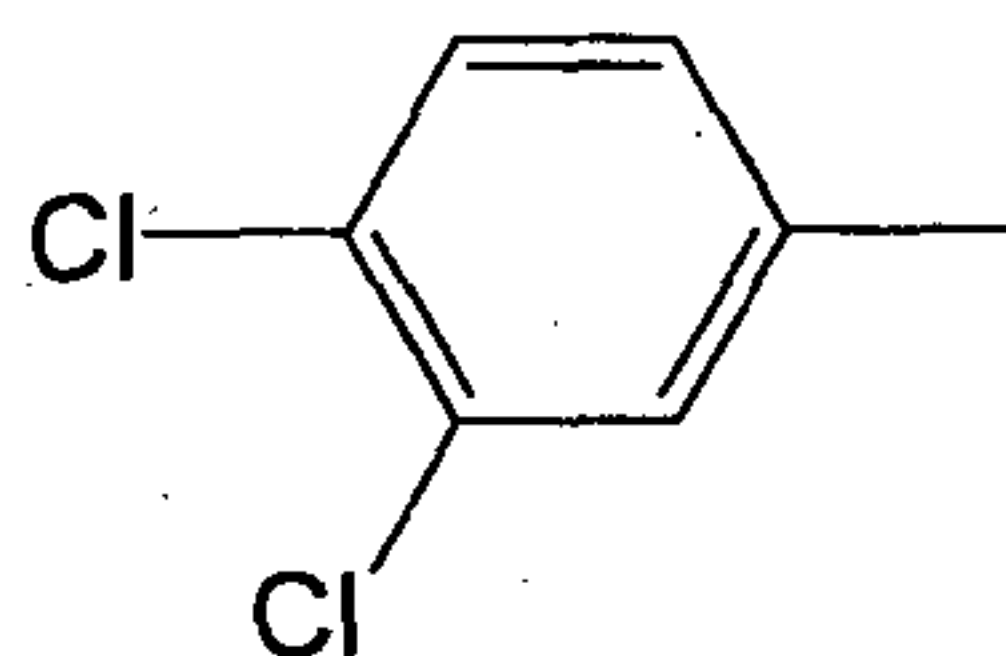


[0092]

[0093]

In another embodiment, preferable specific examples of
10 ring A include,

[0094]

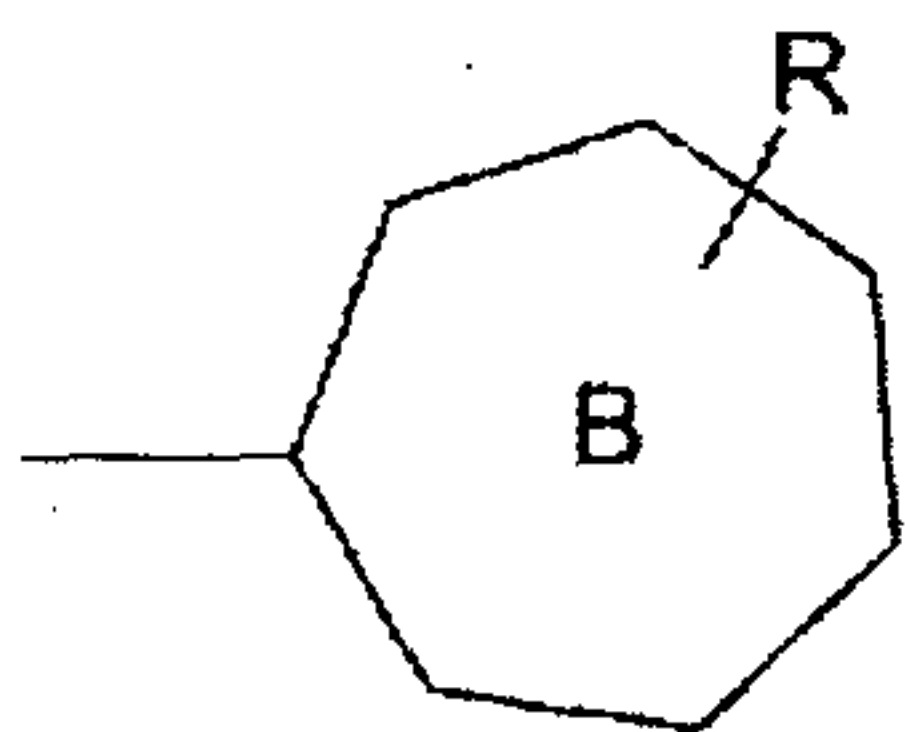


[0095]

and the like.

15 [0096]

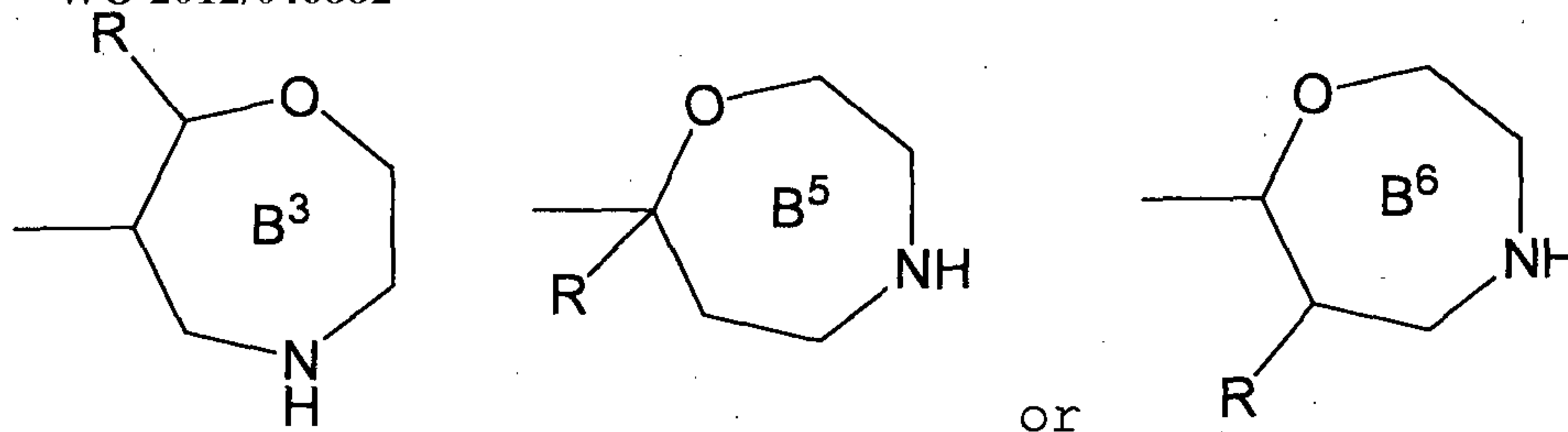
A group represented by



[0097]

is preferably

20 [0098]



[0099]

wherein each symbol is as defined above.

[0100]

5 Rings B¹ - B⁶ are optionally further substituted. However, a hydrogen atom bonded to a nitrogen atom constituting rings B¹ - B⁶ is not substituted. Examples of the substituents that rings B¹ - B⁶ optionally further have include substituents selected from

- 10 (1) a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom),
- (2) a cyano group,
- (3) a hydroxy group,
- (4) a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen
- 15 atoms,
- (5) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atoms,
- (6) an oxo group and the like. The number of the substituents is 1 to 5, preferably 1 to 3, more preferably 1 or 2.

20 [0101]

The substituents that rings B¹ - B⁶ optionally further have are preferably a hydroxy group and a C₁₋₆ alkoxy group (preferably, methoxy).

[0102]

25 The embodiment of rings B¹ - B⁶ is preferably one wherein they are substituted by a hydroxy group or a C₁₋₆ alkoxy group (preferably, methoxy) besides ring A and R or one wherein they do not have substituent other than ring A and R, more preferably one wherein they do not have substituent other than

30 ring A and R.

[0103]

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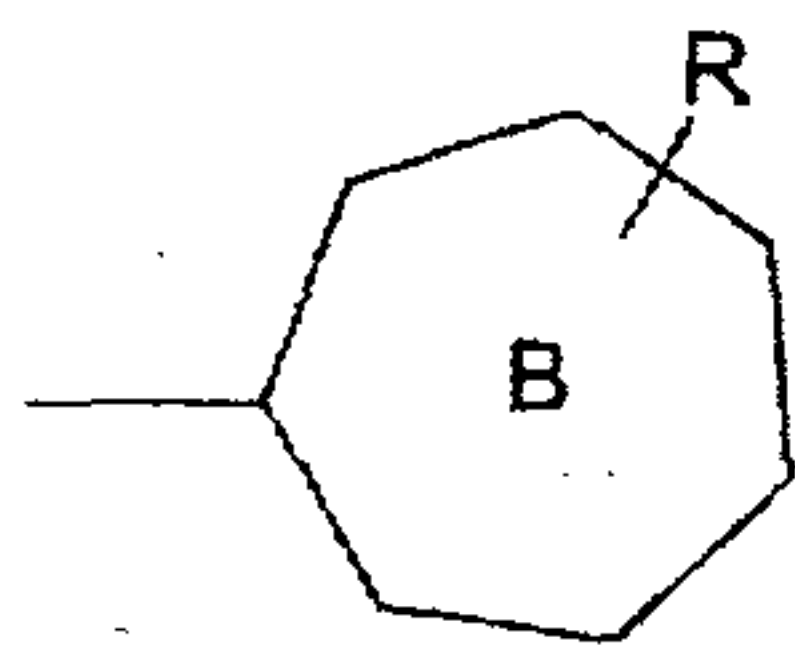
PCT/JP2011/073745

In another embodiment, rings $B^1 - B^6$ are more preferably substituted by a hydroxy group or a C_{1-6} alkoxy group (preferably, methoxy) besides ring A and R.

[0104]

5 In another embodiment, a group represented by

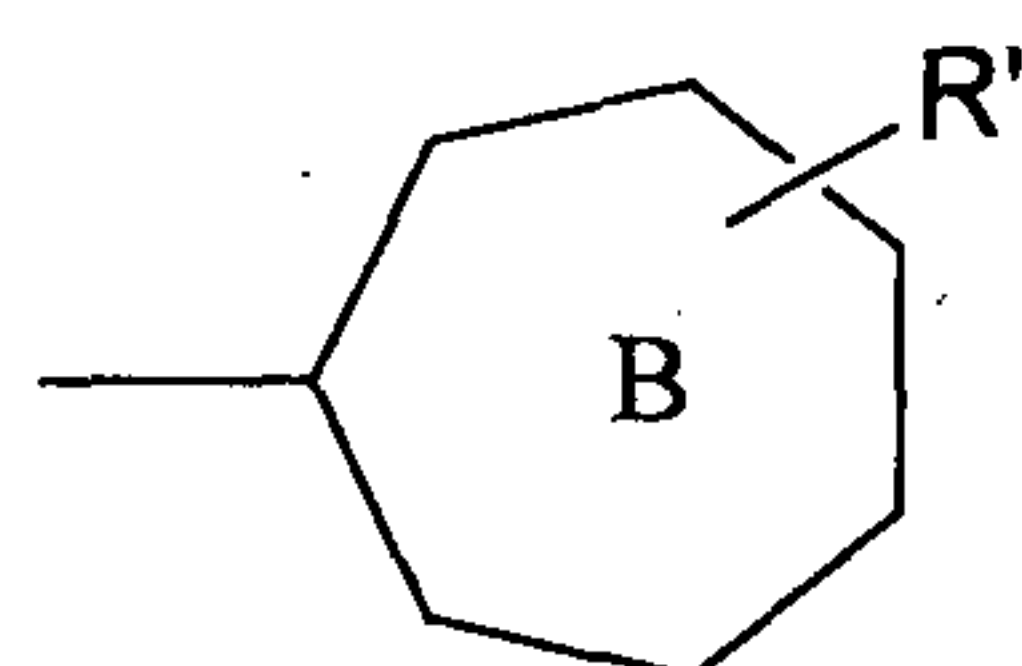
[0105]



[0106]

is preferably

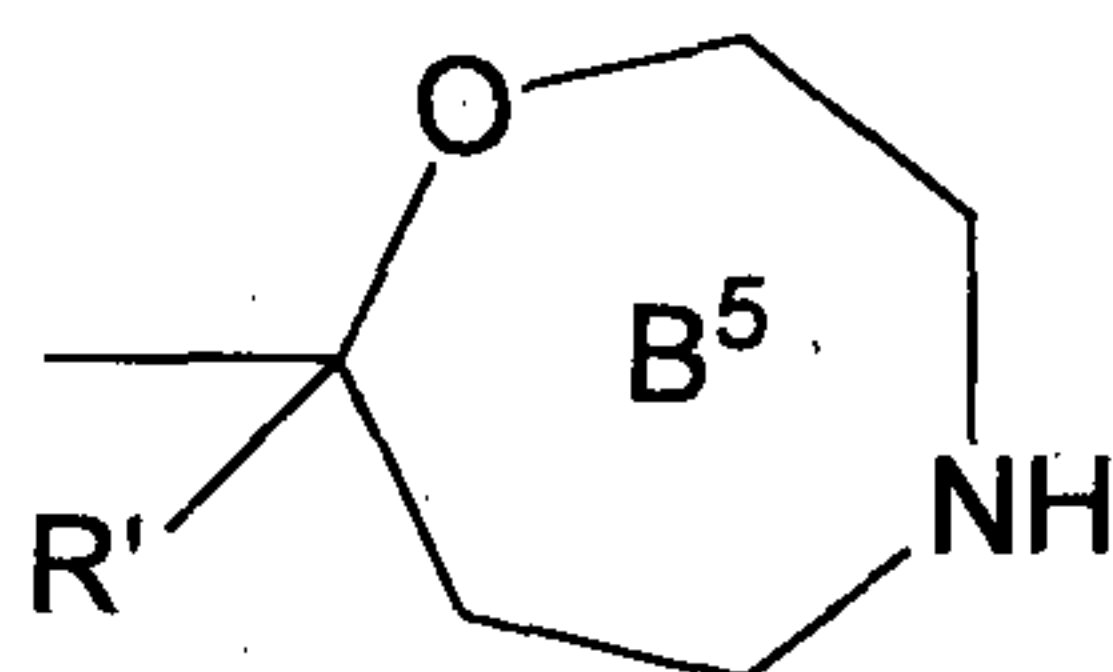
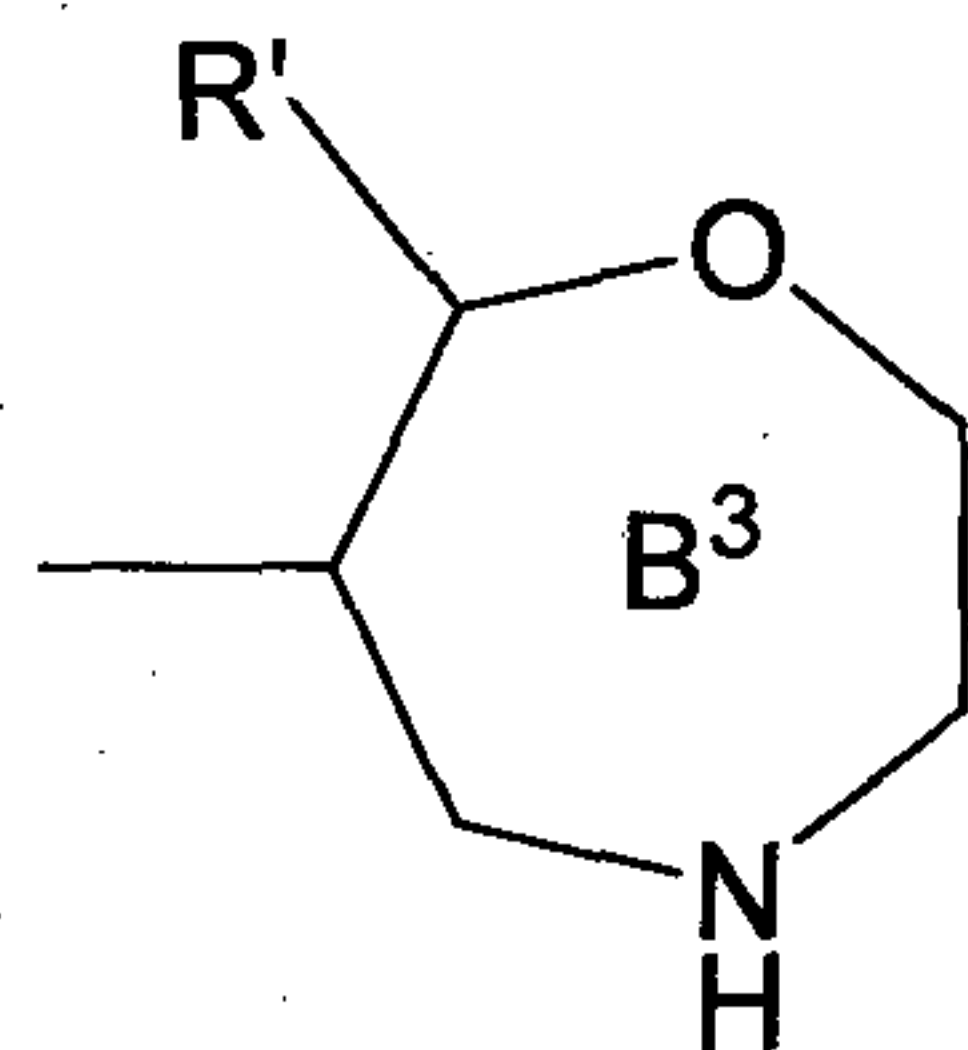
10 [0107]



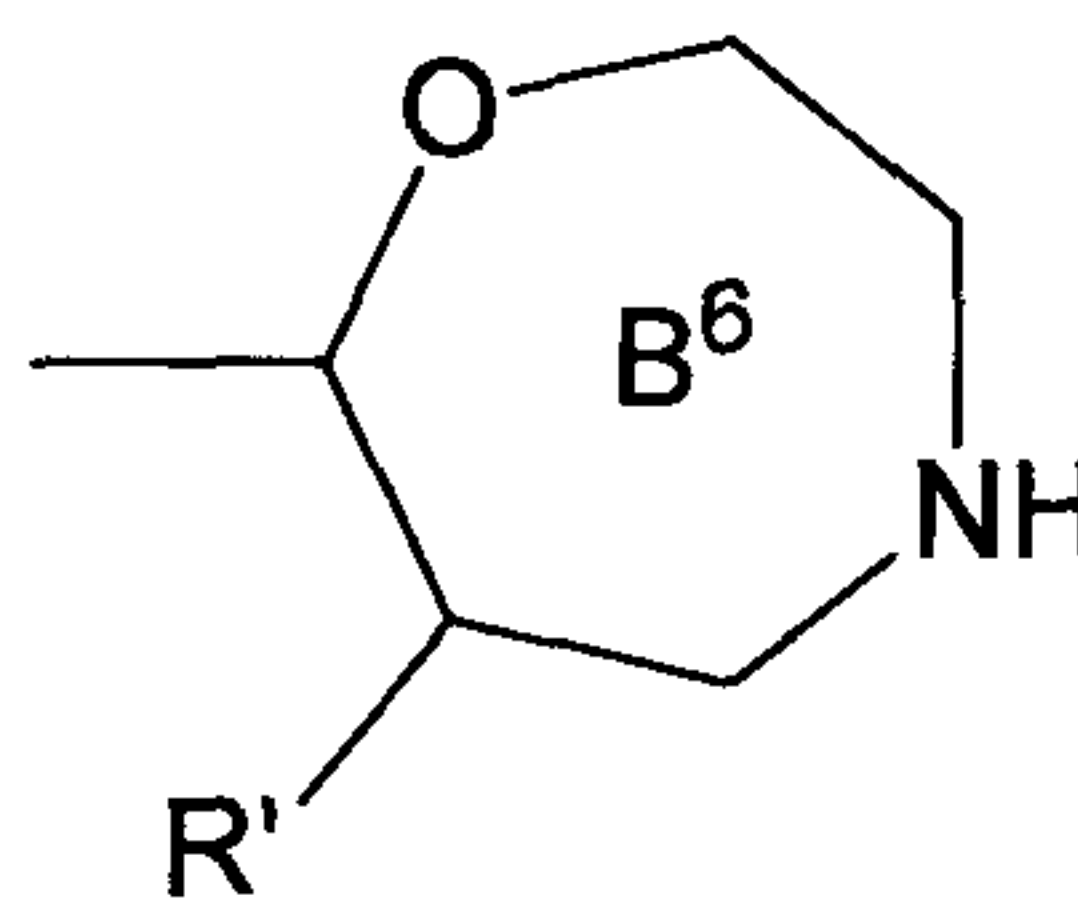
[0108]

wherein each symbol is as defined above, more preferably,

[0109]



or



15

[0110]

wherein each symbol is as defined above.

[0111]

Here, rings $B^1 - B^6$ preferably do not have substituent
20 other than ring A and R' .

[0112]

Examples of the "optionally substituted carboxy group" for R include

- (1) a carboxy group,
- 25 (2) a C_{1-6} alkoxy-carbonyl group,
- (3) a C_{6-12} aryloxy-carbonyl group,

(4) a C₇₋₁₂ aralkyloxy-carbonyl group
and the like.

[0113]

The "optionally substituted carboxy group" for R is
5 preferably a carboxy group or a C₁₋₆ alkoxy-carbonyl group
(preferably, ethoxycarbonyl).

[0114]

Examples of the "optionally substituted amino group" for
R include

- 10 (1) an amino group,
(2) a mono- or di-C₁₋₆ alkylamino group,
(3) a mono- or di-C₃₋₆ cycloalkylamino group,
(4) a mono- or di-C₆₋₁₂ arylamino group,
(5) a mono- or di-C₇₋₁₂ aralkylamino group,
15 (6) a hydrazino group,
(7) a mono- or di-(C₁₋₆ alkylsulfonyl)amino group,
(8) a mono- or di-(C₃₋₆ cycloalkylsulfonyl)amino group,
(9) a mono- or di-(C₆₋₁₂ arylsulfonyl)amino group,
(10) a mono- or di-(aromatic heterocyclyl-sulfonyl)amino
20 group,
(11) -NR^A-CO-R^B

wherein

R^A is

- (a) a hydrogen atom,
25 (b) a C₁₋₆ alkyl group, or
(c) a C₁₋₆ alkyl-carbonyl group, and

R^B is

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

- 30 (i) a halogen atom,
(ii) a hydroxy group,
(iii) a C₁₋₆ alkoxy group,
(iv) an aromatic heterocyclic group, and
(v) a nonaromatic heterocyclic group optionally
35 substituted by an oxo group,

(b) a C₁₋₆ alkoxy group,
(c) a C₃₋₆ cycloalkyl group,
(d) a C₁₋₆ alkyl-carbonyl group,
(e) an amino group,
5 (f) a mono- or di-C₁₋₆ alkylamino group,
(g) a cyclic amino group,
(h) a C₆₋₁₂ aryl group optionally substituted by 1 to 3
substituents selected from

(i) a cyano group,
10 (ii) a carboxy group,
(iii) a C₁₋₆ alkoxy-carbonyl group,
(iv) a C₁₋₆ alkylsulfonylamino group, and
(v) a nonaromatic heterocyclic group optionally
substituted by an oxo group,

15 (i) a C₇₋₁₂ aralkyl group optionally substituted by a
heterocyclic group optionally substituted by an oxo group, or
(j) an aromatic heterocyclic group,

(12) -NR^C-SO₂-N(R^D)(R^E)

wherein

20 R^C is

(a) a hydrogen atom, or
(b) a C₁₋₆ alkyl group, and

R^D and R^E are each independently,

(a) a hydrogen atom,
25 (b) a C₁₋₆ alkyl group, or
(c) a C₃₋₆ cycloalkyl group,

(13) an optionally substituted cyclic amino group
and the like.

[0115]

30 Here, examples of the substituent that the "cyclic amino
group" of the "optionally substituted cyclic amino group"
optionally has include substituents selected from

(1) an oxo group,
(2) a halogen atom,

35 (3) a cyano group,

- (4) a hydroxy group,
- (5) a nitro group,
- (6) a formyl group,
- (7) an amino group,
- 5 (8) a mono- or di-C₁₋₆ alkylamino group,
- (9) a C₁₋₆ alkyl-carbonylamino group,
- (10) a C₁₋₆ alkoxy-carbonylamino group,
- (11) a C₁₋₆ alkoxy group optionally substituted by 1 to 3
halogen atoms,
- 10 (12) a C₇₋₁₂ aralkyloxy group,
- (13) a C₆₋₁₂ aryloxy group,
- (14) a C₁₋₆ alkyl-carbonyloxy group,
- (15) a carboxy group,
- (16) a C₁₋₆ alkoxy-carbonyl group,
- 15 (17) a C₇₋₁₂ aralkyloxy-carbonyl group,
- (18) a C₆₋₁₂ aryloxy-carbonyl group,
- (19) a C₁₋₆ alkyl-carbonyl group,
- (20) a C₃₋₆ cycloalkyl-carbonyl group,
- (21) a C₇₋₁₂ aralkyl-carbonyl group,
- 20 (22) a C₆₋₁₂ aryl-carbonyl group,
- (23) a carbamoyl group,
- (24) a thiocarbamoyl group,
- (25) a mono- or di-(C₁₋₆ alkyl)carbamoyl group,
- (26) a mono- or di-(C₇₋₁₂ aralkyl)carbamoyl group,
- 25 (27) a thiol group,
- (28) a C₁₋₆ alkylthio group,
- (29) a C₇₋₁₂ aralkylthio group,
- (30) a C₁₋₆ alkylsulfonyl group,
- (31) a C₃₋₆ cycloalkylsulfonyl group,
- 30 (32) a C₆₋₁₂ arylsulfonyl group,
- (33) a C₇₋₁₂ aralkylsulfonyl group,
- (34) an ureido group,
- (35) a mono- or di-(C₁₋₆ alkyl)ureido group,
- (36) a mono- or di-(C₆₋₁₂ aryl)ureido group,
- 35 (37) a sulfamoyl group,

- (38) a C₁₋₆ alkylsulfonylamino group,
(39) a sulfamoylamino group,
(40) a mono- or di-(C₁₋₆ alkyl)sulfamoylamino group,
(41) a nonaromatic heterocyclic group optionally substituted
5 by 1 to 3 substituents selected from

(a) a nonaromatic heterocyclic group optionally substituted by an oxo group,

(b) a carboxy group, and

(c) an oxo group

10 and the like. The number of the substituents is 1 to 4, preferably 1 to 3.

[0116]

The "optionally substituted amino group" for R is preferably

- 15 (1) an amino group,
(2) a mono- or di-C₁₋₆ alkylamino group (preferably, dimethylamino),
(3) a mono- or di-C₇₋₁₂ aralkylamino group (preferably, benzylamino),
20 (4) a mono- or di-(C₁₋₆ alkylsulfonyl)amino group (preferably, methylsulfonylamino, ethylsulfonylamino),
(5) a mono- or di-(C₃₋₆ cycloalkylsulfonyl)amino group (preferably, cyclopropylsulfonylamino),
(6) a mono- or di-(C₆₋₁₂ arylsulfonyl)amino group (preferably,
25 phenylsulfonylamino),
(7) a mono- or di-(aromatic heterocyclyl-sulfonyl)amino group (preferably, pyridylsulfonylamino (preferably, pyridin-3-ylsulfonylamino)),
(8) -NR^A-CO-R^B

30 wherein

R^A is

(a) a hydrogen atom, or

(b) a C₁₋₆ alkyl group (preferably, methyl), and

R^B is

35 (a) a C₁₋₆ alkyl group (preferably, methyl, ethyl)

optionally substituted by 1 to 3 (preferably, 1 or 2)

substituents selected from

- (i) a halogen atom (preferably, fluorine atom),
- (ii) a hydroxy group,
- 5 (iii) a C₁₋₆ alkoxy group (preferably, methoxy),
- (iv) an aromatic heterocyclic group (preferably, triazolyl (preferably, 1,2,4-triazol-1-yl)), and
- (v) a heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,
- 10 (b) a C₃₋₆ cycloalkyl group (preferably, cyclopropyl),
- (c) a C₁₋₆ alkyl-carbonyl group (preferably, acetyl),
- (d) an amino group,
- (e) a mono- or di-C₁₋₆ alkylamino group (preferably, methylamino),
- 15 (f) a cyclic amino group (preferably, morpholino),
- (g) a C₆₋₁₂ aryl group (preferably, phenyl) optionally substituted by 1 to 3 (preferably, 1) substituents selected from
- 20 (i) a cyano group,
- (ii) a carboxy group,
- (iii) a C₁₋₆ alkoxy-carbonyl group (preferably, ethoxycarbonyl),
- (iv) a C₁₋₆ alkylsulfonylamino group (preferably, methylsulfonylamino), and
- 25 (v) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,
- (h) a C₇₋₁₂ aralkyl group (preferably, benzyl)
- 30 optionally substituted by a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,
- or
- (i) an aromatic heterocyclic group (preferably, oxazolyl (preferably, oxazol-5-yl)),
- 35

(9) $-\text{NR}^{\text{C}}-\text{SO}_2-\text{N}(\text{R}^{\text{D}})(\text{R}^{\text{E}})$

wherein

R^{C} is

(a) a hydrogen atom, or

5 (b) a C_{1-6} alkyl group (preferably, methyl), and

R^{D} and R^{E} are each independently,

(a) a hydrogen atom,

(b) a C_{1-6} alkyl group (preferably, methyl, ethyl), or

(c) a C_{3-6} cycloalkyl group (preferably, cyclopropyl),

10 or

(10) an optionally substituted cyclic amino group (preferably, a cyclic amino group (preferably, 1-imidazolidinyl) optionally substituted by 1 or 2 oxo groups).

[0117]

15 In another embodiment, the "optionally substituted amino group" for R is preferably

(1) a mono- or di- $(\text{C}_{1-6}$ alkyl-carbonyl)amino group (preferably, acetylamino), or

(2) a sulfamoylamino group.

20 [0118]

The " C_{1-6} alkyl group" of the "optionally substituted C_{1-6} alkyl group" for R is preferably methyl, ethyl, propyl or isopropyl.

[0119]

25 Examples of the substituent that the " C_{1-6} alkyl group" optionally has include

(1) a halogen atom,

(2) a cyano group,

(3) a hydroxy group,

30 (4) a carboxy group,

(5) an amino group,

(6) a carbamoyl group,

(7) a mono- or di- $(\text{C}_{1-6}$ alkyl)carbamoyl group (said C_{1-6} alkyl is optionally substituted by a hydroxy group or a carboxy group),

35 (8) a mono- or di- $(\text{C}_{6-12}$ aryl)carbamoyl group (said C_{6-12} aryl is

optionally substituted by a carboxy group),

(9) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from

(i) a hydroxy group,

(ii) a carboxy group,

(iii) a carbamoyl group,

(iv) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group,

(v) a mono- or di-(C₁₋₆ alkylsulfonyl)amino group,

(vi) a C₁₋₆ alkoxy-carbonyl group, and

(vii) a cyclic amino-carbonyl group optionally substituted by a hydroxy group,

(10) a C₁₋₆ alkyl-carboxyloxy group,

(11) a C₁₋₆ alkylsulfonyloxy group,

(12) a C₁₋₆ alkoxy-carbonyl group,

(13) a C₆₋₁₂ aryloxy group optionally substituted by 1 to 3 substituents selected from

(i) a halogen atom,

(ii) a cyano group,

(iii) a carboxy group,

(iv) a C₁₋₆ alkoxy group,

(v) a C₁₋₆ alkoxy-carbonyl group,

(vi) a C₁₋₆ alkylsulfonyl group,

(vii) a mono- or di-(C₁₋₆ alkylsulfonyl)carbamoyl

group,

(viii) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl) optionally substituted by an oxo group or a thioxo group, and

(ix) a cyclic amino-carbonyl group optionally substituted by a hydroxy group,

(14) a C₇₋₁₂ aralkyloxy group optionally substituted by a nonaromatic heterocyclic group optionally substituted by an oxo group,

(15) an aromatic heterocyclyl-oxy group optionally substituted by 1 to 3 substituents selected from

(i) a carboxy group,

(ii) a C₁₋₆ alkoxy-carbonyl group, and

(iii) a nonaromatic heterocyclic group optionally substituted by an oxo group,

(16) a C₁₋₆ alkylthio group,

5 (17) a C₆₋₁₂ arylthio group optionally substituted by a carboxy group,

(18) a C₁₋₆ alkylsulfinyl group,

(19) a C₁₋₆ alkylsulfonyl group,

(20) a C₆₋₁₂ arylsulfonyl group optionally substituted by 1 to 3
10 substituents selected from

(i) a carboxy group, and

(ii) a nonaromatic heterocyclic group optionally substituted by an oxo group,

(21) a mono- or di-C₁₋₆ alkylsulfamoyl group,

15 (22) an aromatic heterocyclyl-amino group optionally substituted by 1 to 3 substituents selected from

(i) a carboxy group, and

(ii) a nonaromatic heterocyclic group optionally substituted by an oxo group,

20 (23) -NR^F-CO-R^G

wherein

R^F is

(i) a hydrogen atom,

(ii) a C₁₋₆ alkyl group optionally substituted by a
25 hydroxy group, or

(iii) a C₁₋₆ alkyl-carbonyl group, and

R^G is

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

30 (1) a halogen atom,

(2) a cyano group,

(3) a hydroxy group,

(4) a C₁₋₆ alkoxy group optionally substituted by 1
to 3 substituents selected from a halogen atom and a C₃₋₆

35 cycloalkyl group,

- (5) a C₃₋₆ cycloalkyloxy group,
- (6) an aromatic heterocyclyl-oxy group optionally substituted by 1 to 3 substituents selected from a halogen atom, a cyano group and a carboxy group,
- 5 (7) a mono- or di-C₁₋₆ alkylamino group,
- (8) an N-(C₁₋₆ alkyl-carbonyl)-N-(C₁₋₆ alkyl)amino group,
- (9) a mono- or di-(C₆₋₁₂ aryl-carbonyl)amino group,
- (10) a mono- or di-(aromatic heterocyclyl-carbonyl)amino group,
- 10 (11) an N-(aromatic heterocyclyl-carbonyl)-N-(C₁₋₆ alkyl)amino group,
- (12) a mono- or di-(C₆₋₁₂ arylsulfonyl)amino group,
- (13) a C₁₋₆ alkylthio group,
- 15 (14) a C₁₋₆ alkylsulfonyl group,
- (15) a C₁₋₆ alkyl-carbonyloxy group,
- (16) a C₆₋₁₂ aryloxy group optionally substituted by 1 to 3 substituents selected from a nonaromatic heterocyclic group optionally substituted by an oxo group, and a carboxy group,
- 20 (17) an aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from a carboxy group and a C₁₋₆ alkyl group,
- (18) a cyclic amino group optionally substituted by 1 to 3 substituents selected from a halogen atom and an oxo group, and
- 25 (19) a nonaromatic heterocyclic group optionally substituted by an oxo group,
- (ii) a C₁₋₆ alkoxy group,
- 30 (iii) a C₃₋₆ cycloalkyl group,
- (iv) a C₆₋₁₂ aryl group optionally substituted by 1 to 3 substituents selected from
- (1) a halogen atom,
- (2) a cyano group,
- 35 (3) a hydroxy group,

(4) a carboxy group,
(5) a C₁₋₆ alkyl group optionally substituted by a nonaromatic heterocyclic group optionally substituted by an oxo group,

5 (6) a C₁₋₆ alkoxy group,
(7) a C₁₋₆ alkylsulfonyl group,
(8) a mono- or di-(C₁₋₆ alkylsulfonyl)amino group,
(9) a C₆₋₁₂ aryl group,
(10) an aromatic heterocyclic group optionally
10 substituted by a C₁₋₆ alkyl group,
(11) a cyclic amino group optionally substituted by an oxo group, and

(12) a nonaromatic heterocyclic group optionally substituted by an oxo group,

15 (v) a C₇₋₁₂ aralkyl group optionally substituted by a nonaromatic heterocyclic group optionally substituted by an oxo group,

(vi) an aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from

20 (1) a C₁₋₆ alkyl group,
(2) a mono- or di-(C₁₋₆ alkylsulfonyl)amino group,
and

(3) a nonaromatic heterocyclic group optionally substituted by an oxo group,

25 (vii) a cyclic amino group optionally substituted by 1 or 2 oxo groups,

(viii) a nonaromatic heterocyclic group optionally substituted by 1 or 2 oxo groups,

(ix) a C₁₋₆ alkyl-carbonyl group, or

30 (x) a cyclic amino-carbonyl group,

(24) -NR^H-SO₂-R^I

wherein

R^H is

(i) a hydrogen atom,

35 (ii) a C₁₋₆ alkyl group, or

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(iii) a C₇₋₁₂ aralkyl group optionally substituted by a C₁₋₆ alkoxy group, and

R^I is

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

- (1) a halogen atom,
- (2) a C₁₋₆ alkoxy group, and
- (3) a cyclic amino group,

(ii) a C₆₋₁₂ aryl group optionally substituted by 1 to 3 substituents selected from

- (1) a carboxy group, and
- (2) a nonaromatic heterocyclic group optionally substituted by an oxo group, or

(iii) an aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from

- (1) a carboxy group, and
- (2) a nonaromatic heterocyclic group optionally substituted by an oxo group,

(25) -NR^J-CO-NR^KR^L

wherein

R^J is

- (i) a hydrogen atom, or
- (ii) a C₁₋₆ alkyl group optionally substituted by a hydroxy group, and

R^K and R^L are each independently,

- (i) a hydrogen atom,
- (ii) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from a hydroxy group and a C₁₋₆ alkoxy group, or

(iii) a C₁₋₆ alkoxy group,

(26) -NR^M-SO₂-NR^NR^O

wherein

R^M is

- (i) a hydrogen atom, or
- (ii) a C₁₋₆ alkyl group, and

R^N and R^O are each independently,

- (i) a hydrogen atom,
- (ii) a C_{1-6} alkyl group, or
- (iii) a C_{1-6} alkoxy group,

5 (27) an aromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from

(i) a carboxy group,

(ii) a C_{1-6} alkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom, a hydroxy group
10 and a carboxy group,

(iii) a C_{1-6} alkoxy group optionally substituted by a C_{1-6} alkoxy group,

(iv) a C_{3-6} cycloalkyl group, and

(v) a nonaromatic heterocyclic group optionally
15 substituted by an oxo group,

(28) a cyclic amino group optionally substituted by 1 to 4 substituents selected from

(i) a halogen atom,

(ii) a cyano group,

20 (iii) a carboxy group,

(iv) a carbamoyl group,

(v) a C_{1-6} alkyl group,

(vi) a C_{1-6} alkoxy-carbonyl group,

(vii) a mono- or di- (C_{1-6} alkyl-carbonyl) amino group,

25 (viii) an aromatic heterocyclic group optionally substituted by a C_{1-6} alkyl group,

(ix) a nonaromatic heterocyclic group optionally substituted by an oxo group, and

(x) an oxo group,

30 (29) a nonaromatic heterocyclic group optionally substituted by an oxo group

and the like. The number of the substituents is 1 to 4, preferably 1 to 3.

[0120]

35 The "optionally substituted C_{1-6} alkyl group" for R is

preferably a C₁₋₆ alkyl group (preferably, methyl, ethyl, propyl, isopropyl) optionally substituted by 1 to 4 (preferably 1 to 3, more preferably 1 or 2) substituents selected from

- 5 (1) a halogen atom (preferably, a fluorine atom),
- (2) a cyano group,
- (3) a hydroxy group,
- (4) a carboxy group,
- (5) an amino group,
- 10 (6) a carbamoyl group,
- (7) a mono- or di-(C₁₋₆ alkyl)carbamoyl group (preferably, isopropylcarbamoyl) (said C₁₋₆ alkyl is optionally substituted by a carboxy group),
- (8) a mono- or di-(C₆₋₁₂ aryl)carbamoyl group (preferably,
- 15 phenylcarbamoyl) (said C₆₋₁₂ aryl is optionally substituted by a carboxy group),
- (9) a C₁₋₆ alkoxy group (preferably, methoxy, ethoxy, propoxy) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from
- 20 (i) a hydroxy group,
- (ii) a carboxy group,
- (iii) a carbamoyl group,
- (iv) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group (preferably, acetylamino),
- 25 (v) a mono- or di-(C₁₋₆ alkylsulfonyl)amino group (preferably, methylsulfonylamino),
- (vi) a C₁₋₆ alkoxy-carbonyl group (preferably, ethoxycarbonyl), and
- (vii) a cyclic amino-carbonyl group (preferably,
- 30 azetidin-1-ylcarbonyl, 1,1-dioxide-thiomorpholinocarbonyl) optionally substituted by a hydroxy group,
- (10) a C₁₋₆ alkyl-carbonyloxy group (preferably, acetyloxy),
- (11) a C₁₋₆ alkylsulfonyloxy group (preferably, methylsulfonyloxy),
- 35 (12) a C₆₋₁₂ aryloxy group (preferably, phenoxy) optionally

substituted by 1 to 3 (preferably, 1 or 2) substituents
selected from

(i) a halogen atom (preferably, a fluorine atom, a
chlorine atom),

5 (ii) a cyano group,

(iii) a carboxy group,

(iv) a C₁₋₆ alkoxy group (preferably, methoxy),

(v) a C₁₋₆ alkoxy-carbonyl group (preferably,
methoxycarbonyl),

10 (vi) a C₁₋₆ alkylsulfonyl group (preferably,
methylsulfonyl),

(vii) a mono- or di-(C₁₋₆ alkylsulfonyl)carbamoyl group
(preferably, methylsulfonylcarbamoyl),

(viii) a nonaromatic heterocyclic group (preferably,
15 dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-
yl)) optionally substituted by an oxo group or a thioxo group,
and

(ix) a cyclic amino-carbonyl group (preferably,
azetidin-1-ylcarbonyl) optionally substituted by a hydroxy
20 group,

(13) a C₇₋₁₂ aralkyloxy group (preferably, benzyloxy) optionally
substituted by a nonaromatic heterocyclic group (preferably,
dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-
yl)) optionally substituted by an oxo group,

25 (14) an aromatic heterocyclyl-oxy group (preferably,
pyridyloxy (preferably, pyridin-2-yloxy)) optionally
substituted by 1 to 3 (preferably, 1) substituents selected
from

(i) a carboxy group,

30 (ii) a C₁₋₆ alkoxy-carbonyl group (preferably,
methoxycarbonyl), and

(iii) a nonaromatic heterocyclic group (preferably,
dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-
yl, 2,3-dihydro-1,3,4-oxadiazol-5-yl)) optionally substituted
35 by an oxo group,

(15) a C₁₋₆ alkylthio group (preferably, methylthio),

(16) a C₆₋₁₂ arylthio group (preferably, phenylthio) optionally substituted by a carboxy group,

(17) a C₁₋₆ alkylsulfinyl group (preferably, methylsulfinyl),

5 (18) a C₁₋₆ alkylsulfonyl group (preferably, methylsulfonyl),

(19) a C₆₋₁₂ arylsulfonyl group (preferably, phenylsulfonyl) optionally substituted by 1 to 3 (preferably, 1) substituents selected from

(i) a carboxy group, and

10 (ii) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(20) a mono- or di-C₁₋₆ alkylsulfamoyl group (preferably, isopropylsulfamoyl),

15 (21) an aromatic heterocyclyl-amino group (preferably, pyridylamino (preferably, pyridin-2-ylamino), pyrimidinylamino (preferably, pyrimidin-2-ylamino), benzooxazolylamino (preferably, benzooxazol-2-ylamino)) optionally substituted by 1 to 3 (preferably, 1) substituents selected from

20 (i) a carboxy group, and

(ii) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(22) -NR^F-CO-R^G

25 wherein

R^F is

(i) a hydrogen atom, or

(ii) a C₁₋₆ alkyl group (preferably, methyl, ethyl)

optionally substituted by a hydroxy group, and

30 R^G is

(i) a C₁₋₆ alkyl group (preferably, methyl, ethyl, propyl, isopropyl) optionally substituted by 1 to 3 substituents selected from

(1) a halogen atom (preferably, a fluorine atom),

35 (2) a cyano group,

- (3) a hydroxy group,
- (4) a C₁₋₆ alkoxy group (preferably, methoxy, ethoxy, isopropoxy, isobutoxy) optionally substituted by 1 to 3 substituents selected from a halogen atom (preferably, a fluorine atom) and a C₃₋₆ cycloalkyl group (preferably, cyclopropyl),
- (5) a C₃₋₆ cycloalkyloxy group (preferably, cyclopropyloxy),
- (6) an aromatic heterocyclyl-oxy group (preferably, pyridyloxy (preferably, pyridin-2-yloxy), pyrimidinyloxy (preferably, pyrimidin-2-yloxy)) optionally substituted by 1 to 3 (preferably, 1) substituents selected from a halogen atom (preferably, a fluorine atom, a chlorine atom), a cyano group and a carboxy group,
- (7) a mono- or di-C₁₋₆ alkylamino group (preferably, methylamino, dimethylamino),
- (8) an N-(C₁₋₆ alkyl-carbonyl)-N-(C₁₋₆ alkyl)amino group (preferably, N-acetyl-N-methylamino),
- (9) a mono- or di-(C₆₋₁₂ aryl-carbonyl)amino group (preferably, benzoylamino),
- (10) a mono- or di-(aromatic heterocyclyl-carbonyl)amino group (preferably, pyridylcarbonylamino (preferably, pyridin-2-ylcarbonylamino)),
- (11) an N-(aromatic heterocyclyl-carbonyl)-N-(C₁₋₆ alkyl)amino group (preferably, N-(pyridylcarbonyl)-N-methylamino (preferably, N-(pyridin-2-ylcarbonyl)-N-methylamino)),
- (12) a mono- or di-(C₆₋₁₂ arylsulfonyl)amino group (preferably, phenylsulfonylamino),
- (13) a C₁₋₆ alkylthio group (preferably, methylthio),
- (14) a C₁₋₆ alkylsulfonyl group (preferably, methylsulfonyl),
- (15) a C₁₋₆ alkyl-carbonyloxy group (preferably, acetyloxy),

(16) a C₆₋₁₂ aryloxy group (preferably, phenoxy) optionally substituted by 1 to 3 (preferably, 1) substituents selected from a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group, and a carboxy group,

(17) an aromatic heterocyclic group (preferably, pyridyl (preferably, pyridin-2-yl), pyrazolyl (preferably, pyrazol-1-yl), isoxazolyl (preferably, isoxazol-5-yl), triazolyl (preferably, 1H-1,2,4-triazol-1-yl), tetrazolyl (preferably, tetrazol-1-yl)) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from a carboxy group and a C₁₋₆ alkyl group (preferably, methyl),

(18) a cyclic amino group (preferably, 1-pyrrolidinyl, piperidino, 1-imidazolidinyl, morpholino, 8-oxa-3-azabicyclo[3.2.1]octan-3-yl) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from a halogen atom (preferably, a fluorine atom, a chlorine atom) and an oxo group, and

(19) a nonaromatic heterocyclic group (preferably, dihydropyridyl (preferably, 1,2-dihydropyridin-1-yl), dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from a halogen atom (preferably, a chlorine atom) and an oxo group,

(ii) a C₁₋₆ alkoxy group (preferably, methoxy, isopropoxy),

(iii) a C₃₋₆ cycloalkyl group (preferably, cyclopropyl),

(iv) a C₆₋₁₂ aryl group (preferably, phenyl) optionally substituted by 1 to 3 substituents selected from

(1) a halogen atom (preferably, a fluorine atom, a chlorine atom),

(2) a cyano group,

(3) a hydroxy group,

- (4) a carboxy group,
- (5) a C₁₋₆ alkyl group (preferably, methyl, tert-butyl) optionally substituted by a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,
- (6) a C₁₋₆ alkoxy group (preferably, methoxy, ethoxy),
- (7) a C₁₋₆ alkylsulfonyl group (preferably, methylsulfonyl),
- (8) a mono- or di-(C₁₋₆ alkylsulfonyl)amino group (preferably, methylsulfonylamino),
- (9) a C₆₋₁₂ aryl group (preferably, phenyl), and
- (10) an aromatic heterocyclic group (preferably, oxadiazolyl (preferably, 1,2,4-oxadiazol-3-yl), tetrazolyl (preferably, tetrazol-5-yl)) optionally substituted by a C₁₋₆ alkyl group (preferably, methyl),
- (11) a cyclic amino group (preferably, 1-pyrrolidinyl) optionally substituted by an oxo group, and
- (12) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,
- (v) a C₇₋₁₂ aralkyl group (preferably, benzyl) optionally substituted by a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,
- (vi) an aromatic heterocyclic group (preferably, pyridyl (preferably, pyridin-2-yl, pyridin-3-yl), thiazolyl (preferably, thiazol-5-yl)) optionally substituted by 1 to 3 substituents selected from
- (1) a C₁₋₆ alkyl group (preferably, methyl),
- (2) a mono- or di-(C₁₋₆ alkylsulfonyl)amino group (preferably, methylsulfonylamino), and
- (3) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-

yl)) optionally substituted by an oxo group,

(vii) a cyclic amino group (preferably, 1-pyrrolidinyl, morpholino, 1,1-dioxide-thiomorpholino) optionally substituted by 1 or 2 oxo groups,

5 (viii) a nonaromatic heterocyclic group (preferably, dihydropyridyl (preferably, 1,2-dihydropyridin-3-yl), tetrahydrofuryl (preferably, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl), tetrahydropyranyl (preferably, tetrahydropyran-2-yl, tetrahydropyran-4-yl), dioxanyl
10 (preferably, 1,4-dioxan-2-yl)) optionally substituted by 1 or 2 oxo groups,

(ix) a C₁₋₆ alkyl-carbonyl group (preferably, acetyl, ethylcarbonyl), or

(x) a cyclic amino-carbonyl group (preferably,
15 pyrrolidin-1-ylcarbonyl),

(23) -NR^H-SO₂-R^I

wherein

R^H is

(i) a hydrogen atom,

20 (ii) a C₁₋₆ alkyl group (preferably, methyl), or

(iii) a C₇₋₁₂ aralkyl group (preferably, benzyl) optionally substituted by a C₁₋₆ alkoxy group (preferably, methoxy), and

R^I is

25 (i) a C₁₋₆ alkyl group (preferably, methyl, ethyl, isopropyl) optionally substituted by 1 to 3 substituents selected from

(1) a halogen atom (preferably, a fluorine atom),

(2) a C₁₋₆ alkoxy group (preferably, methoxy), and

30 (3) a cyclic amino group (preferably, morpholino),

(ii) a C₆₋₁₂ aryl group (preferably, phenyl) optionally substituted by 1 to 3 (preferably, 1) substituents selected from

(1) a carboxy group, and

35 (2) a nonaromatic heterocyclic group (preferably,

dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group, or

(iii) an aromatic heterocyclic group (preferably, pyridyl (preferably, pyridin-2-yl, pyridin-3-yl), furyl

5 (preferably, furan-2-yl)) optionally substituted by 1 to 3 (preferably, 1) substituents selected from

(1) a carboxy group, and

(2) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(24) $-NR^J-CO-NR^KR^L$

wherein

R^J is

(i) a hydrogen atom, or

15 (ii) a C_{1-6} alkyl group (preferably, methyl, ethyl) optionally substituted by a hydroxy group, and

R^K and R^L are each independently,

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group (preferably, methyl, ethyl, 20 tert-butyl) optionally substituted by 1 to 3 (preferably, 1) substituents selected from a hydroxy group and a C_{1-6} alkoxy group (preferably, methoxy), or

(iii) a C_{1-6} alkoxy group (preferably, methoxy),

(25) $-NR^M-SO_2-NR^NR^O$

25 wherein

R^M is

(i) a hydrogen atom, or

(ii) a C_{1-6} alkyl group (preferably, methyl), and

R^N and R^O are each independently,

30 (i) a hydrogen atom,

(ii) a C_{1-6} alkyl group (preferably, methyl), or

(iii) a C_{1-6} alkoxy group (preferably, methoxy),

(26) an aromatic heterocyclic group (preferably, pyrazolyl (preferably, pyrazol-1-yl, pyrazol-3-yl), oxadiazolyl

35 (preferably, 1,2,4-oxadiazol-3-yl), thiazolyl (preferably,

thiazol-2-yl, thiazol-4-yl), triazolyl (preferably, 1H-1,2,3-triazol-1-yl, 1H-1,2,4-triazol-3-yl), indazolyl (preferably, 1H-indazol-1-yl), benzimidazolyl (preferably, 1H-benzimidazol-2-yl)) optionally substituted by 1 to 3 (preferably, 1 or 2)

5 substituents selected from

(i) a carboxy group,

(ii) a C₁₋₆ alkyl group (preferably, methyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (preferably, a fluorine atom), a hydroxy group and a
10 carboxy group,

(iii) a C₁₋₆ alkoxy group (preferably, ethoxy, tert-butoxy) optionally substituted by a C₁₋₆ alkoxy group (preferably, methoxy),

(iv) a C₃₋₆ cycloalkyl group (preferably, cyclopropyl),
15 and

(v) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(27) a cyclic amino group (preferably, 1-azetidiny, 1-pyrrolidinyl, piperidino, 1-imidazolidinyl, 1-dihydropyridazinyl (preferably, 2,3-dihydropyridazin-2-yl), 1-hexahydropyrimidinyl, 2-dihydroisoindolyl (preferably, 1,3-dihydro-2H-isoindol-2-yl), 3-dihydroquinazolinyl (preferably, 3,4-dihydroquinazolin-3-yl), 3-tetrahydroquinazolinyl
25 (preferably, 1,2,3,4-tetrahydroquinazolin-3-yl), 3-tetrahydropyrido[3,2-d]pyrimidinyl (preferably, 1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-3-yl), 3-tetrahydropteridinyl (preferably, 1,2,3,4-tetrahydropteridin-3-yl)) optionally substituted by 1 to 4 substituents selected from

30 (i) a cyano group,

(ii) a carboxy group,

(iii) a C₁₋₆ alkyl group (preferably, methyl),

(iv) a C₁₋₆ alkoxy-carbonyl group (preferably, ethoxycarbonyl),

35 (v) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group

(preferably, acetylamino),

(vi) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group, and

5 (vii) an oxo group, or

(28) a nonaromatic heterocyclic group (preferably, 1-dihydropyridyl (preferably, 1,2-dihydropyridin-1-yl), dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by 1 to 3 substituents selected

10 from

(i) a halogen atom (preferably, a chlorine atom),

(ii) a cyano group,

(iii) a carboxy group,

(iv) a carbamoyl group,

15 (v) a C₁₋₆ alkoxy-carbonyl group (preferably, methoxycarbonyl),

(vi) an aromatic heterocyclic group (preferably, triazolyl (preferably, 1,2,4-triazol-3-yl), tetrazolyl (preferably, tetrazol-5-yl)) optionally substituted by a C₁₋₆

20 alkyl group (preferably, methyl),

(vii) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl, 4,5-dihydro-1,3,4-oxadiazol-2-yl), dihydrotriazolyl (preferably, 4,5-dihydrotriazol-3-yl)) optionally substituted

25 by an oxo group, and

(viii) an oxo group.

[0121]

In another embodiment, the "optionally substituted C₁₋₆ alkyl group" for R is preferably a C₁₋₆ alkyl group (preferably, methyl, ethyl, propyl, isopropyl) optionally substituted by 1 to 3 substituents selected from

(1) a hydroxyl group,

(2) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group (preferably, acetyl),

35 (3) a sulfamoylamino group,

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(4) a C₁₋₆ alkoxy-C₁₋₆ alkyl-carbonylamino group (preferably, (2-methoxyacetyl)amino, (2-ethoxyacetyl)amino, (2-isopropoxyacetyl)amino),

(5) a C₁₋₆ alkylsulfonylamino group (preferably, methylsulfonylamino), and

(6) a 2-oxo-1,2-dihydropyridin-1-yl optionally substituted by 1 to 3 substituents selected from a carboxy group and 5-oxo-4,5-dihydro-1,2,4-oxadiazolyl.

[0122]

10 Here, the "C₁₋₆ alkoxy-C₁₋₆ alkyl-carbonylamino group" means a C₁₋₆ alkyl-carbonylamino group substituted by a C₁₋₆ alkoxy group.

[0123]

The "C₁₋₆ alkoxy group" of the "optionally substituted C₁₋₆ alkoxy group" for R is preferably methoxy or ethoxy.

15 Examples of the substituent that the "C₁₋₆ alkoxy group" optionally has include those similar to the substituents that the "C₁₋₆ alkyl group" of the aforementioned "optionally substituted C₁₋₆ alkyl group" optionally has. The number of the substituents is 1 to 4, preferably 1 to 3, more preferably 1.

In another embodiment, the number of the substituents that the "C₁₋₆ alkoxy group" optionally has is preferably 1 or 2.

[0124]

25 The "optionally substituted C₁₋₆ alkoxy group" for R is preferably a C₁₋₆ alkoxy group, more preferably, methoxy or ethoxy.

[0125]

The "C₁₋₆ alkyl-carbonyl group" of the "optionally substituted C₁₋₆ alkyl-carbonyl group" for R is preferably acetyl.

35 Examples of the substituent that the "C₁₋₆ alkyl-carbonyl group" optionally has include those similar to the substituents that the "C₁₋₆ alkyl group" of the aforementioned "optionally substituted C₁₋₆ alkyl group" optionally has. The

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number of the substituents is 1 to 4, preferably 1 to 3, more preferably 1.

In another embodiment, the number of the substituents that the "C₁₋₆ alkyl-carbonyl group" optionally has is preferably 1 or 2.

[0126]

The "optionally substituted C₁₋₆ alkyl-carbonyl group" for R is preferably a C₁₋₆ alkyl-carbonyl group, more preferably, acetyl.

10 [0127]

The "optionally substituted carbamoyl group" for R is -CO-NR^PR^Q

wherein

R^P and R^Q are each independently,

15 (a) a hydrogen atom,

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

(i) a hydroxy group,

(ii) a C₁₋₆ alkylsulfonyl group, and20 (iii) a C₁₋₆ alkoxy group,(c) a C₁₋₆ alkoxy group,(d) a C₆₋₁₂ aryl group optionally substituted by a carboxy group,(e) a C₇₋₁₂ aralkyl group,25 (f) a C₁₋₆ alkylsulfonyl group, or(g) a C₆₋₁₂ arylsulfonyl group optionally substituted by 1 to 3 substituents selected from(i) a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atoms, and30 (ii) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atoms

and the like.

[0128]

The "optionally substituted carbamoyl group" for R is preferably -CO-NR^PR^Q

R^P and R^Q are each independently,

(a) a hydrogen atom,

(b) a C₁₋₆ alkyl group (preferably, methyl, ethyl, isobutyl)
5 optionally substituted by 1 to 3 (preferably 1 or 2, more preferably 1) substituents selected from

(i) a hydroxy group,

(ii) a C₁₋₆ alkylsulfonyl group (preferably, methylsulfonyl), and

10 (iii) a C₁₋₆ alkoxy group (preferably, methoxy),

(c) a C₁₋₆ alkoxy group (preferably, methoxy),

(d) a C₆₋₁₂ aryl group (preferably, phenyl) optionally substituted by a carboxy group,

(e) a C₁₋₆ alkylsulfonyl group (preferably, methylsulfonyl), or

15 (f) a C₆₋₁₂ arylsulfonyl group (preferably, phenylsulfonyl) optionally substituted by 1 to 3 (preferably, 1) substituents selected from

(i) a C₁₋₆ alkyl group (preferably, methyl) optionally substituted by 1 to 3 halogen atoms (preferably, a fluorine
20 atom), and

(ii) a C₁₋₆ alkoxy group (preferably, methoxy) optionally substituted by 1 to 3 (preferably, 1 or 2) halogen atoms (preferably, a fluorine atom).

[0129]

25 The "C₆₋₁₂ aryloxy group" of the "optionally substituted C₆₋₁₂ aryloxy group" for R is preferably phenoxy.

Examples of the substituent that the "C₆₋₁₂ aryloxy group" optionally has include those similar to the substituents that the "C₁₋₆ alkyl group" of the aforementioned "optionally
30 substituted C₁₋₆ alkyl group" optionally has. The number of the substituents is 1 to 4, preferably 1 to 3, more preferably 1.

[0130]

The "optionally substituted C₆₋₁₂ aryloxy group" for R is preferably a C₆₋₁₂ aryloxy group (preferably, phenoxy)
35 optionally substituted by a nonaromatic heterocyclic group

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(preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group.
[0131]

The "aromatic heterocyclyl-oxy group" of the "optionally substituted aromatic heterocyclyl-oxy group" for R is preferably pyridyloxy (preferably, pyridin-3-yloxy, pyridin-4-yloxy).

Examples of the substituent that the "aromatic heterocyclyl-oxy group" optionally has include those similar to the substituents that the "C₁₋₆ alkyl group" of the aforementioned "optionally substituted C₁₋₆ alkyl group" optionally has. The number of the substituents is 1 to 4, preferably 1 to 3, more preferably 1.

[0132]

The "optionally substituted aromatic heterocyclyl-oxy group" for R is preferably an aromatic heterocyclyl-oxy group (preferably, pyridyloxy (preferably, pyridin-3-yloxy, pyridin-4-yloxy)) optionally substituted by 1 to 3 (preferably, 1) substituents selected from

- (a) a cyano group,
- (b) a carboxy group,
- (c) a C₁₋₆ alkoxy-carbonyl group (preferably, methoxycarbonyl),
- (d) a carbamoyl group,
- (e) a mono- or di-C₁₋₆ alkylcarbamoyl group (preferably, methylcarbamoyl, ethylcarbamoyl)

(said C₁₋₆ alkyl is optionally substituted by a hydroxy group),

- (f) an aromatic heterocyclic group (preferably, triazolyl (preferably, 1H-1,2,4-triazol-3-yl), tetrazolyl (preferably, tetrazol-5-yl)) optionally substituted by a C₁₋₆ alkyl group (preferably, methyl), and

- (g) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl), dihydrotriazolyl (preferably, 4,5-dihydro-1H-1,2,4-triazol-3-yl)) optionally substituted by an oxo group.

The "aromatic heterocyclic group" of the "optionally substituted aromatic heterocyclic group" for R is preferably thiazolyl (preferably, thiazol-2-yl).

5 Examples of the substituent that the "aromatic heterocyclic group" optionally has include those similar to the substituents that the "C₁₋₆ alkyl group" of the aforementioned "optionally substituted C₁₋₆ alkyl group" optionally has. The number of the substituents is 1 to 4,
10 preferably 1 to 3, more preferably 1.

[0134]

The "optionally substituted aromatic heterocyclic group" for R is preferably an aromatic heterocyclic group (preferably, thiazolyl (preferably, thiazol-2-yl)) optionally
15 substituted by a carboxy group.

[0135]

The "nonaromatic heterocyclic group" of the "optionally substituted nonaromatic heterocyclic group" for R is preferably dihydropyridyl (preferably, 1,2-dihydropyridin-1-
20 yl), dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl).

Examples of the substituent that the "nonaromatic heterocyclic group" optionally has include those similar to the substituents that the "C₁₋₆ alkyl group" of the
25 aforementioned "optionally substituted C₁₋₆ alkyl group" optionally has. The number of the substituents is 1 to 4, preferably 1 to 3, more preferably 1.

[0136]

The "optionally substituted nonaromatic heterocyclic
30 group" for R is preferably a nonaromatic heterocyclic group (preferably, dihydropyridyl (preferably, 1,2-dihydropyridin-1-yl), dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from

35 (a) a nonaromatic heterocyclic group (preferably,

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dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)), and

(b) an oxo group.

[0137]

5 R is preferably

(1) a hydroxy group,

(2) a cyano group,

(3) a carboxy group,

(4) a C₁₋₆ alkoxy-carbonyl group (preferably, ethoxycarbonyl),

10 (5) an amino group,

(6) a mono- or di-C₁₋₆ alkylamino group (preferably, dimethylamino),

(7) a mono- or di-C₇₋₁₂ aralkylamino group (preferably, benzylamino),

15 (8) a mono- or di-(C₁₋₆ alkylsulfonyl)amino group (preferably, methylsulfonylamino, ethylsulfonylamino),

(9) a mono- or di-(C₃₋₆ cycloalkylsulfonyl)amino group (preferably, cyclopropylsulfonylamino),

(10) a mono- or di-(C₆₋₁₂ arylsulfonyl)amino group (preferably, phenylsulfonylamino),

(11) a mono- or di-(aromatic heterocycl-yl-sulfonyl)amino group (preferably, pyridylsulfonylamino (preferably, pyridin-3-ylsulfonylamino)),

(12) -NR^A-CO-R^B

25 wherein

R^A is

(a) a hydrogen atom, or

(b) a C₁₋₆ alkyl group (preferably, methyl), and

R^B is

30 (a) a C₁₋₆ alkyl group (preferably, methyl, ethyl)

optionally substituted by 1 to 3 (preferably, 1 or 2)

substituents selected from

(i) a halogen atom (preferably, fluorine atom),

(ii) a hydroxy group,

35 (iii) a C₁₋₆ alkoxy group (preferably, methoxy),

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(iv) an aromatic heterocyclic group (preferably, triazolyl (preferably, 1,2,4-triazol-1-yl)), and

(v) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(b) a C₃₋₆ cycloalkyl group (preferably, cyclopropyl),

(c) a C₁₋₆ alkyl-carbonyl group (preferably, acetyl),

(d) an amino group,

(e) a mono- or di-C₁₋₆ alkylamino group (preferably, methylamino),

(f) a cyclic amino group (preferably, morpholino),

(g) a C₆₋₁₂ aryl group (preferably, phenyl) optionally substituted by 1 to 3 (preferably, 1) substituents selected from

(i) a cyano group,

(ii) a carboxy group,

(iii) a C₁₋₆ alkoxy-carbonyl group (preferably, ethoxycarbonyl),

(iv) a C₁₋₆ alkylsulfonylamino group (preferably, methylsulfonylamino), and

(v) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(h) a C₇₋₁₂ aralkyl group (preferably, benzyl)

optionally substituted by a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group, or

(i) an aromatic heterocyclic group (preferably, oxazolyl (preferably, oxazol-5-yl)),

(13) -NR^C-SO₂-N(R^D)(R^E)

wherein

R^C is

(a) a hydrogen atom, or

(b) a C₁₋₆ alkyl group (preferably, methyl), and

R^D and R^E are each independently,

- (a) a hydrogen atom,
- (b) a C_{1-6} alkyl group (preferably, methyl, ethyl), or
- (c) a C_{3-6} cycloalkyl group (preferably, cyclopropyl),

5 or

(14) an optionally substituted cyclic amino group (preferably, a cyclic amino group (preferably, imidazolidinyl (preferably, imidazolidin-1-yl)) optionally substituted by 1 or 2 oxo groups, and

10 (b) an oxo group,

(15) a C_{1-6} alkyl group (preferably, methyl, ethyl, propyl, isopropyl) optionally substituted by 1 to 4 (preferably 1 to 3, more preferably 1 or 2) substituents selected from

(a) a halogen atom (preferably, a fluorine atom),

15 (b) a cyano group,

(c) a hydroxy group,

(d) a carboxy group,

(e) an amino group,

(f) a carbamoyl group,

20 (g) a mono- or di- $(C_{1-6}$ alkyl)carbamoyl group

(preferably, isopropylcarbamoyl) (said C_{1-6} alkyl is optionally substituted by a carboxy group),

(h) a mono- or di- $(C_{6-12}$ aryl)carbamoyl group

25 (preferably, phenylcarbamoyl) (said C_{6-12} aryl is optionally substituted by a carboxy group),

(i) a C_{1-6} alkoxy group (preferably, methoxy, ethoxy, propoxy) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from

(i) a hydroxy group,

30 (ii) a carboxy group,

(iii) a carbamoyl group,

(iv) a mono- or di- $(C_{1-6}$ alkyl-carbonyl)amino group (preferably, acetylamino),

35 (v) a mono- or di- $(C_{1-6}$ alkylsulfonyl)amino group (preferably, methylsulfonylamino),

(vi) a C₁₋₆ alkoxy-carbonyl group (preferably, ethoxycarbonyl), and

(vii) a cyclic amino-carbonyl group (preferably, azetidin-1-ylcarbonyl, 1,1-dioxide-thiomorpholinocarbonyl) optionally substituted by a hydroxy group,

(j) a C₁₋₆ alkyl-carbonyloxy group (preferably, acetyloxy),

(k) a C₁₋₆ alkylsulfonyloxy group (preferably, methylsulfonyloxy),

10 (l) a C₆₋₁₂ aryloxy group (preferably, phenoxy) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from

(i) a halogen atom (preferably, a fluorine atom, a chlorine atom),

15 (ii) a cyano group,

(iii) a carboxy group,

(iv) a C₁₋₆ alkoxy group (preferably, methoxy),

(v) a C₁₋₆ alkoxy-carbonyl group (preferably, methoxycarbonyl),

20 (vi) a C₁₋₆ alkylsulfonyl group (preferably, methylsulfonyl),

(vii) a mono- or di-(C₁₋₆ alkylsulfonyl)carbamoyl group (preferably, methylsulfonylcarbamoyl),

(viii) a nonaromatic heterocyclic group
25 (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group or a thioxo group, and

(ix) a cyclic amino-carbonyl group (preferably, azetidin-1-ylcarbonyl) optionally substituted by a hydroxy
30 group,

(m) a C₇₋₁₂ aralkyloxy group (preferably, benzyloxy) optionally substituted by a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

35 (n) an aromatic heterocyclyl-oxy group (preferably,

pyridyloxy (preferably, pyridin-2-yloxy)) optionally substituted by 1 to 3 (preferably, 1) substituents selected from

(i) a carboxy group,

5 (ii) a C₁₋₆ alkoxy-carbonyl group (preferably, methoxycarbonyl), and

(iii) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl, 2,3-dihydro-1,3,4-oxadiazol-5-yl)) optionally substituted
10 by an oxo group,

(o) a C₁₋₆ alkylthio group (preferably, methylthio),

(p) a C₆₋₁₂ arylthio group (preferably, phenylthio) optionally substituted by a carboxy group,

(q) a C₁₋₆ alkylsulfinyl group (preferably,
15 methylsulfinyl),

(r) a C₁₋₆ alkylsulfonyl group (preferably, methylsulfonyl),

(s) a C₆₋₁₂ arylsulfonyl group (preferably, phenylsulfonyl) optionally substituted by 1 to 3 (preferably,
20 1) substituents selected from

(i) a carboxy group, and

(ii) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

25 (t) a mono- or di-C₁₋₆ alkylsulfamoyl group (preferably, isopropylsulfamoyl),

(u) an aromatic heterocyclyl-amino group (preferably, pyridylamino (preferably, pyridin-2-ylamino), pyrimidinylamino (preferably, pyrimidin-2-ylamino), benzooxazolylamino
30 (preferably, benzooxazol-2-ylamino)) optionally substituted by 1 to 3 (preferably, 1) substituents selected from

(i) a carboxy group, and

(ii) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,
35

(v) $-NR^F-CO-R^G$

wherein

R^F is

(i) a hydrogen atom, or

5 (ii) a C_{1-6} alkyl group (preferably, methyl, ethyl)
optionally substituted by a hydroxy group, and

R^G is

(i) a C_{1-6} alkyl group (preferably, methyl, ethyl,
propyl, isopropyl) optionally substituted by 1 to 3

10 substituents selected from

(1) a halogen atom (preferably, a fluorine atom),

(2) a cyano group,

(3) a hydroxy group,

(4) a C_{1-6} alkoxy group (preferably, methoxy,
15 ethoxy, isopropoxy, isobutoxy) optionally substituted by 1 to
3 substituents selected from a halogen atom (preferably, a
fluorine atom) and a C_{3-6} cycloalkyl group (preferably,
cyclopropyl),

(5) a C_{3-6} cycloalkyloxy group (preferably,
20 cyclopropyloxy),

(6) an aromatic heterocyclyl-oxy group
(preferably, pyridyloxy (preferably, pyridin-2-yloxy),
pyrimidinyloxy (preferably, pyrimidin-2-yloxy)) optionally
substituted by 1 to 3 (preferably, 1) substituents selected
25 from a halogen atom (preferably, a fluorine atom, a chlorine
atom), a cyano group and a carboxy group,

(7) a mono- or di- C_{1-6} alkylamino group
(preferably, methylamino, dimethylamino),

(8) an N-(C_{1-6} alkyl-carbonyl)-N-(C_{1-6} alkyl)amino
30 group (preferably, N-acetyl-N-methylamino),

(9) a mono- or di-(C_{6-12} aryl-carbonyl)amino group
(preferably, benzoylamino),

(10) a mono- or di-(aromatic heterocyclyl-
carbonyl)amino group (preferably, pyridylcarbonylamino
35 (preferably, pyridin-2-ylcarbonylamino)),

(11) an N-(aromatic heterocycl-yl-carbonyl)-N-(C₁₋₆ alkyl)amino group (preferably, N-(pyridylcarbonyl)-N-methylamino (preferably, N-(pyridin-2-ylcarbonyl)-N-methylamino)),

5 (12) a mono- or di-(C₆₋₁₂ arylsulfonyl)amino group (preferably, phenylsulfonylamino),

(13) a C₁₋₆ alkylthio group (preferably, methylthio),

(14) a C₁₋₆ alkylsulfonyl group (preferably, 10 methylsulfonyl),

(15) a C₁₋₆ alkyl-carbonyloxy group (preferably, acetyloxy),

(16) a C₆₋₁₂ aryloxy group (preferably, phenoxy) optionally substituted by 1 to 3 (preferably, 1) substituents 15 selected from a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group, and a carboxy group,

(17) an aromatic heterocyclic group (preferably, 20 pyridyl (preferably, pyridin-2-yl), pyrazolyl (preferably, pyrazol-1-yl), isoxazolyl (preferably, isoxazol-5-yl), triazolyl (preferably, 1H-1,2,4-triazol-1-yl), tetrazolyl (preferably, tetrazol-1-yl)) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from a carboxy 25 group and a C₁₋₆ alkyl group (preferably, methyl),

(18) a cyclic amino group (preferably, 1-pyrrolidinyl, piperidino, 1-imidazolidinyl, morpholino, 8-oxa-3-azabicyclo[3.2.1]octan-3-yl) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from a halogen 30 atom (preferably, a fluorine atom, a chlorine atom) and an oxo group, and

(19) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 1-dihydropyridyl (preferably, 1,2-dihydropyridin-1-yl), 4,5-dihydro-1,2,4-oxadiazol-3-yl)) 35 optionally substituted by 1 to 3 (preferably, 1 or 2)

substituents selected from a halogen atom (preferably, a chlorine atom) and an oxo group,

(ii) a C₁₋₆ alkoxy group (preferably, methoxy, isopropoxy),

5 (iii) a C₃₋₆ cycloalkyl group (preferably, cyclopropyl),

(iv) a C₆₋₁₂ aryl group (preferably, phenyl) optionally substituted by 1 to 3 substituents selected from

10 (1) a halogen atom (preferably, a fluorine atom, a chlorine atom),

(2) a cyano group,

(3) a hydroxy group,

(4) a carboxy group,

15 (5) a C₁₋₆ alkyl group (preferably, methyl, tert-butyl) optionally substituted by a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

20 (6) a C₁₋₆ alkoxy group (preferably, methoxy, ethoxy),

(7) a C₁₋₆ alkylsulfonyl group (preferably, methylsulfonyl),

(8) a mono- or di-(C₁₋₆ alkylsulfonyl)amino group (preferably, methylsulfonylamino),

25 (9) a C₆₋₁₂ aryl group (preferably, phenyl), and

(10) an aromatic heterocyclic group (preferably, oxadiazolyl (preferably, 1,2,4-oxadiazol-3-yl), tetrazolyl (preferably, tetrazol-5-yl)) optionally substituted by a C₁₋₆ alkyl group (preferably, methyl),

30 (11) a cyclic amino group (preferably, 1-pyrrolidinyl) optionally substituted by an oxo group, and

(12) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

35 (v) a C₇₋₁₂ aralkyl group (preferably, benzyl)

optionally substituted by a nonaromatic heterocyclic group
(preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-
1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(vi) an aromatic heterocyclic group (preferably,
5 pyridyl (preferably, pyridin-2-yl, pyridin-3-yl), thiazolyl
(preferably, thiazol-5-yl)) optionally substituted by 1 to 3
(preferably, 1) substituents selected from

(1) a C₁₋₆ alkyl group (preferably, methyl),

(2) a mono- or di-(C₁₋₆ alkylsulfonyl)amino group
10 (preferably, methylsulfonylamino), and

(3) a nonaromatic heterocyclic group (preferably,
dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-
yl)) optionally substituted by an oxo group,

(vii) a cyclic amino group (preferably, 1-
15 pyrrolidinyl, morpholino, 1,1-dioxide-thiomorpholino)
optionally substituted by 1 or 2 oxo groups,

(viii) a nonaromatic heterocyclic group (preferably,
dihydropyridyl (preferably, 1,2-dihydropyridin-3-yl),
tetrahydrofuryl (preferably, tetrahydrofuran-2-yl,
20 tetrahydrofuran-3-yl), tetrahydropyranyl (preferably,
tetrahydropyran-2-yl, tetrahydropyran-4-yl), dioxanyl
(preferably, 1,4-dioxan-2-yl)) optionally substituted by 1 or
2 oxo group,

(ix) a C₁₋₆ alkyl-carbonyl group (preferably, acetyl,
25 ethylcarbonyl), or

(x) a cyclic amino-carbonyl group (preferably,
pyrrolidin-1-ylcarbonyl),

(w) $-NR^H-SO_2-R^I$

wherein

30 R^H is

(i) a hydrogen atom,

(ii) a C₁₋₆ alkyl group (preferably, methyl), or

(iii) a C₇₋₁₂ aralkyl group (preferably, benzyl)

optionally substituted by a C₁₋₆ alkoxy group (preferably,
35 methoxy), and

R^I is

(i) a C₁₋₆ alkyl group (preferably, methyl, ethyl, isopropyl) optionally substituted by 1 to 3 substituents selected from

- 5 (1) a halogen atom (preferably, a fluorine atom),
 (2) a C₁₋₆ alkoxy group (preferably, methoxy), and
 (3) a cyclic amino group (preferably, morpholino),
 (ii) a C₆₋₁₂ aryl group (preferably, phenyl)

optionally substituted by 1 to 3 (preferably, 1) substituents
10 selected from

- (1) a carboxy group, and
 (2) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group, or
15 (iii) an aromatic heterocyclic group (preferably, pyridyl (preferably, pyridin-2-yl, pyridin-3-yl), furyl (preferably, furan-2-yl)) optionally substituted by 1 to 3 (preferably, 1) substituents selected from

- (1) a carboxy group, and
20 (2) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(x) -NR^J-CO-NR^KR^L

wherein

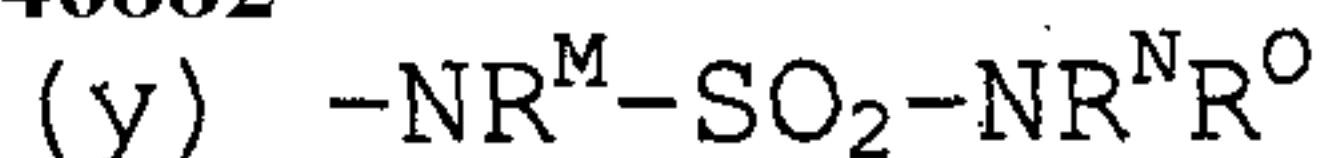
25 R^J is

 (i) a hydrogen atom, or
 (ii) a C₁₋₆ alkyl group (preferably, methyl, ethyl) optionally substituted by a hydroxy group, and

R^K and R^L are each independently,

- 30 (i) a hydrogen atom,
 (ii) a C₁₋₆ alkyl group (preferably, methyl, ethyl, tert-butyl) optionally substituted by 1 to 3 (preferably, 1) substituents selected from a hydroxy group and a C₁₋₆ alkoxy group (preferably, methoxy), or

35 (iii) a C₁₋₆ alkoxy group (preferably, methoxy),



wherein

R^M is

(i) a hydrogen atom, or

(ii) a C_{1-6} alkyl group (preferably, methyl),

R^N and R^O are each independently,

(i) a hydrogen atom,

(ii) a C_{1-6} alkyl group (preferably, methyl), or

(iii) a C_{1-6} alkoxy group (preferably, methoxy),

(z) an aromatic heterocyclic group (preferably, pyrazolyl (preferably, pyrazol-1-yl, pyrazol-3-yl), oxadiazolyl (preferably, 1,2,4-oxadiazol-3-yl), thiazolyl (preferably, thiazol-2-yl, thiazol-4-yl), triazolyl (preferably, 1H-1,2,3-triazol-1-yl, 1H-1,2,4-triazol-3-yl), indazolyl (preferably, 1H-indazol-1-yl), benzimidazolyl (preferably, 1H-benzimidazol-2-yl)) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from

(i) a carboxy group,

(ii) a C_{1-6} alkyl group (preferably, methyl)

optionally substituted by 1 to 3 substituents selected from a halogen atom (preferably, a fluorine atom), a hydroxy group and a carboxy group,

(iii) a C_{1-6} alkoxy group (preferably, ethoxy, tert-butoxy) optionally substituted by a C_{1-6} alkoxy group

(preferably, methoxy),

(iv) a C_{3-6} cycloalkyl group (preferably, cyclopropyl), and

(v) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(aa) a cyclic amino group (preferably, 1-azetidiny, 1-pyrrolidinyl, piperidino, 1-imidazolidinyl, 1-dihydropyridazinyl (preferably, 2,3-dihydropyridazin-2-yl), 1-hexahydropyrimidinyl, 2-dihydroisoindolyl (preferably, 1,3-dihydro-2H-isoindol-2-yl), 3-dihydroquinazolinyl (preferably,

3,4-dihydroquinazolin-3-yl), 3-tetrahydroquinazolinyl

(preferably, 1,2,3,4-tetrahydroquinazolin-3-yl), 3-

tetrahydropyrido[3,2-d]pyrimidinyl (preferably, 1,2,3,4-

tetrahydropyrido[3,2-d]pyrimidin-3-yl), 3-tetrahydropteridinyl

5 (preferably, 1,2,3,4-tetrahydropteridin-3-yl)) optionally

substituted by 1 to 4 substituents selected from

(i) a cyano group,

(ii) a carboxy group,

(iii) a C₁₋₆ alkyl group (preferably, methyl),

10 (iv) a C₁₋₆ alkoxy-carbonyl group (preferably, ethoxycarbonyl),

(v) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group (preferably, acetylamino),

(vi) a nonaromatic heterocyclic group (preferably, 15 dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

and

(vii) an oxo group, and

(bb) a nonaromatic heterocyclic group (preferably, 20 dihydrooxadiazolyl (preferably, 1-dihydropyridyl (preferably, 1,2-dihydropyridin-1-yl), dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl) optionally substituted by 1 to 3 substituents selected from

(i) a halogen atom (preferably, a chlorine atom),

25 (ii) a cyano group,

(iii) a carboxy group,

(iv) a carbamoyl group,

(v) a C₁₋₆ alkoxy-carbonyl group (preferably, methoxycarbonyl),

30 (vi) an aromatic heterocyclic group (preferably, triazolyl (preferably, 1,2,4-triazol-3-yl), tetrazolyl (preferably, tetrazol-5-yl)) optionally substituted by a C₁₋₆ alkyl group (preferably, methyl),

(vii) a nonaromatic heterocyclic group (preferably, 35 dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-

yl, 4,5-dihydro-1,3,4-oxadiazol-2-yl), dihydrotriazolyl
(preferably, 4,5-dihydrotriazol-3-yl)) optionally substituted
by an oxo group,

(16) a C₁₋₆ alkoxy group (preferably, methoxy, ethoxy),

5 (17) a C₁₋₆ alkyl-carbonyl group (preferably, acetyl),

(18) -CO-NR^PR^Q

wherein

R^P and R^Q are each independently,

(a) a hydrogen atom,

10 (b) a C₁₋₆ alkyl group (preferably, methyl, ethyl,
isobutyl) optionally substituted by 1 to 3 (preferably, 1)
substituents selected from

(i) a hydroxy group,

(ii) a C₁₋₆ alkylsulfonyl group (preferably,
15 methylsulfonyl), and

(iii) a C₁₋₆ alkoxy group (preferably, methoxy),

(c) a C₁₋₆ alkoxy group (preferably, methoxy),

(d) a C₆₋₁₂ aryl group (preferably, phenyl) optionally
substituted by a carboxy group,

20 (e) a C₁₋₆ alkylsulfonyl group (preferably,
methylsulfonyl), or

(f) a C₆₋₁₂ arylsulfonyl group (preferably,
phenylsulfonyl) optionally substituted by 1 to 3 (preferably,
1) substituents selected from

25 (i) a C₁₋₆ alkyl group (preferably, methyl)
optionally substituted by 1 to 3 halogen atoms (preferably, a
fluorine atom), and

(ii) a C₁₋₆ alkoxy group (preferably, methoxy)
optionally substituted by 1 to 3 (preferably, 1 or 2) halogen
30 atoms (preferably, a fluorine atom),

(19) a C₆₋₁₂ aryloxy group (preferably, phenoxy) optionally
substituted by a nonaromatic heterocyclic group (preferably,
dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-
yl)) optionally substituted by an oxo group,

35 (20) an aromatic heterocyclyl-oxy group (preferably,

pyridyloxy (preferably, pyridin-3-yloxy, pyridin-4-yloxy)) optionally substituted by 1 to 3 (preferably, 1) substituents selected from

- (a) a cyano group,
- 5 (b) a carboxy group,
- (c) a C₁₋₆ alkoxy-carbonyl group (preferably, methoxycarbonyl),
- (d) a carbamoyl group,
- (e) a mono- or di-C₁₋₆ alkylcarbamoyl group
- 10 (preferably, methylcarbamoyl, ethylcarbamoyl)
- (said C₁₋₆ alkyl is optionally substituted by a hydroxy group),
- (f) an aromatic heterocyclic group (preferably, triazolyl (preferably, 1H-1,2,4-triazol-3-yl), tetrazolyl
- 15 (preferably, tetrazol-5-yl)) optionally substituted by a C₁₋₆ alkyl group (preferably, methyl), and
- (g) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl), dihydrotriazolyl (preferably, 4,5-dihydro-1H-1,2,4-
- 20 triazol-3-yl)) optionally substituted by an oxo group,
- (21) an aromatic heterocyclic group (preferably, thiazolyl (preferably, thiazol-2-yl)) optionally substituted by a carboxy group, or
- (22) a nonaromatic heterocyclic group (preferably,
- 25 dihydropyridyl (preferably, 1,2-dihydropyridin-1-yl), dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by
- (a) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-
- 30 yl)) optionally substituted by an oxo group, and
- (b) an oxo group.

[0138]

In another embodiment, R is preferably

- (1) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group (preferably,
- 35 acetyl),

(2) a sulfamoylamino group,

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

5 (a) a hydroxy group,

(b) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group (preferably, acetyl),

(c) a sulfamoylamino group,

10 (d) a C₁₋₆ alkoxy-C₁₋₆ alkyl-carbonylamino group (preferably, (2-methoxyacetyl)amino, (2-ethoxyacetyl)amino, (2-isopropoxyacetyl)amino),

(e) a C₁₋₆ alkylsulfonylamino group (preferably, methylsulfonylamino), and

15 (f) 2-oxopyridin-1(2H)-yl optionally substituted by 1 to 3 substituents selected from a carboxy group and 5-oxo-4,5-dihydro-1,2,4-oxadiazolyl.

[0139]

In another embodiment, R is preferably R'.

[0140]

20 Examples of the substituent that the "C₁₋₆ alkyl group" of the "optionally substituted C₁₋₆ alkyl group" for R' optionally has include substituents selected from

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

25 (2) a cyano group,

(3) a hydroxy group,

(4) a nitro group,

(5) a formyl group,

(6) an amino group,

30 (7) a mono- or di-C₁₋₆ alkylamino group (e.g., methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, ethylmethylamino etc.),

(8) a C₁₋₆ alkyl-carbonylamino group (e.g., acetylamino, ethylcarbonylamino etc.),

35 (9) a C₁₋₆ alkoxy-carbonylamino group (e.g.,

methoxycarbonylamino, ethoxycarbonylamino,

propoxycarbonylamino, tert-butoxycarbonylamino etc.),

(10) a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy etc.)

5 optionally substituted by 1 to 3 halogen atoms (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom),

(11) a C₇₋₁₂ aralkyloxy group (e.g., benzyloxy etc.),

(12) a C₆₋₁₂ aryloxy group (e.g., phenoxy etc.),

10 (13) a C₁₋₆ alkyl-carbonyloxy group (e.g., acetyloxy etc.),

(14) a carboxy group,

(15) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl etc.),

15 (16) a C₇₋₁₂ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl etc.),

(17) a C₆₋₁₂ aryloxy-carbonyl group (e.g., phenyloxycarbonyl etc.),

20 (18) a C₁₋₆ alkyl-carbonyl group (e.g., acetyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, 2,2-dimethylpropylcarbonyl etc.),

(19) a C₃₋₆ cycloalkyl-carbonyl group (e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl),

25 (20) a C₇₋₁₂ aralkyl-carbonyl group (e.g., benzylcarbonyl etc.),

(21) a C₆₋₁₂ aryl-carbonyl group (e.g., benzoyl etc.),

(22) a carbamoyl group,

(23) a thiocarbamoyl group,

30 (24) a mono- or di-(C₁₋₆ alkyl)carbamoyl group (e.g., methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl etc.),

(25) a mono- or di-(C₇₋₁₂ aralkyl)carbamoyl group (e.g., benzylcarbamoyl, dibenzylcarbamoyl etc.),

35 (26) a thiol group,

(27) a C₁₋₆ alkylthio group (e.g., methylthio, ethylthio, propylthio etc.),

(28) a C₇₋₁₂ aralkylthio group (e.g., benzylthio etc.),

(29) a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl etc.),

(30) a C₃₋₆ cycloalkylsulfonyl group (e.g., cyclopropylsulfonyl, cyclobutylsulfonyl, cyclopentylsulfonyl etc.),

(31) a C₆₋₁₂ arylsulfonyl group (e.g., phenylsulfonyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl etc.),

(32) a C₇₋₁₂ aralkylsulfonyl group (e.g., benzylsulfonyl etc.),

(33) an ureido group,

(34) a mono- or di-(C₁₋₆ alkyl)ureido group (e.g., methylureido, ethylureido, propylureido etc.),

(35) a mono- or di-(C₆₋₁₂ aryl)ureido group (e.g., phenylureido, 1-naphthylureido, 2-naphthylureido etc.),

(36) a sulfamoyl group,

(37) a C₁₋₆ alkylsulfonylamino group (e.g., methylsulfonylamino, ethylsulfonylamino etc.),

(38) a sulfamoylamino group,

(39) a mono- or di-(C₁₋₆ alkyl)sulfamoylamino group (e.g., methylsulfamoylamino, ethylsulfamoylamino, dimethylsulfamoylamino)

(40) a nonaromatic heterocyclic group optionally substituted by 1 to 3 substituents selected from (a) a nonaromatic heterocyclic group optionally substituted by oxo group, (b) a carboxy group, and (c) an oxo group and the like. The number of the substituents is 1 to 4, preferably 1 to 3, more preferably 1.

[0141]

Examples of the substituent that the "C₁₋₆ alkoxy group" of the "optionally substituted C₁₋₆ alkoxy group" for R' optionally has include those similar to the substituents that the "C₁₋₆ alkyl group" of the aforementioned "optionally substituted C₁₋₆ alkyl group" optionally has. The number of the substituents is 1 to 4, preferably 1 to 3, more preferably 1.

Examples of the "optionally substituted carboxy group" for R' include

- (1) a carboxy group,
 - 5 (2) a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl etc.),
 - (3) a C₆₋₁₂ aryloxy-carbonyl group (e.g., phenoxycarbonyl, naphthoxycarbonyl etc.),
 - 10 (4) a C₇₋₁₂ aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, 2-phenylethyloxycarbonyl etc.)
- and the like.

[0143]

Examples of the "optionally substituted amino group" for
15 R' include

- (1) an amino group,
- (2) a mono- or di-C₁₋₆ alkylamino group (e.g., methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, ethylmethylamino etc.),
- 20 (3) a C₃₋₆ cycloalkylamino group (e.g., cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino),
- (4) a C₆₋₁₂ arylamino group (e.g., phenylamino, 1-naphthylamino, 2-naphthylamino etc.),
- (5) a C₇₋₁₂ aralkylamino group (e.g., benzylamino, 2-phenylethylamino, 1-phenylethylamino etc.)
- 25 (6) a hydrazino group,
- (7) a mono- or di-(C₁₋₆ alkylsulfonyl)amino group (e.g., methylsulfonylamino etc.),
- (8) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group (e.g., acetylamino etc.),
- 30 (9) a mono- or di-(C₁₋₆ alkoxy-carbonyl)amino group (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, tert-butoxycarbonylamino etc.),
- (10) a sulfamoylamino group,
- 35 (11) an optionally substituted cyclic amino group

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and the like.

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[0144]

Here, examples of the substituent that the "cyclic amino group" of the "optionally substituted cyclic amino group" optionally has include substituents selected from

- (a) an oxo group, and
- (b) the substituent that the "C₁₋₆ alkyl group" of the aforementioned "optionally substituted C₁₋₆ alkyl group" for R' optionally has. The number of the substituents is 1 to 4,

preferably 1 to 3.

[0145]

Examples of the "optionally substituted carbamoyl group" for R' include

- (1) a carbamoyl group,
 - (2) a mono- or di-(C₁₋₆ alkyl)carbamoyl group (e.g., methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl etc.),
 - (3) a mono- or di-(C₆₋₁₂ aryl)carbamoyl group (e.g., phenylcarbamoyl, naphthylcarbamoyl, diphenylcarbamoyl, dinaphthylcarbamoyl etc.),
 - (4) a mono- or di-(C₇₋₁₂ aralkyl)carbamoyl group (e.g., benzylcarbamoyl, dibenzylcarbamoyl etc.)
- and the like.

[0146]

Preferable examples of the "optionally substituted C₁₋₆ alkyl group" for R' include a C₁₋₆ alkyl group substituted by 1 to 4 (preferably 1 to 3, more preferably 1) substituents selected from

- (a) a halogen atom,
- (b) a hydroxy group,
- (c) a C₁₋₆ alkoxy group,
- (d) -S-R^{1a},
- (e) -SO₂-R^{1a},
- (f) -N(R^{1b})(R^{1c}),

- (g) $-\text{NH}-\text{CO}-\text{R}^{1a}$,
- (h) $-\text{NH}-\text{CO}-\text{N}(\text{R}^{1b})(\text{R}^{1c})$,
- (i) $-\text{NH}-\text{SO}_2-\text{R}^{1a}$, and
- (j) $-\text{NH}-\text{SO}_2-\text{N}(\text{R}^{1b})(\text{R}^{1c})$

5 wherein R^{1a} is a C_{1-6} alkyl group, and R^{1b} and R^{1c} are each independently a hydrogen atom or a C_{1-6} alkyl group.

[0147]

In another embodiment, preferable examples of the "optionally substituted C_{1-6} alkyl group" for R' include
 10 a C_{1-6} alkyl group (preferably, methyl, ethyl) optionally substituted by 1 to 4 (preferably 1 to 3, more preferably 1 or 2) substituents selected from

- (a) a halogen atom,
- (b) a hydroxy group,
- 15 (c) a C_{1-6} alkoxy group (preferably, methoxy),
- (d) $-\text{S}-\text{R}^{1a}$,
- (e) $-\text{SO}_2-\text{R}^{1a}$,
- (f) $-\text{N}(\text{R}^{1b})(\text{R}^{1c})$,
- (g) $-\text{NH}-\text{CO}-\text{R}^{1a}$,
- 20 (h) $-\text{NH}-\text{CO}-\text{N}(\text{R}^{1b})(\text{R}^{1c})$,
- (i) $-\text{NH}-\text{SO}_2-\text{R}^{1a}$,
- (j) $-\text{NH}-\text{SO}_2-\text{N}(\text{R}^{1b})(\text{R}^{1c})$

wherein

R^{1a} is a C_{1-6} alkyl group (preferably, methyl) optionally
 25 substituted by 1 to 3 (preferably, 1) C_{1-6} alkoxy groups (preferably, methoxy, ethoxy, isopropoxy), and
 R^{1b} and R^{1c} are each independently a hydrogen atom or a C_{1-6} alkyl group (preferably, a hydrogen atom), and
 (k) a nonaromatic heterocyclic group (preferably,
 30 dihydropyridyl (preferably, 1,2-dihydropyridin-1-yl)) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from

- (i) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-
 35 yl)) optionally substituted by an oxo group,

(ii) a carboxy group, and

(iii) an oxo group.

More preferred are

a C₁₋₆ alkyl group (preferably, methyl, ethyl) optionally
5 substituted by 1 to 4 (preferably 1 to 3, more preferably 1 or
2) substituents selected from

(a) a hydroxy group,

(b) a C₁₋₆ alkoxy group (preferably, methoxy),

(c) -SO₂-R^{1a},

10 (d) -NH-CO-R^{1a},

(e) -NH-CO-N(R^{1b})(R^{1c}),

(f) -NH-SO₂-R^{1a},

(g) -NH-SO₂-N(R^{1b})(R^{1c})

wherein

15 R^{1a} is a C₁₋₆ alkyl group (preferably, methyl) optionally
substituted by 1 to 3 (preferably, 1) C₁₋₆ alkoxy groups
(preferably, methoxy, ethoxy, isopropoxy), and
R^{1b} and R^{1c} are each independently a hydrogen atom or a C₁₋₆
alkyl group (preferably, a hydrogen atom), and

20 (h) a nonaromatic heterocyclic group (preferably,
dihydropyridyl (preferably, 1,2-dihydropyridin-1-yl))
optionally substituted by 1 to 3 (preferably, 1 or 2)
substituents selected from

(i) a nonaromatic heterocyclic group (preferably,
25 dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-
yl)) optionally substituted by an oxo group,

(ii) a carboxy group, and

(iii) an oxo group.

[0148]

30 In another embodiment, preferable examples of the
"optionally substituted C₁₋₆ alkyl group" for R' include
a C₁₋₆ alkyl group (preferably, methyl, ethyl, propyl,
isopropyl) optionally substituted by 1 to 3 substituents
selected from

35 (1) a hydroxyl group,

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(2) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group (preferably, acetyl),

(3) a sulfamoylamino group,

(4) a C₁₋₆ alkoxy-C₁₋₆ alkyl-carbonylamino group (preferably, (2-methoxyacetyl)amino, (2-ethoxyacetyl)amino, (2-isopropoxyacetyl)amino),

(5) a C₁₋₆ alkylsulfonylamino group (preferably, methylsulfonylamino), and

(6) 2-oxopyridin-1(2H)-yl optionally substituted by 1 to 3 substituents selected from a carboxy group and 5-oxo-4,5-dihydro-1,2,4-oxadiazolyl.

[0149]

Preferable examples of the "optionally substituted C₁₋₆ alkoxy group" for R' include a C₁₋₆ alkoxy group (preferably, methoxy, ethoxy).

[0150]

Preferable examples of the "optionally substituted carboxy group" for R' include

(1) a carboxy group,

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

and the like.

[0151]

Preferable examples of the "optionally substituted amino group" for R' include

(1) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group (preferably, acetylamino),

(2) a sulfamoylamino group

and the like.

[0152]

Preferable examples of R' include

(1) a hydroxy group,

(2) a C₁₋₆ alkoxy-carbonyl group,

(3) a C₁₋₆ alkoxy group, or

(4) a C₁₋₆ alkyl group optionally substituted by one substituent selected from

- (a) a halogen atom,
- (b) a hydroxy group,
- (c) a C₁₋₆ alkoxy group,
- (d) -S-R^{1a},
- (e) -SO₂-R^{1a},
- (f) -N(R^{1b})(R^{1c}),
- (g) -NH-CO-R^{1a},
- (h) -NH-CO-N(R^{1b})(R^{1c}),
- (i) -NH-SO₂-R^{1a}, and
- (j) -NH-SO₂-N(R^{1b})(R^{1c})

wherein R^{1a} is a C₁₋₆ alkyl group, and R^{1b} and R^{1c} are each independently a hydrogen atom or a C₁₋₆ alkyl group.

[0153]

In another embodiment, preferable examples of R' include

- (1) a hydroxy group,
- (2) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group (preferably, acetylamino),

- (3) a sulfamoylamino group,
- (4) a C₁₋₆ alkoxy group (preferably, methoxy, ethoxy), or
- (5) a C₁₋₆ alkyl group (preferably, methyl, ethyl) optionally substituted by 1 to 4 (preferably 1 to 3, more preferably 1 or 2) substituents selected from

- (a) a halogen atom,
- (b) a hydroxy group,
- (c) a C₁₋₆ alkoxy group (preferably, methoxy),
- (d) -S-R^{1a},
- (e) -SO₂-R^{1a},
- (f) -N(R^{1b})(R^{1c}),
- (g) -NH-CO-R^{1a},
- (h) -NH-CO-N(R^{1b})(R^{1c}),
- (i) -NH-SO₂-R^{1a},
- (j) -NH-SO₂-N(R^{1b})(R^{1c})

wherein

R^{1a} is a C₁₋₆ alkyl group (preferably, methyl) optionally substituted by 1 to 3 (preferably, 1) C₁₋₆ alkoxy groups (preferably, methoxy, ethoxy, isopropoxy), and

R^{1b} and R^{1c} are each independently a hydrogen atom or a C₁₋₆ alkyl group (preferably, a hydrogen atom), and

(k) a nonaromatic heterocyclic group (preferably, dihydropyridyl (preferably, 1,2-dihydropyridin-1-yl)) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from

- 10 (i) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,
- (ii) a carboxy group, and
- (iii) an oxo group.

15 More preferred are

- (1) a hydroxy group,
- (2) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group (preferably, acetylamino),
- (3) a sulfamoylamino group,
- 20 (4) a C₁₋₆ alkoxy group (preferably, methoxy, ethoxy), or
- (5) a C₁₋₆ alkyl group (preferably, methyl, ethyl) optionally substituted by 1 to 4 (preferably 1 to 3, more preferably 1 or 2) substituents selected from

- (a) a hydroxy group,
- 25 (b) a C₁₋₆ alkoxy group (preferably, methoxy),
- (c) -SO₂-R^{1a},
- (d) -NH-CO-R^{1a},
- (e) -NH-CO-N(R^{1b})(R^{1c}),
- (f) -NH-SO₂-R^{1a},
- 30 (g) -NH-SO₂-N(R^{1b})(R^{1c})

wherein

R^{1a} is a C₁₋₆ alkyl group (preferably, methyl) optionally substituted by 1 to 3 (preferably, 1) C₁₋₆ alkoxy groups (preferably, methoxy, ethoxy, isopropoxy), and

35 R^{1b} and R^{1c} are each independently a hydrogen atom or a C₁₋₆

alkyl group (preferably, a hydrogen atom), and

(h) a nonaromatic heterocyclic group (preferably, dihydropyridyl (preferably, 1,2-dihydropyridin-1-yl)) optionally substituted by 1 to 3 (preferably, 1 or 2)

5 substituents selected from

(i) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(ii) a carboxy group, and

10 (iii) an oxo group.

[0154]

In another embodiment, preferable examples of R' include

(1) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group (preferably, acetylamino),

15 (2) a sulfamoylamino group,

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

(a) a hydroxy group,

20 (b) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group (preferably, acetyl),

(c) a sulfamoylamino group,

(d) a C₁₋₆ alkoxy-C₁₋₆ alkyl-carbonylamino group (preferably, (2-methoxyacetyl)amino, (2-ethoxyacetyl)amino, 25 (2-isopropoxyacetyl)amino),

(e) a C₁₋₆ alkylsulfonylamino group (preferably, methylsulfonylamino), and

(f) 2-oxopyridin-1(2H)-yl optionally substituted by 1 to 3 substituents selected from a carboxy group and 5-oxo-4,5-dihydro-1,2,4-oxadiazolyl.

30 [0155]

Preferable examples of a compound represented by the formula (I) or a salt thereof (hereinafter to be referred to as compound (I)) include the following compounds.

35 [compound (I)-1]

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Compound (I) wherein ring A is an optionally substituted benzene ring [preferably, a benzene ring optionally substituted by 1 to 3 (preferably 2) substituents selected from a halogen atom (preferably, a fluorine atom, a chlorine atom) and a C₁₋₆ alkyl group (preferably, methyl)],

R is

- (1) a hydroxy group,
- (2) a cyano group,
- (3) a carboxy group,
- 10 (4) a C₁₋₆ alkoxy-carbonyl group (preferably, ethoxycarbonyl),
- (5) an amino group,
- (6) a mono- or di-C₁₋₆ alkylamino group (preferably, dimethylamino),
- (7) a mono- or di-C₇₋₁₂ aralkylamino group (preferably,
- 15 benzylamino),
- (8) a mono- or di-(C₁₋₆ alkylsulfonyl)amino group (preferably, methylsulfonylamino, ethylsulfonylamino),
- (9) a mono- or di-(C₃₋₆ cycloalkylsulfonyl)amino group (preferably, cyclopropylsulfonylamino),
- 20 (10) a mono- or di-(C₆₋₁₂ arylsulfonyl)amino group (preferably, phenylsulfonylamino),
- (11) a mono- or di-(aromatic heterocyclyl-sulfonyl)amino group (preferably, pyridylsulfonylamino (preferably, pyridin-3-ylsulfonylamino)),
- 25 (12) -NR^A-CO-R^B

wherein

R^A is

- (a) a hydrogen atom, or
- (b) a C₁₋₆ alkyl group (preferably, methyl), and

30 R^B is

(a) a C₁₋₆ alkyl group (preferably, methyl, ethyl) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from

- (i) a halogen atom (preferably, a fluorine atom),
- 35 (ii) a hydroxy group,

(iii) a C₁₋₆ alkoxy group (preferably, methoxy),

(iv) an aromatic heterocyclic group (preferably, triazolyl (preferably, 1,2,4-triazol-1-yl)), and

(v) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(b) a C₃₋₆ cycloalkyl group (preferably, cyclopropyl),

(c) a C₁₋₆ alkyl-carbonyl group (preferably, acetyl),

(d) an amino group,

(e) a mono- or di-C₁₋₆ alkylamino group (preferably, methylamino),

(f) a cyclic amino group (preferably, morpholino),

(g) a C₆₋₁₂ aryl group (preferably, phenyl) optionally substituted by 1 to 3 (preferably, 1) substituents selected

from

(i) a cyano group,

(ii) a carboxy group,

(iii) a C₁₋₆ alkoxy-carbonyl group (preferably, ethoxycarbonyl),

(iv) a C₁₋₆ alkylsulfonylamino group (preferably, methylsulfonylamino), and

(v) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(h) a C₇₋₁₂ aralkyl group (preferably, benzyl) optionally substituted by a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group, or

(i) an aromatic heterocyclic group (preferably, oxazolyl (preferably, oxazol-5-yl)),

(13) -NR^C-SO₂-N(R^D)(R^E)

wherein

R^C is

(a) a hydrogen atom, or

(b) a C₁₋₆ alkyl group (preferably, methyl), and

R^D and R^E are each independently,

(a) a hydrogen atom,

(b) a C₁₋₆ alkyl group (preferably, methyl, ethyl), or

5 (c) a C₃₋₆ cycloalkyl group (preferably, cyclopropyl),

(14) an optionally substituted cyclic amino group (preferably, a cyclic amino group (preferably, 1-imidazolidinyl) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from

10 (a) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group, and

(b) an oxo group,

(15) a C₁₋₆ alkyl group (preferably, methyl, ethyl, propyl, isopropyl) optionally substituted by 1 to 4 (preferably 1 to 3, more preferably 1 or 2) substituents selected from

(a) a halogen atom (preferably, a fluorine atom),

(b) a cyano group,

(c) a hydroxy group,

20 (d) a carboxy group,

(e) an amino group,

(f) a carbamoyl group,

(g) a mono- or di-(C₁₋₆ alkyl)carbamoyl group (preferably, isopropylcarbamoyl) (said C₁₋₆ alkyl is optionally substituted by a carboxy group),

(h) a mono- or di-(C₆₋₁₂ aryl)carbamoyl group (preferably, phenylcarbamoyl) (said C₆₋₁₂ aryl is optionally substituted by a carboxy group),

(i) a C₁₋₆ alkoxy group (preferably, methoxy, ethoxy, propoxy) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from

(i) a hydroxy group,

(ii) a carboxy group,

(iii) a carbamoyl group,

35 (iv) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group

(preferably, acetylamino),

(v) a mono- or di-(C₁₋₆ alkylsulfonyl)amino group
(preferably, methylsulfonylamino),

(vi) a C₁₋₆ alkoxy-carbonyl group (preferably,
5 ethoxycarbonyl), and

(vii) a cyclic amino-carbonyl group (preferably,
azetidin-1-ylcarbonyl, 1,1-dioxide-thiomorpholinocarbonyl)
optionally substituted by a hydroxy group,

(j) a C₁₋₆ alkyl-carbonyloxy group (preferably,
10 acetyloxy),

(k) a C₁₋₆ alkylsulfonyloxy group (preferably,
methylsulfonyloxy),

(l) a C₆₋₁₂ aryloxy group (preferably, phenoxy)
optionally substituted by 1 to 3 (preferably, 1 or 2)
15 substituents selected from

(i) a halogen atom (preferably, a fluorine atom, a
chlorine atom),

(ii) a cyano group,

(iii) a carboxy group,

20 (iv) a C₁₋₆ alkoxy group (preferably, methoxy),

(v) a C₁₋₆ alkoxy-carbonyl group (preferably,
methoxycarbonyl),

(vi) a C₁₋₆ alkylsulfonyl group (preferably,
methylsulfonyl),

25 (vii) a mono- or di-(C₁₋₆ alkylsulfonyl)carbamoyl
group (preferably, methylsulfonylcarbamoyl),

(viii) a nonaromatic heterocyclic group
(preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-
1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group
30 or a thioxo group, and

(ix) a cyclic amino-carbonyl group (preferably,
azetidin-1-ylcarbonyl) optionally substituted by a hydroxy
group,

(m) a C₇₋₁₂ aralkyloxy group (preferably, benzyloxy)
35 optionally substituted by a nonaromatic heterocyclic group

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(preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(n) an aromatic heterocyclyl-oxy group (preferably, pyridyloxy (preferably, pyridin-2-yloxy)) optionally substituted by 1 to 3 (preferably, 1) substituents selected from

(i) a carboxy group,

(ii) a C₁₋₆ alkoxy-carbonyl group (preferably, methoxycarbonyl), and

10 (iii) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl, 2,3-dihydro-1,3,4-oxadiazol-5-yl)) optionally substituted by an oxo group,

(o) a C₁₋₆ alkylthio group (preferably, methylthio),

15 (p) a C₆₋₁₂ arylthio group (preferably, phenylthio) optionally substituted by a carboxy group,

(q) a C₁₋₆ alkylsulfinyl group (preferably, methylsulfinyl),

(r) a C₁₋₆ alkylsulfonyl group (preferably, 20 methylsulfonyl),

(s) a C₆₋₁₂ arylsulfonyl group (preferably, phenylsulfonyl) optionally substituted by 1 to 3 (preferably, 1) substituents selected from

(i) a carboxy group, and

25 (ii) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(t) a mono- or di-C₁₋₆ alkylsulfamoyl group (preferably, isopropylsulfamoyl),

30 (u) an aromatic heterocyclyl-amino group (preferably, pyridylamino (preferably, pyridin-2-ylamino), pyrimidinylamino (preferably, pyrimidin-2-ylamino), benzooxazolylamino (preferably, benzooxazol-2-ylamino)) optionally substituted by 1 to 3 (preferably, 1) substituents selected from

35 (i) a carboxy group, and

(ii) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(v) $-NR^F-CO-R^G$

5 wherein

R^F is

(i) a hydrogen atom, or

(ii) a C_{1-6} alkyl group (preferably, methyl, ethyl) optionally substituted by a hydroxy group, and

10 R^G is

(i) a C_{1-6} alkyl group (preferably, methyl, ethyl, propyl, isopropyl) optionally substituted by 1 to 3 substituents selected from

(1) a halogen atom (preferably, a fluorine atom),

15 (2) a cyano group,

(3) a hydroxy group,

(4) a C_{1-6} alkoxy group (preferably, methoxy, ethoxy, isopropoxy, isobutoxy) optionally substituted by 1 to 3 substituents selected from a halogen atom (preferably, a fluorine atom) and a C_{3-6} cycloalkyl group (preferably, cyclopropyl),

(5) a C_{3-6} cycloalkyloxy group (preferably, cyclopropyloxy),

(6) an aromatic heterocyclyl-oxy group

25 (preferably, pyridyloxy (preferably, pyridin-2-yloxy), pyrimidinyloxy (preferably, pyrimidin-2-yloxy)) optionally substituted by 1 to 3 (preferably, 1) substituents selected from a halogen atom (preferably, a fluorine atom, a chlorine atom), a cyano group and a carboxy group,

30 (7) a mono- or di- C_{1-6} alkylamino group (preferably, methylamino, dimethylamino),

(8) an N-(C_{1-6} alkyl-carbonyl)-N-(C_{1-6} alkyl)amino group (preferably, N-acetyl-N-methylamino),

(9) a mono- or di-(C_{6-12} aryl-carbonyl)amino group
35 (preferably, benzoylamino),

(10) a mono- or di-(aromatic heterocyclyl-carbonyl)amino group (preferably, pyridylcarbonylamino (preferably, pyridin-2-ylcarbonylamino)),

(11) an N-(aromatic heterocyclyl-carbonyl)-N-(C₁₋₆ alkyl)amino group (preferably, N-(pyridylcarbonyl)-N-methylamino (preferably, N-(pyridin-2-ylcarbonyl)-N-methylamino)),

(12) a mono- or di-(C₆₋₁₂ arylsulfonyl)amino group (preferably, phenylsulfonylamino),

(13) a C₁₋₆ alkylthio group (preferably, methylthio),

(14) a C₁₋₆ alkylsulfonyl group (preferably, methylsulfonyl),

(15) a C₁₋₆ alkyl-carbonyloxy group (preferably, acetyloxy),

(16) a C₆₋₁₂ aryloxy group (preferably, phenoxy) optionally substituted by 1 to 3 (preferably, 1) substituents selected from a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group, and a carboxy group,

(17) an aromatic heterocyclic group (preferably, pyridyl (preferably, pyridin-2-yl), pyrazolyl (preferably, pyrazol-1-yl), isoxazolyl (preferably, isoxazol-5-yl), triazolyl (preferably, 1H-1,2,4-triazol-1-yl), tetrazolyl (preferably, tetrazol-1-yl)) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from a carboxy group and a C₁₋₆ alkyl group (preferably, methyl),

(18) a cyclic amino group (preferably, 1-pyrrolidinyl, piperidino, 1-imidazolidinyl, morpholino, 8-oxa-3-azabicyclo[3.2.1]octan-3-yl) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from a halogen atom (preferably, a fluorine atom, a chlorine atom) and an oxo group, and

(19) a nonaromatic heterocyclic group (preferably,

dihydropyridyl (preferably, 1,2-dihydropyridin-1-yl),
dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from a halogen atom (preferably, a chlorine atom) and an oxo group,

(ii) a C₁₋₆ alkoxy group (preferably, methoxy, isopropoxy),

(iii) a C₃₋₆ cycloalkyl group (preferably, cyclopropyl),

(iv) a C₆₋₁₂ aryl group (preferably, phenyl) optionally substituted by 1 to 3 substituents selected from

(1) a halogen atom (preferably, a fluorine atom, a chlorine atom),

(2) a cyano group,

(3) a hydroxy group,

(4) a carboxy group,

(5) a C₁₋₆ alkyl group (preferably, methyl, tert-butyl) optionally substituted by a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(6) a C₁₋₆ alkoxy group (preferably, methoxy, ethoxy),

(7) a C₁₋₆ alkylsulfonyl group (preferably, methylsulfonyl),

(8) a mono- or di-(C₁₋₆ alkylsulfonyl)amino group (preferably, methylsulfonylamino),

(9) a C₆₋₁₂ aryl group (preferably, phenyl),

(10) an aromatic heterocyclic group (preferably, oxadiazolyl (preferably, 1,2,4-oxadiazol-3-yl), tetrazolyl (preferably, tetrazol-5-yl)) optionally substituted by a C₁₋₆ alkyl group (preferably, methyl),

(11) a cyclic amino group (preferably, 1-pyrrolidinyl) optionally substituted by an oxo group, and

(12) a nonaromatic heterocyclic group

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(preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(v) a C₇₋₁₂ aralkyl group (preferably, benzyl) optionally substituted by a nonaromatic heterocyclic group

5 (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(vi) an aromatic heterocyclic group (preferably, pyridyl (preferably, pyridin-2-yl, pyridin-3-yl), thiazolyl (preferably, thiazol-5-yl)) optionally substituted by 1 to 3

10 (preferably, 1) substituents selected from

(1) a C₁₋₆ alkyl group (preferably, methyl),

(2) a mono- or di-(C₁₋₆ alkylsulfonyl)amino group (preferably, methylsulfonylamino), and

(3) a nonaromatic heterocyclic group (preferably, 15 dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(vii) a cyclic amino group (preferably, 1-pyrrolidinyl, morpholino, 1,1-dioxide-thiomorpholino) optionally substituted by 1 or 2 oxo groups,

20 (viii) a nonaromatic heterocyclic group (preferably, dihydropyridyl (preferably, 1,2-dihydropyridin-3-yl), tetrahydrofuryl (preferably, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl), tetrahydropyranyl (preferably, tetrahydropyran-2-yl, tetrahydropyran-4-yl), dioxanyl 25 (preferably, 1,4-dioxan-2-yl)) optionally substituted by 1 or 2 oxo groups,

(ix) a C₁₋₆ alkyl-carbonyl group (preferably, acetyl, ethylcarbonyl), or

(x) a cyclic amino-carbonyl group (preferably, 30 pyrrolidin-1-ylcarbonyl),

(w) $-NR^H-SO_2-R^I$

wherein

R^H is

(i) a hydrogen atom,

35 (ii) a C₁₋₆ alkyl group (preferably, methyl), or

(iii) a C₇₋₁₂ aralkyl group (preferably, benzyl) optionally substituted by a C₁₋₆ alkoxy group (preferably, methoxy), and

R^I is

5 (i) a C₁₋₆ alkyl group (preferably, methyl, ethyl, isopropyl) optionally substituted by 1 to 3 substituents selected from

(1) a halogen atom (preferably, a fluorine atom),

(2) a C₁₋₆ alkoxy group (preferably, methoxy), and

10 (3) a cyclic amino group (preferably, morpholino),

(ii) a C₆₋₁₂ aryl group (preferably, phenyl)

optionally substituted by 1 to 3 (preferably, 1) substituents selected from

(1) a carboxy group, and

15 (2) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group, or

(iii) an aromatic heterocyclic group (preferably, pyridyl (preferably, pyridin-2-yl, pyridin-3-yl), furyl

20 (preferably, furan-2-yl)) optionally substituted by 1 to 3 (preferably, 1) substituents selected from

(1) a carboxy group, and

(2) a nonaromatic heterocyclic group

(preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-
25 1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(x) -NR^J-CO-NR^KR^L

wherein

R^J is

(i) a hydrogen atom, or

30 (ii) a C₁₋₆ alkyl group (preferably, methyl, ethyl) optionally substituted by a hydroxy group, and

R^K and R^L are each independently,

(i) a hydrogen atom,

(ii) a C₁₋₆ alkyl group (preferably, methyl, ethyl, tert-butyl) optionally substituted by 1 to 3 (preferably, 1)

substituents selected from a hydroxy group and a C₁₋₆ alkoxy group (preferably, methoxy), or

(iii) a C₁₋₆ alkoxy group (preferably, methoxy),

(y) -NR^M-SO₂-NR^NR^O

5 wherein

R^M is

(i) a hydrogen atom, or

(ii) a C₁₋₆ alkyl group (preferably, methyl), and

R^N and R^O are each independently,

10 (i) a hydrogen atom,

(ii) a C₁₋₆ alkyl group (preferably, methyl), or

(iii) a C₁₋₆ alkoxy group (preferably, methoxy),

(z) an aromatic heterocyclic group (preferably,

pyrazolyl (preferably, pyrazol-1-yl, pyrazol-3-yl),

15 oxadiazolyl (preferably, 1,2,4-oxadiazol-3-yl), thiazolyl

(preferably, thiazol-2-yl, thiazol-4-yl), triazolyl

(preferably, 1H-1,2,3-triazol-1-yl, 1H-1,2,4-triazol-3-yl),

indazolyl (preferably, 1H-indazol-1-yl), benzimidazolyl

(preferably, 1H-benzimidazol-2-yl)) optionally substituted by

20 1 to 3 (preferably, 1 or 2) substituents selected from

(i) a carboxy group,

(ii) a C₁₋₆ alkyl group (preferably, methyl)

optionally substituted by 1 to 3 substituents selected from a halogen atom (preferably, a fluorine atom), a hydroxy group

25 and a carboxy group,

(iii) a C₁₋₆ alkoxy group (preferably, ethoxy, tert-butoxy) optionally substituted by a C₁₋₆ alkoxy group (preferably, methoxy),

(iv) a C₃₋₆ cycloalkyl group (preferably, 30 cyclopropyl), and

(v) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(aa) a cyclic amino group (preferably, 1-azetidiny, 35 1-pyrrolidiny, piperidino, 1-imidazolidiny, 1-

dihydropyridazinyl (preferably, 2,3-dihydropyridazin-2-yl), 1-hexahydropyrimidinyl, 2-dihydroisoindolyl (preferably, 1,3-dihydro-2H-isoindol-2-yl), 3-dihydroquinazolinyl (preferably, 3,4-dihydroquinazolin-3-yl), 3-tetrahydroquinazolinyl (preferably, 1,2,3,4-tetrahydroquinazolin-3-yl), 3-tetrahydropyrido[3,2-d]pyrimidinyl (preferably, 1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-3-yl), 3-tetrahydropteridinyl (preferably, 1,2,3,4-tetrahydropteridin-3-yl)) optionally substituted by 1 to 4 substituents selected from

- (i) a cyano group,
- (ii) a carboxy group,
- (iii) a C₁₋₆ alkyl group (preferably, methyl),
- (iv) a C₁₋₆ alkoxy-carbonyl group (preferably, ethoxycarbonyl),
- (v) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group (preferably, acetylamino),
- (vi) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

and

- (vii) an oxo group, and
- (bb) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 1-dihydropyridyl (preferably, 1,2-dihydropyridin-1-yl), dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl) optionally substituted by 1 to 3 substituents selected from

- (i) a halogen atom (preferably, a chlorine atom),
- (ii) a cyano group,
- (iii) a carboxy group,
- (iv) a carbamoyl group,
- (v) a C₁₋₆ alkoxy-carbonyl group (preferably, methoxycarbonyl),

- (vi) an aromatic heterocyclic group (preferably, triazolyl (preferably, 1,2,4-triazol-3-yl), tetrazolyl (preferably, tetrazol-5-yl)) optionally substituted by a C₁₋₆

alkyl group (preferably, methyl),

(vii) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl, 4,5-dihydro-1,3,4-oxadiazol-2-yl), dihydrotriazolyl

5 (preferably, 4,5-dihydrotriazol-3-yl)) optionally substituted by an oxo group,

(16) a C₁₋₆ alkoxy group (preferably, methoxy, ethoxy),

(17) a C₁₋₆ alkyl-carbonyl group (preferably, acetyl),

(18) -CO-NR^PR^Q

10 wherein

R^P and R^Q are each independently,

(a) a hydrogen atom,

(b) a C₁₋₆ alkyl group (preferably, methyl, ethyl, isobutyl) optionally substituted by 1 to 3 (preferably, 1)

15 substituents selected from

(i) a hydroxy group,

(ii) a C₁₋₆ alkylsulfonyl group (preferably, methylsulfonyl), and

(iii) a C₁₋₆ alkoxy group (preferably, methoxy),

20 (c) a C₁₋₆ alkoxy group (preferably, methoxy),

(d) a C₆₋₁₂ aryl group (preferably, phenyl) optionally substituted by a carboxy group,

(e) a C₁₋₆ alkylsulfonyl group (preferably, methylsulfonyl), or

25 (f) a C₆₋₁₂ arylsulfonyl group (preferably, phenylsulfonyl) optionally substituted by 1 to 3 (preferably, 1) substituents selected from

(i) a C₁₋₆ alkyl group (preferably, methyl)

optionally substituted by 1 to 3 halogen atoms (preferably, 30 fluorine atom), and

(ii) a C₁₋₆ alkoxy group (preferably, methoxy)

optionally substituted by 1 to 3 (preferably, 1 or 2) halogen atoms (preferably, a fluorine atom),

(19) a C₆₋₁₂ aryloxy group (preferably, phenoxy) optionally

35 substituted by a nonaromatic heterocyclic group (preferably,

dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(20) an aromatic heterocyclyl-oxy group (preferably, pyridyloxy (preferably, pyridin-3-yloxy, pyridin-4-yloxy))

5 optionally substituted by 1 to 3 (preferably, 1) substituents selected from

(a) a cyano group,

(b) a carboxy group,

(c) a C₁₋₆ alkoxy-carbonyl group (preferably, methoxycarbonyl),

(d) a carbamoyl group,

(e) a mono- or di-C₁₋₆ alkylcarbamoyl group (preferably, methylcarbamoyl, ethylcarbamoyl)

(said C₁₋₆ alkyl is optionally substituted by a hydroxy group),

(f) an aromatic heterocyclic group (preferably, triazolyl (preferably, 1H-1,2,4-triazol-3-yl), tetrazolyl (preferably, tetrazol-5-yl)) optionally substituted by a C₁₋₆ alkyl group (preferably, methyl), and

20 (g) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl), dihydrotriazolyl (preferably, 4,5-dihydro-1H-1,2,4-triazol-3-yl)) optionally substituted by an oxo group,

(21) an aromatic heterocyclic group (preferably, thiazolyl (preferably, thiazol-2-yl)) optionally substituted by a carboxy group, or

(22) a nonaromatic heterocyclic group (preferably, dihydropyridyl (preferably, 1,2-dihydropyridin-1-yl), dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from

(a) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group, and

35 (b) an oxo group, and

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rings B¹ - B⁶ are optionally substituted by a hydroxy group or a C₁₋₆ alkoxy group (preferably, methoxy) besides ring A and R.
[compound (I)-1']

Compound (I) wherein rings B¹ - B⁶ are free of a
5 substituent other than ring A and R.

[compound (I)-1'']

Compound (I) wherein rings B¹ - B⁶ are substituted by a hydroxy group or a C₁₋₆ alkoxy group (preferably, methoxy) besides ring A and R.

10 [0156]

[compound (I)-2]

Compound (I) wherein ring A is an optionally substituted benzene ring.

[0157]

15 [compound (I)-3]

Compound (I)-2 wherein

R is

- (1) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group,
- (2) a sulfamoylamino group, or
- 20 (3) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from

(a) a hydroxy group,

(b) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group,

(c) a sulfamoylamino group,

25 (d) a C₁₋₆ alkoxy-C₁₋₆ alkyl-carbonylamino group,

(e) a C₁₋₆ alkylsulfonylamino group, and

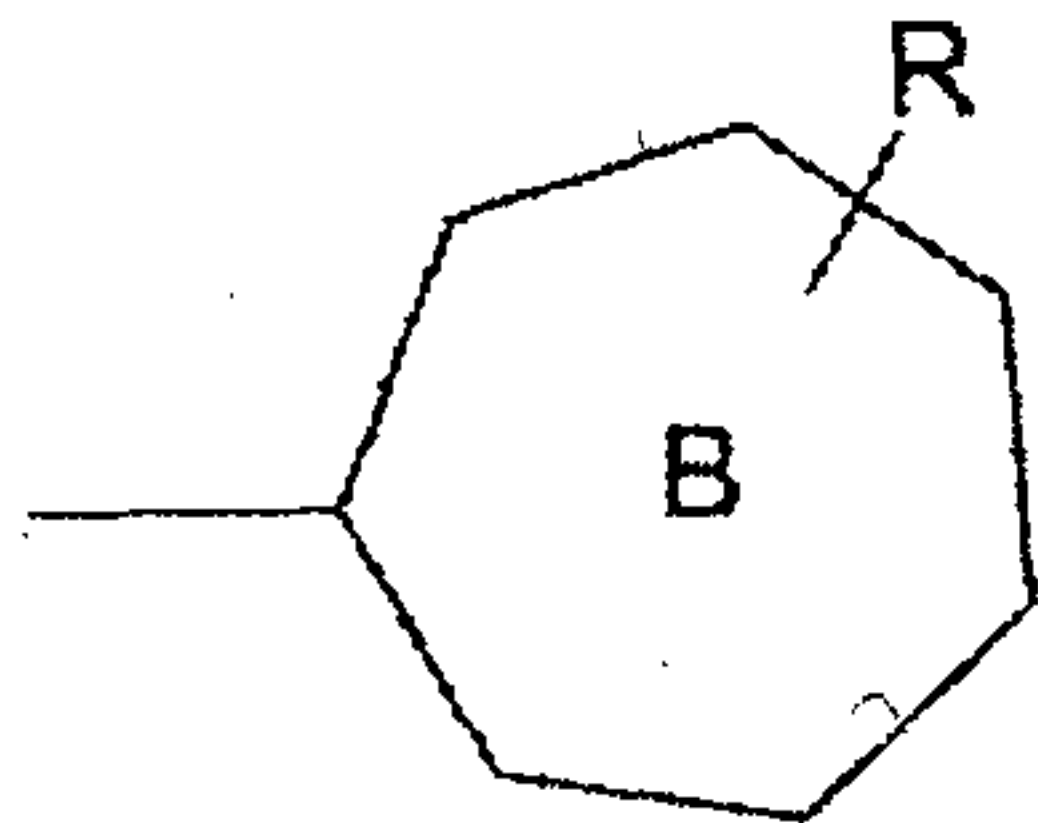
(f) 2-oxopyridin-1(2H)-yl optionally substituted by 1 to 3 substituents selected from a carboxy group and 5-oxo-4,5-dihydro-1,2,4-oxadiazoly.

30 [0158]

[compound (I)-4]

[0159]

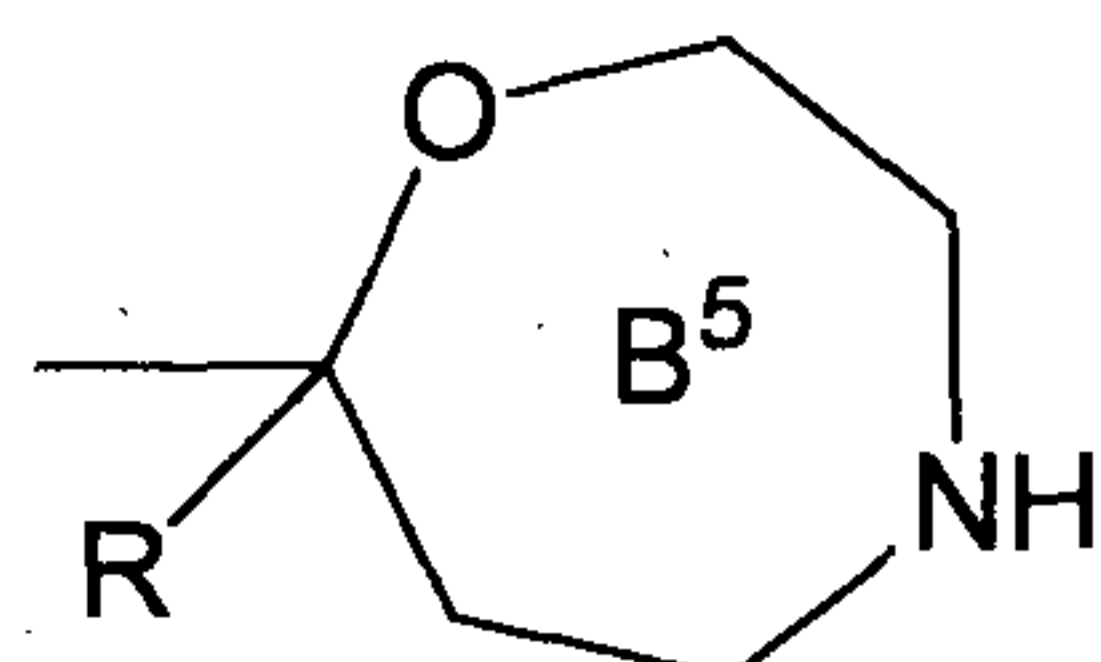
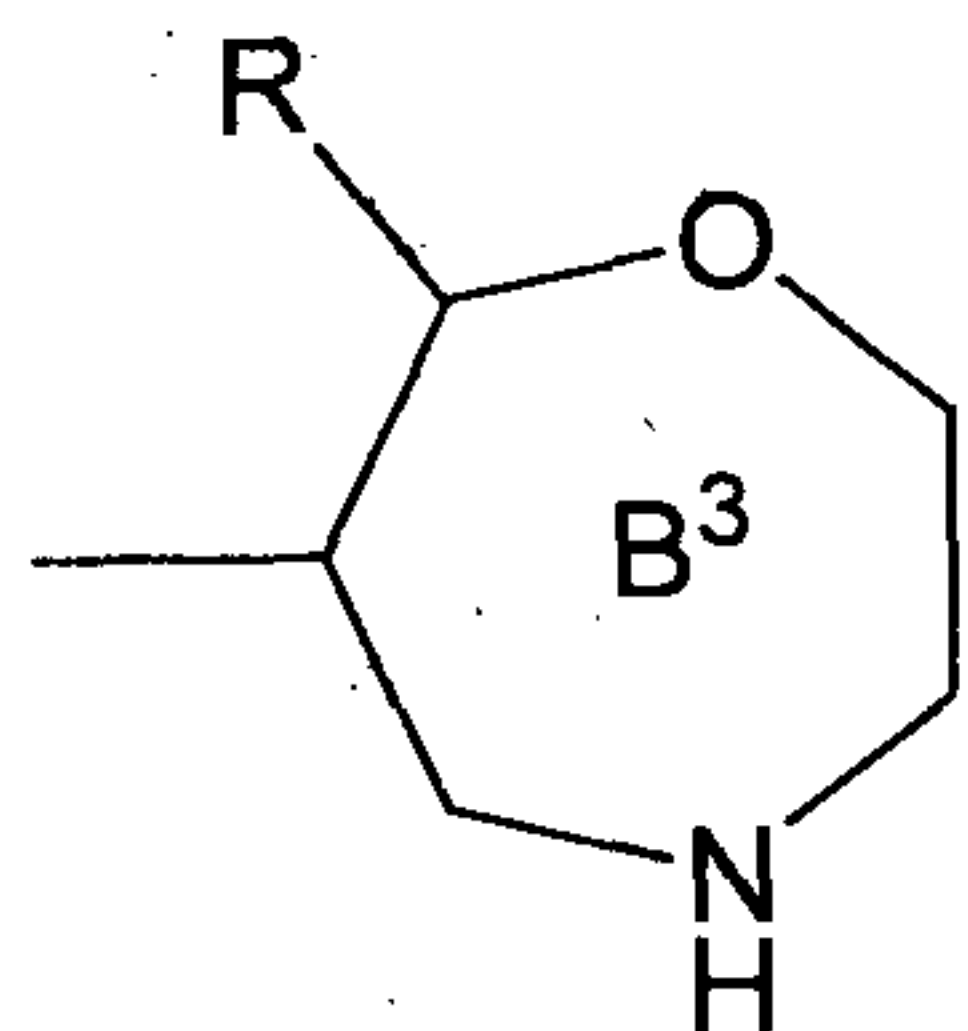
Compound (I)-2 or (I)-3 wherein the group represented by



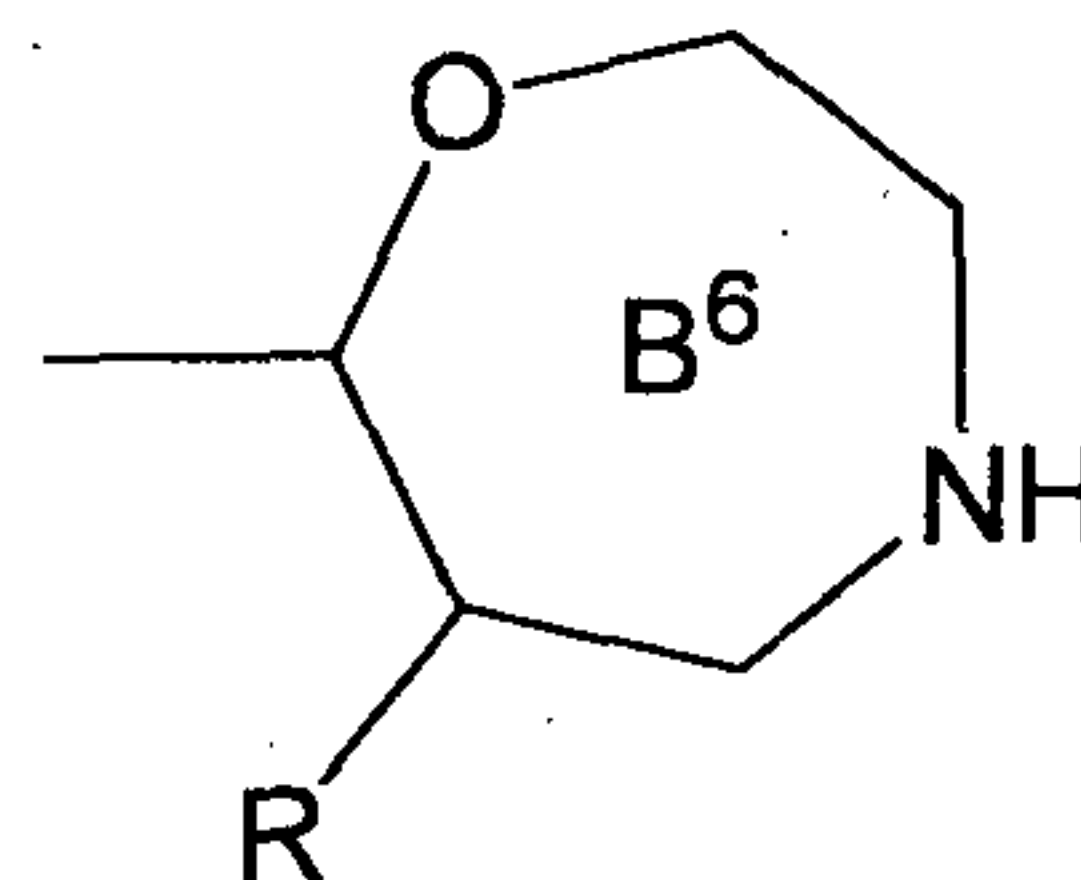
[0160]

is

[0161]



or



5

[0162]

wherein each symbol is as defined above.

[0163]

[compound (I)-5]

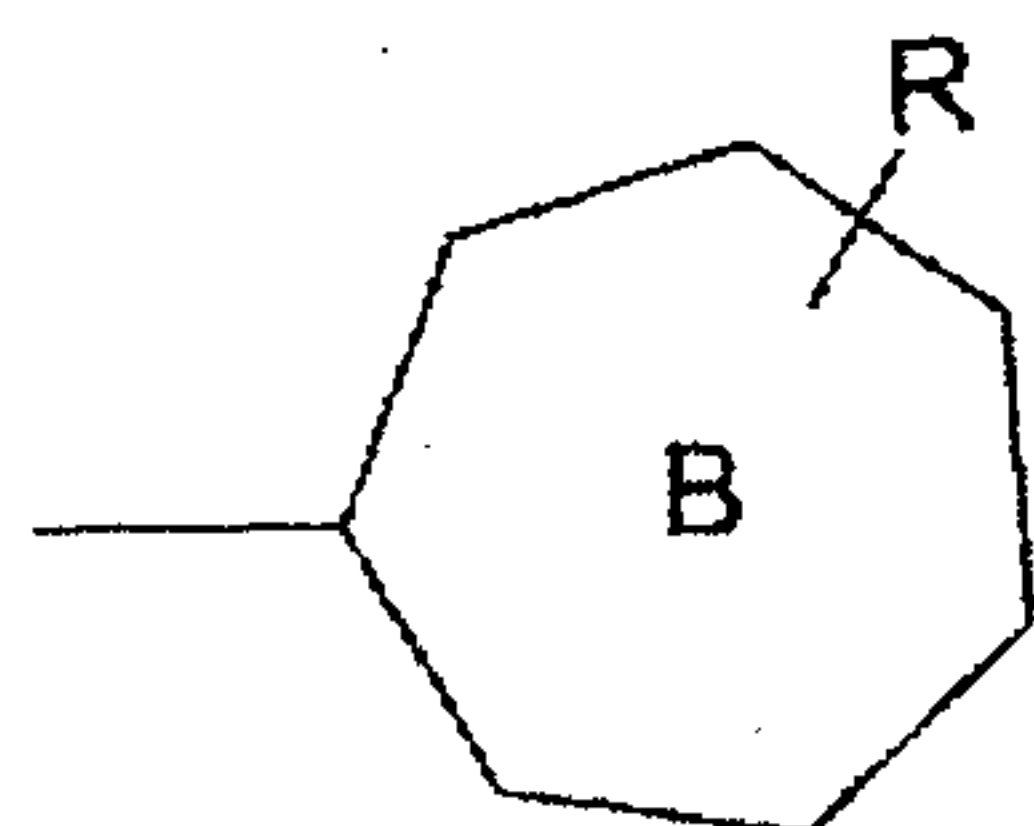
10

Compound (I) wherein

ring A is a benzene ring substituted by 2 substituents
selected from a fluorine atom and a chlorine atom,

[0164]

the group represented by

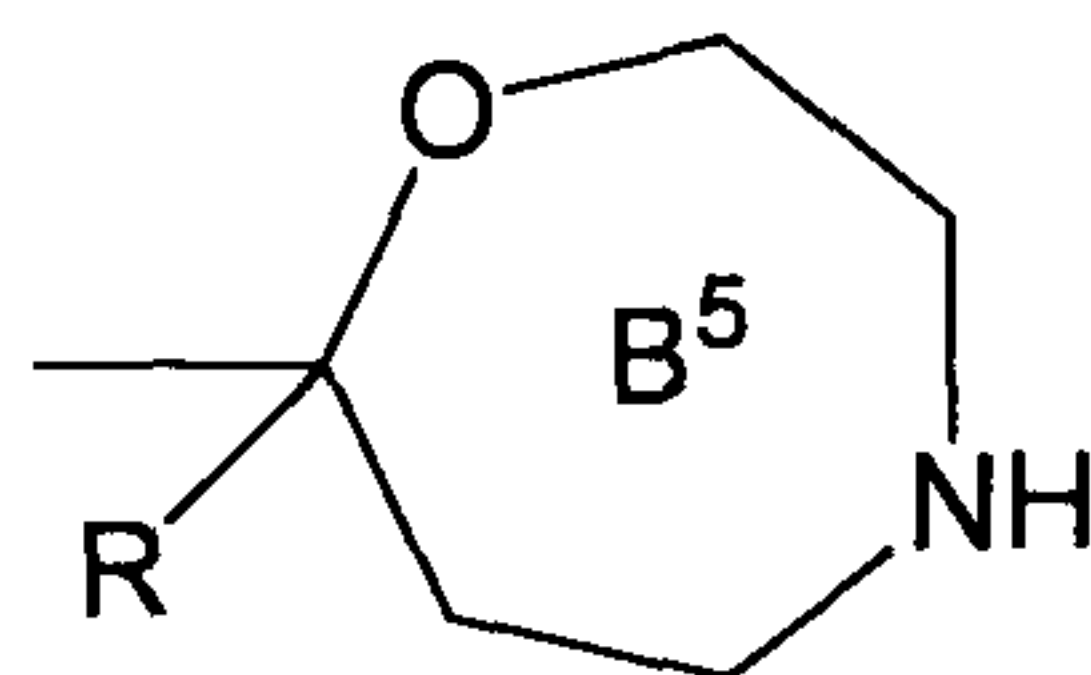
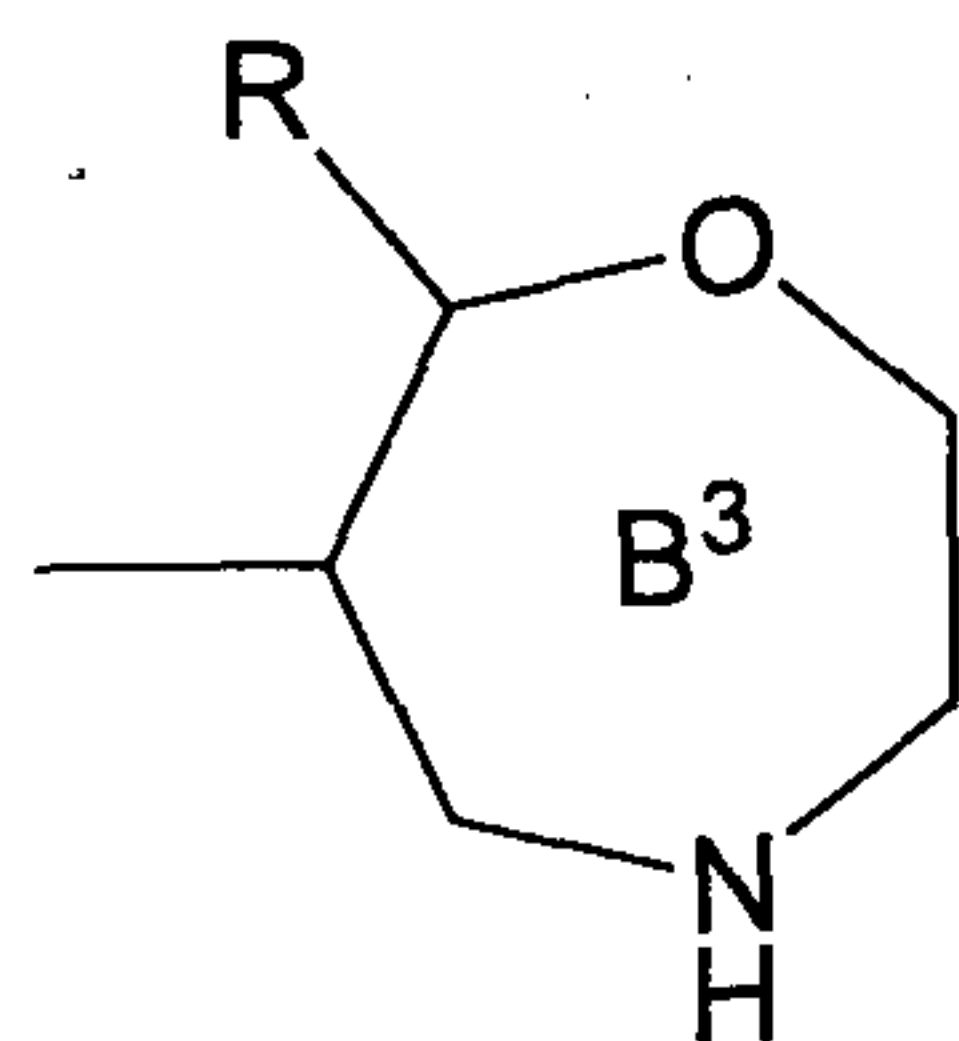


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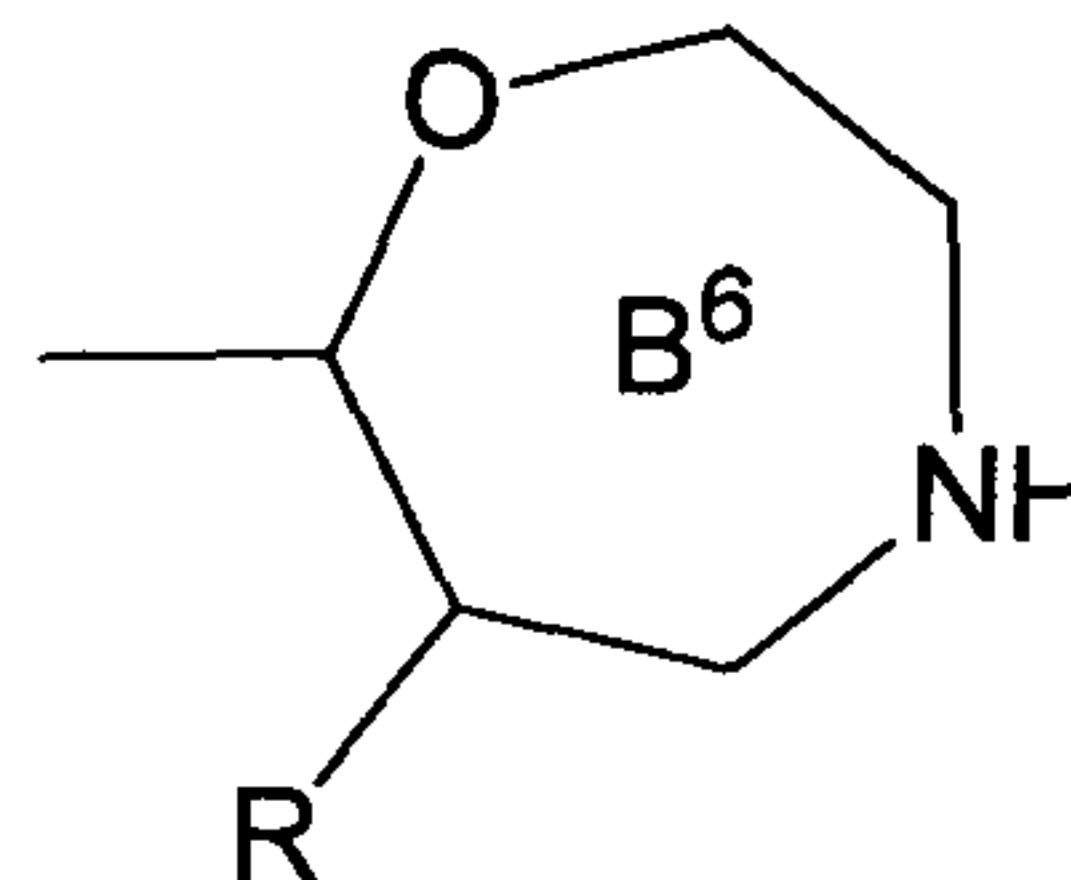
[0165]

is

[0166]



or



20

[0167]

wherein

R is

- (1) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group,
 - (2) a sulfamoylamino group, or
 - 5 (3) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from
 - (a) a hydroxy group,
 - (b) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group,
 - (c) a sulfamoylamino group,
 - 10 (d) a C₁₋₆ alkoxy-C₁₋₆ alkyl-carbonylamino group,
 - (e) a C₁₋₆ alkylsulfonylamino group, and
 - (f) 2-oxopyridin-1(2H)-yl optionally substituted by 1 to 3 substituents selected from a carboxy group and 5-oxo-4,5-dihydro-1,2,4-oxadiazolyl,
- 15 and other symbols are as defined above.

[0168]

In another embodiment, compound (I) is preferably a compound represented by the formula (I') or a salt thereof (hereinafter to be referred to as compound (I')).

20 [0169]

Preferable examples of compound (I') are the following compounds.

[compound (I')-1]

Compound (I') wherein

25 ring A is a benzene ring substituted by two halogen atoms,

R' is

- (1) a hydroxy group,
- (2) a C₁₋₆ alkoxy-carbonyl group,
- (3) a C₁₋₆ alkoxy group, or
- 30 (4) a C₁₋₆ alkyl group optionally substituted by 1 substituent selected from
 - (a) a halogen atom,
 - (b) a hydroxy group,
 - (c) a C₁₋₆ alkoxy group,
 - 35 (d) -S-R^{1a},

- (e) $-\text{SO}_2-\text{R}^{1a}$,
 (f) $-\text{N}(\text{R}^{1b})(\text{R}^{1c})$,
 (g) $-\text{NH}-\text{CO}-\text{R}^{1a}$,
 (h) $-\text{NH}-\text{CO}-\text{N}(\text{R}^{1b})(\text{R}^{1c})$,
 5 (i) $-\text{NH}-\text{SO}_2-\text{R}^{1a}$, and
 (j) $-\text{NH}-\text{SO}_2-\text{N}(\text{R}^{1b})(\text{R}^{1c})$

wherein R^{1a} is a C_{1-6} alkyl group, and R^{1b} and R^{1c} are each independently a hydrogen atom or a C_{1-6} alkyl group, and rings $\text{B}^1 - \text{B}^6$ are free of a substituent other than ring A and
 10 R' .

[compound (I')-1']

Compound (I') wherein

ring A is a benzene ring substituted by two halogen atoms,
 R' is

- 15 (1) a hydroxy group,
 (2) a C_{1-6} alkoxy-carbonyl group,
 (3) a C_{1-6} alkoxy group, or
 (4) a C_{1-6} alkyl group optionally substituted by 1 substituent
 selected from

- 20 (a) a halogen atom,
 (b) a hydroxy group,
 (c) a C_{1-6} alkoxy group,
 (d) $-\text{S}-\text{R}^{1a}$,
 (e) $-\text{SO}_2-\text{R}^{1a}$,
 25 (f) $-\text{N}(\text{R}^{1b})(\text{R}^{1c})$,
 (g) $-\text{NH}-\text{CO}-\text{R}^{1a}$,
 (h) $-\text{NH}-\text{CO}-\text{N}(\text{R}^{1b})(\text{R}^{1c})$,
 (i) $-\text{NH}-\text{SO}_2-\text{R}^{1a}$, and
 (j) $-\text{NH}-\text{SO}_2-\text{N}(\text{R}^{1b})(\text{R}^{1c})$

30 wherein R^{1a} is a C_{1-6} alkyl group, and R^{1b} and R^{1c} are each independently a hydrogen atom or a C_{1-6} alkyl group, and rings $\text{B}^1 - \text{B}^6$ are substituted by a hydroxy group or a C_{1-6} alkoxy group (preferably, methoxy) besides ring A and R' .

[0170]

35 [compound (I')-2]

Compound (I') wherein

ring A is an optionally substituted benzene ring [preferably, a benzene ring optionally substituted by 1 to 3 (preferably 1 or 2) halogen atoms (preferably, a fluorine atom, a chlorine atom)],

R' is

- (1) a hydroxy group,
- (2) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group (preferably, acetylamino),
- 10 (3) a sulfamoylamino group,
- (4) a C₁₋₆ alkoxy group (preferably, methoxy, ethoxy), or
- (5) a C₁₋₆ alkyl group (preferably, methyl, ethyl) optionally substituted by 1 to 4 (preferably 1 to 3, more preferably 1 or 2) substituents selected from
- 15 (a) a hydroxy group,
- (b) a C₁₋₆ alkoxy group (preferably, methoxy),
- (c) -SO₂-R^{1a},
- (d) -NH-CO-R^{1a},
- (e) -NH-CO-N(R^{1b})(R^{1c}),
- 20 (f) -NH-SO₂-R^{1a},
- (g) -NH-SO₂-N(R^{1b})(R^{1c})

wherein

R^{1a} is a C₁₋₆ alkyl group (preferably, methyl) optionally substituted by 1 to 3 (preferably, 1) C₁₋₆ alkoxy groups

25 (preferably, methoxy, ethoxy, isopropoxy), and

R^{1b} and R^{1c} are each independently a hydrogen atom or a C₁₋₆ alkyl group (preferably, a hydrogen atom), and

(h) a nonaromatic heterocyclic group (preferably, dihydropyridyl (preferably, 1,2-dihydropyridin-1-yl)) optionally substituted by 1 to 3 (preferably, 1 or 2) substituents selected from

(i) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

35 (ii) a carboxy group, and

(iii) an oxo group, and
rings B¹ - B⁶ are free of a substituent other than ring A and R'.

[compound (I')-2']

5 Compound (I') wherein

ring A is an optionally substituted benzene ring [preferably, a benzene ring optionally substituted by 1 to 3 (preferably 1 or 2) halogen atoms (preferably, a fluorine atom, a chlorine atom)],

10 R' is

(1) a hydroxy group,

(2) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group (preferably, acetylamino),

(3) a sulfamoylamino group,

15 (4) a C₁₋₆ alkoxy group (preferably, methoxy, ethoxy), or

(5) a C₁₋₆ alkyl group (preferably, methyl, ethyl) optionally substituted by 1 to 4 (preferably 1 to 3, more preferably 1 or 2) substituents selected from

(a) a hydroxy group,

20 (b) a C₁₋₆ alkoxy group (preferably, methoxy),

(c) -SO₂-R^{1a},

(d) -NH-CO-R^{1a},

(e) -NH-CO-N(R^{1b})(R^{1c}),

(f) -NH-SO₂-R^{1a},

25 (g) -NH-SO₂-N(R^{1b})(R^{1c})

wherein

R^{1a} is a C₁₋₆ alkyl group (preferably, methyl) optionally substituted by 1 to 3 (preferably, 1) C₁₋₆ alkoxy groups (preferably, methoxy, ethoxy, isopropoxy), and

30 R^{1b} and R^{1c} are each independently a hydrogen atom or a C₁₋₆ alkyl group (preferably, a hydrogen atom), and

(h) a nonaromatic heterocyclic group (preferably, dihydropyridyl (preferably, 1,2-dihydropyridin-1-yl)) optionally substituted by 1 to 3 (preferably, 1 or 2)

35 substituents selected from

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(i) a nonaromatic heterocyclic group (preferably, dihydrooxadiazolyl (preferably, 4,5-dihydro-1,2,4-oxadiazol-3-yl)) optionally substituted by an oxo group,

(ii) a carboxy group, and

5 (iii) an oxo group, and

rings B¹ - B⁶ are substituted by a hydroxy group or a C₁₋₆ alkoxy group (preferably, methoxy) besides ring A and R'.

[0171]

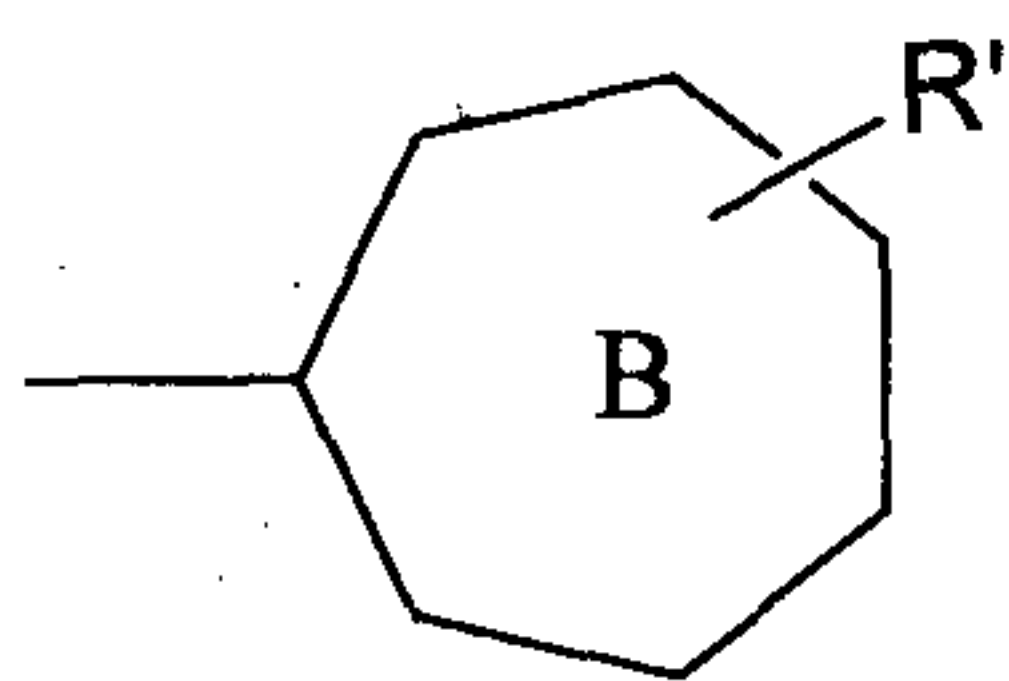
[compound (I')-3]

10 Compound (I') wherein

ring A is a benzene ring substituted by 2 substituents selected from a fluorine atom and a chlorine atom,

[0172]

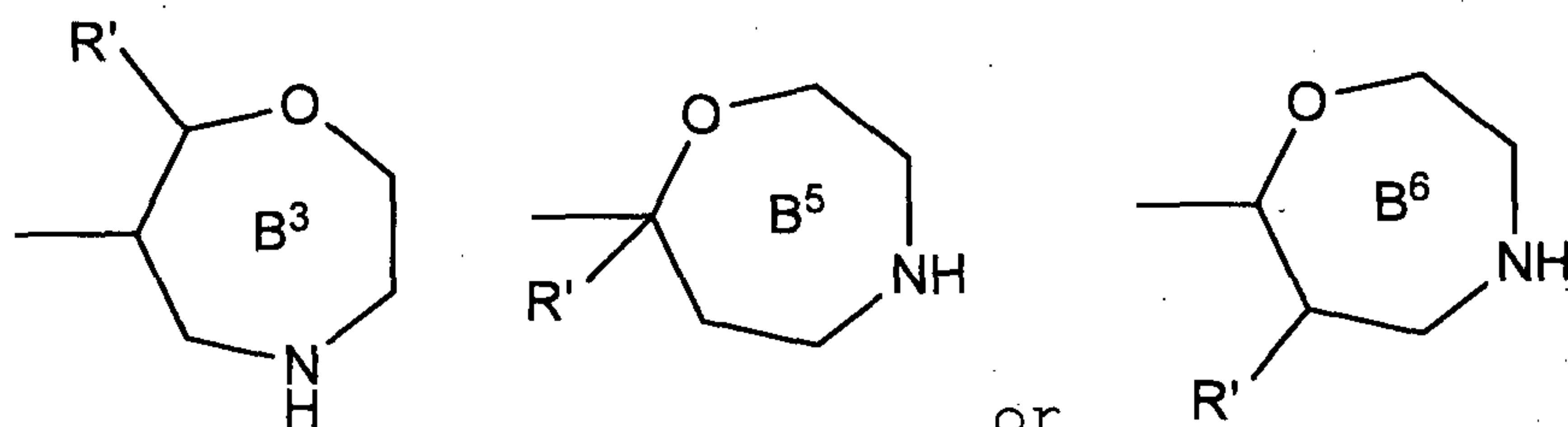
the group represented by



[0173]

is

[0174]



20 [0175]

wherein

R' is

(1) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group,

(2) a sulfamoylamino group, or

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

(a) a hydroxy group,

(b) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group,

(c) a sulfamoylamino group,

(d) a C₁₋₆ alkoxy-C₁₋₆ alkyl-carbonylamino group,

(e) a C₁₋₆ alkylsulfonylamino group, and

(f) 2-oxopyridin-1(2H)-yl optionally substituted by 1

5 to 3 substituents selected from a carboxy group and 5-oxo-4,5-dihydro-1,2,4-oxadiazolyl, and other symbols are as defined above.

[0176]

When compound (I) is a salt, examples of the salt include
10 salt with inorganic base, ammonium salt, salt with organic base, salt with inorganic acid, salt with organic acid, salt with basic or acidic amino acid and the like.

[0177]

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

[0178]

20 Preferable examples of the salt with organic base include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like.

[0179]

25 Preferable examples of the salt with inorganic acid include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like.

[0180]

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

[0181]

35 Preferable examples of the salt with basic amino acid

include salts with arginine, lysine, ornithine and the like.

[0182]

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

5 [0183]

Of these salts, pharmaceutically acceptable salts are preferable. When the compound has a basic functional group, preferable examples of the pharmaceutically acceptable salt include salts with inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like salts with inorganic acids, or organic acids such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid and the like.

15 When the compound has an acidic functional group, preferable examples of the pharmaceutically acceptable salt include inorganic salts such as alkali metal salts (e.g., sodium salt, potassium salt etc.), alkaline earth metal salts (e.g., calcium salt, magnesium salt, barium salt etc.) and the like, ammonium salt and the like.

[0184]

Compound (I) encompasses solvates (e.g., hydrate) and non-solvates. In addition, compound (I) may be labeled with an isotope (e.g., ^3H , ^{11}C , ^{14}C , ^{18}F , ^{35}S , ^{125}I and the like) and the like. Furthermore, a deuterium converter wherein ^1H is converted to $^2\text{H}(\text{D})$ is also encompassed in compound (I).

[0185]

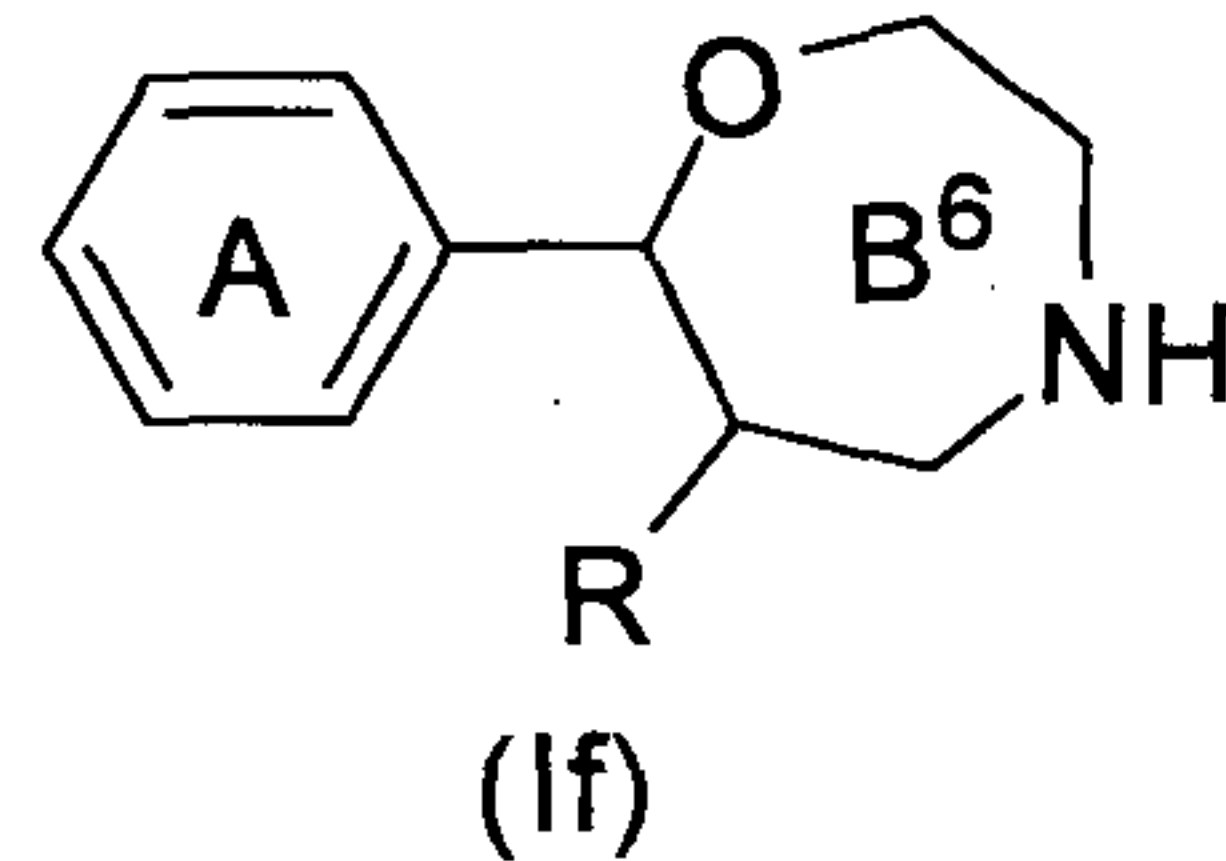
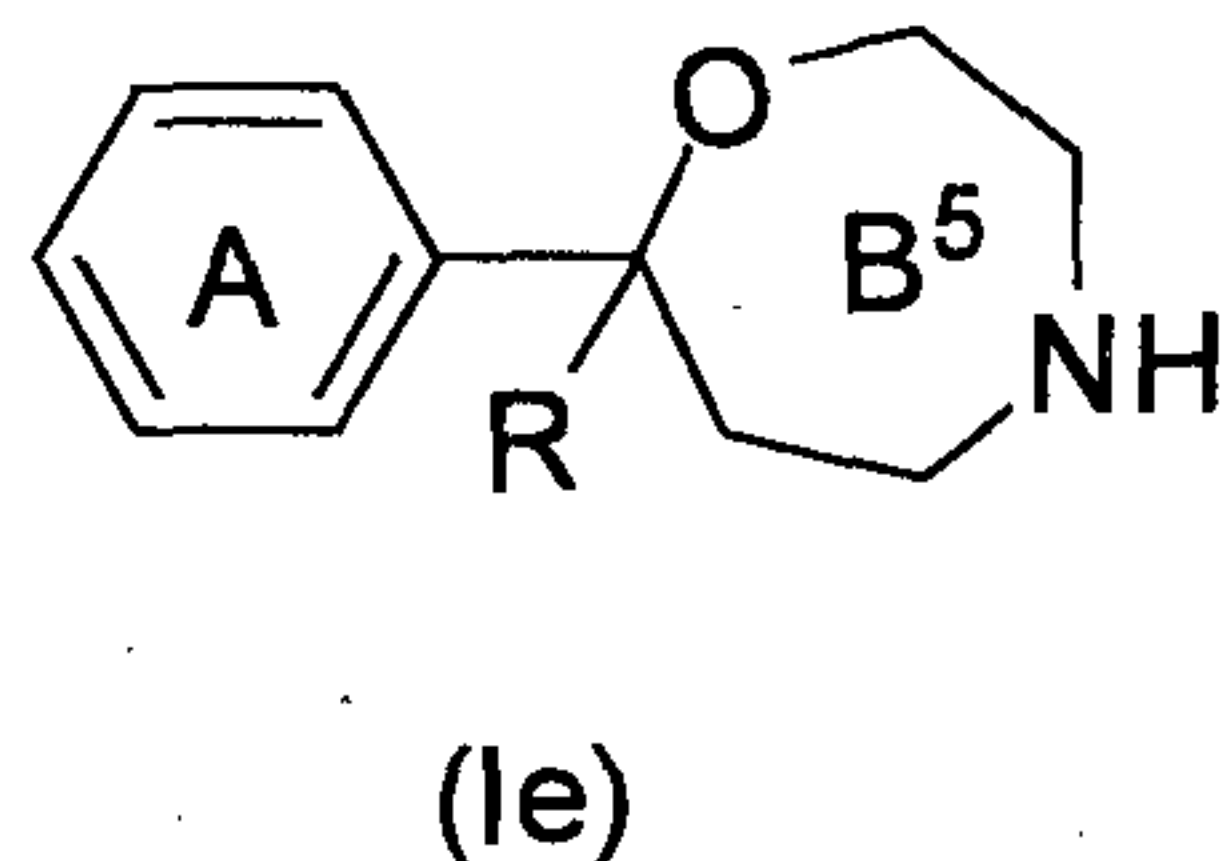
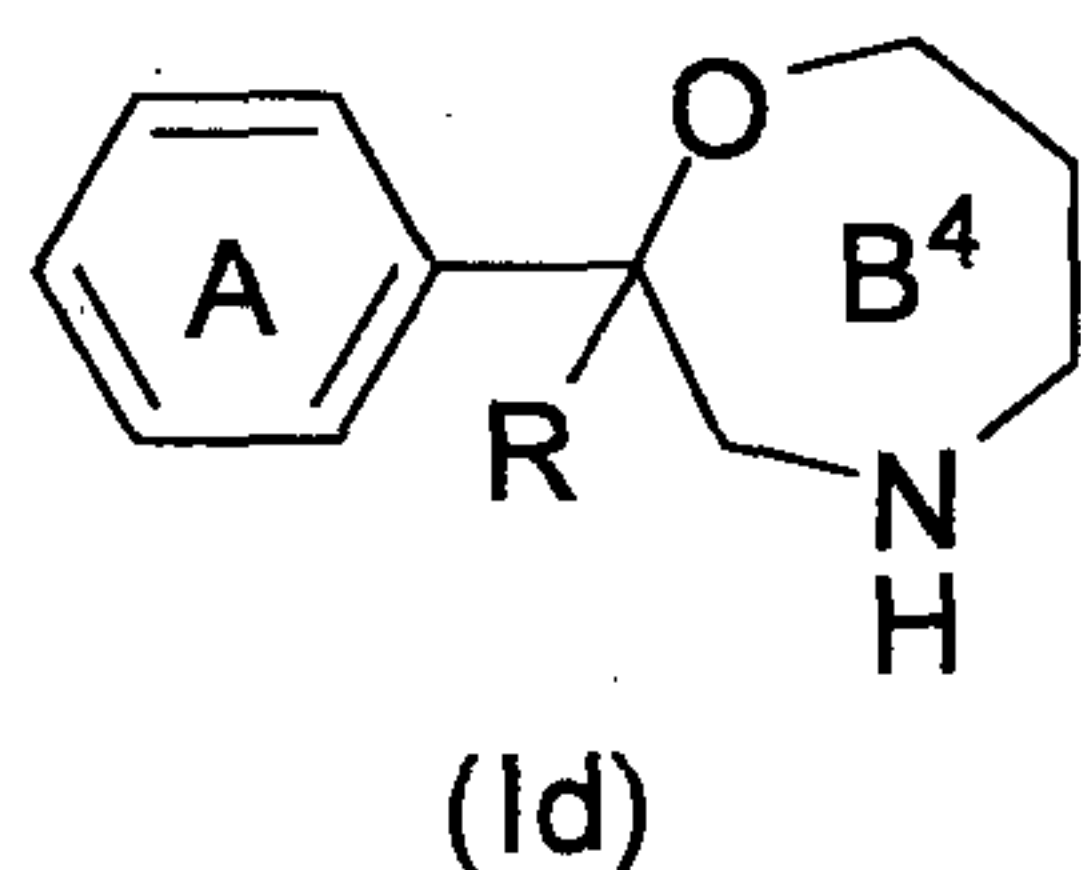
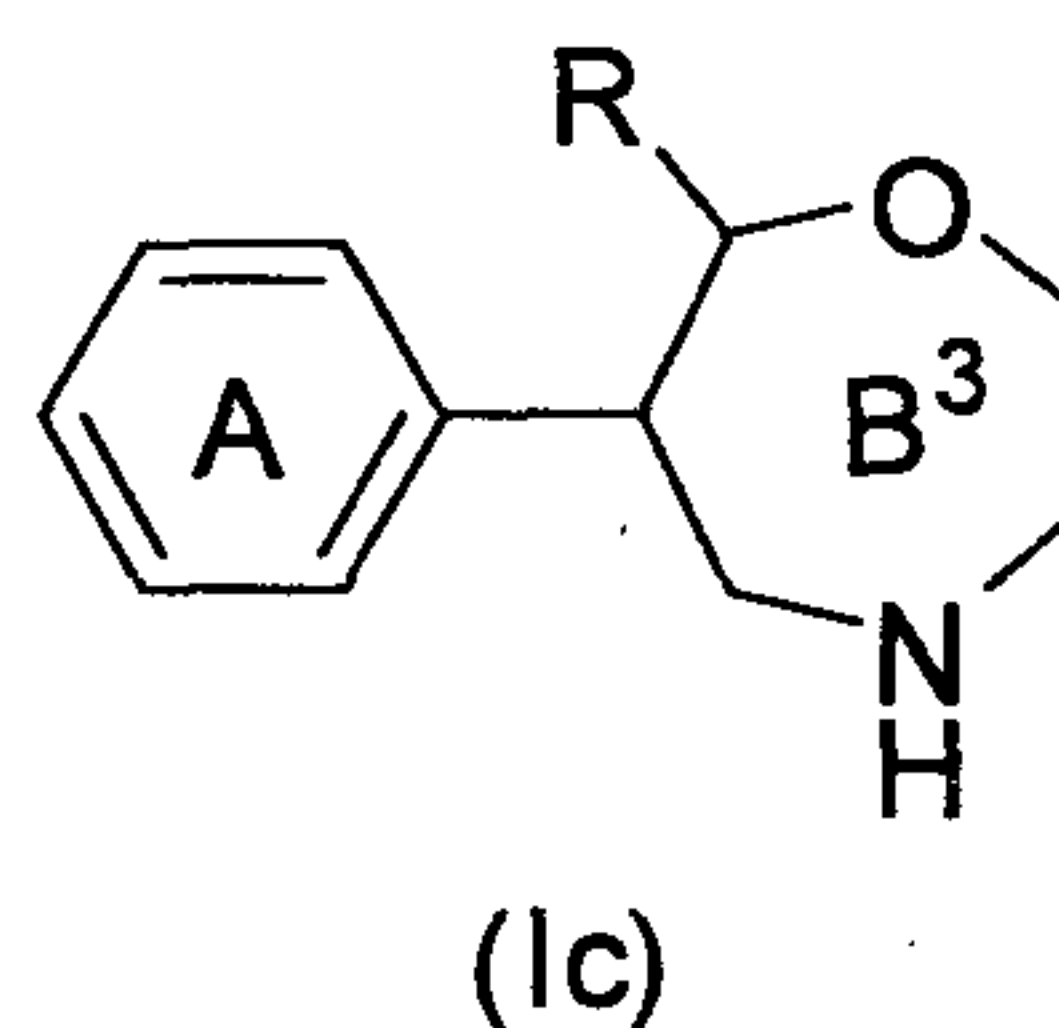
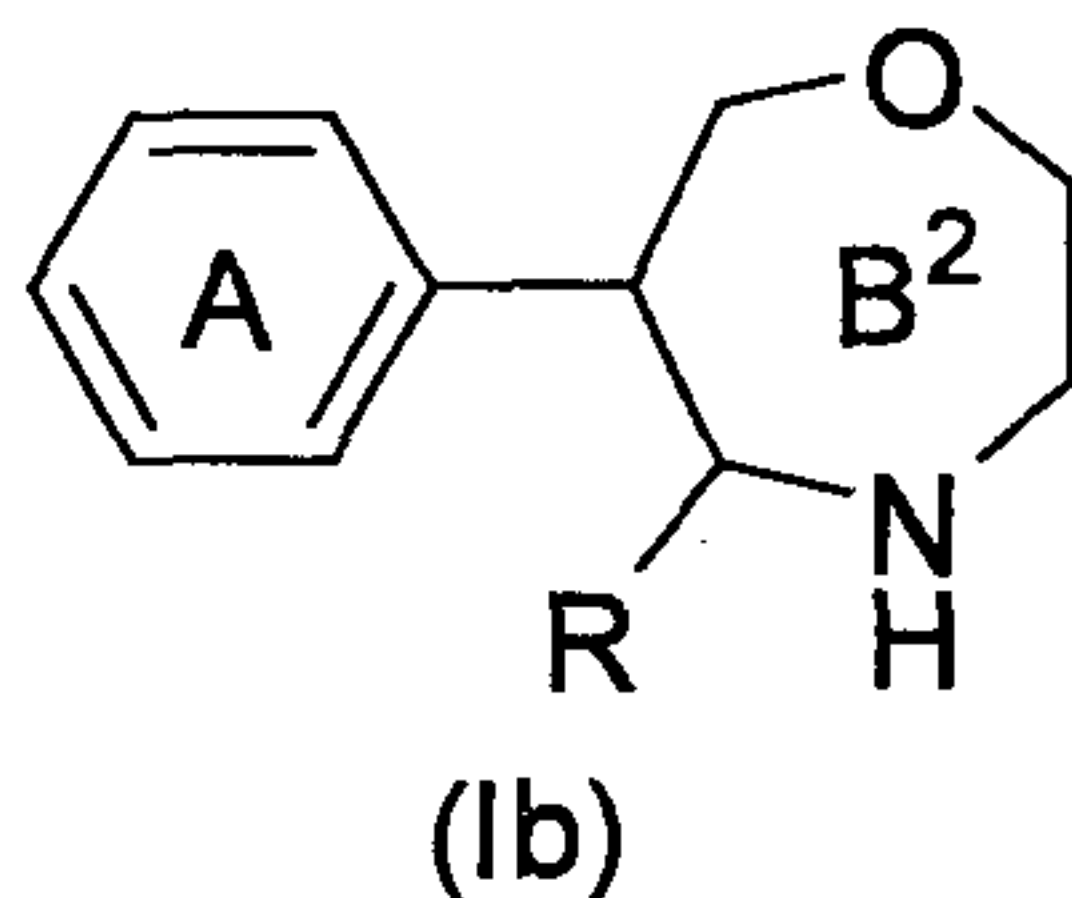
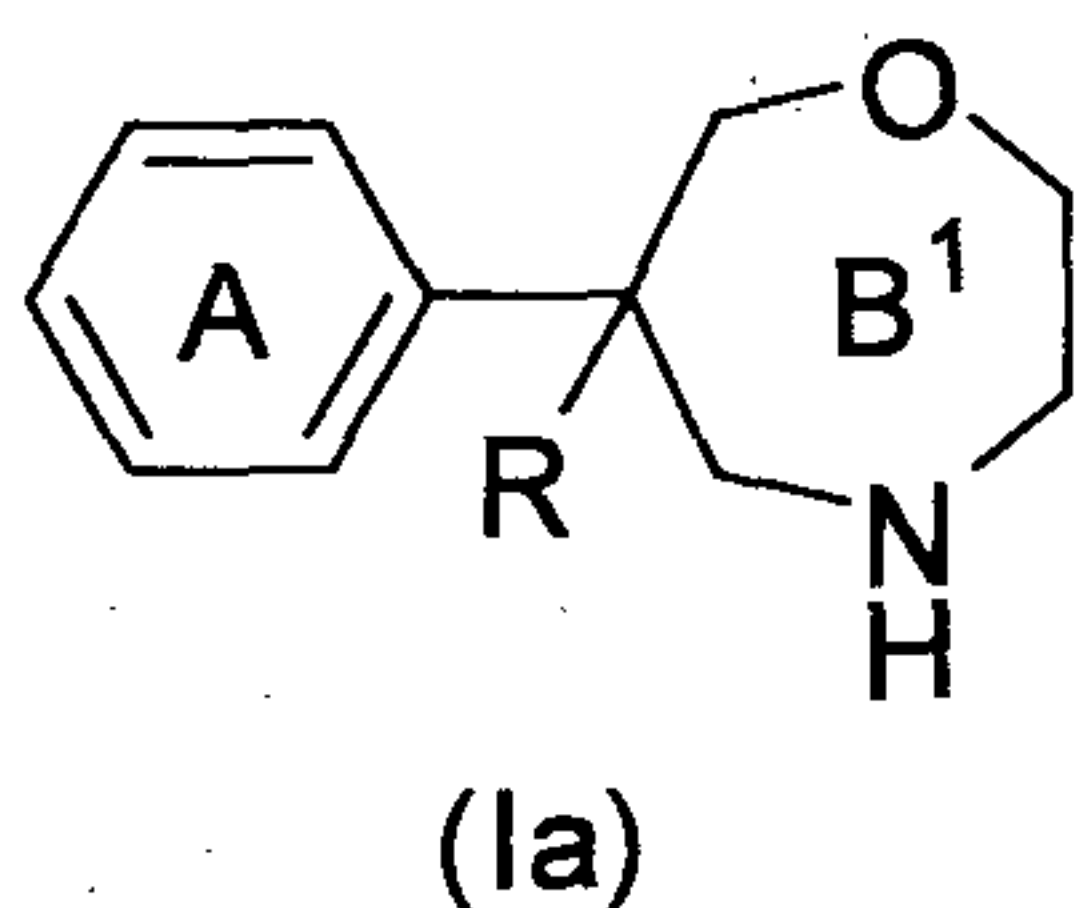
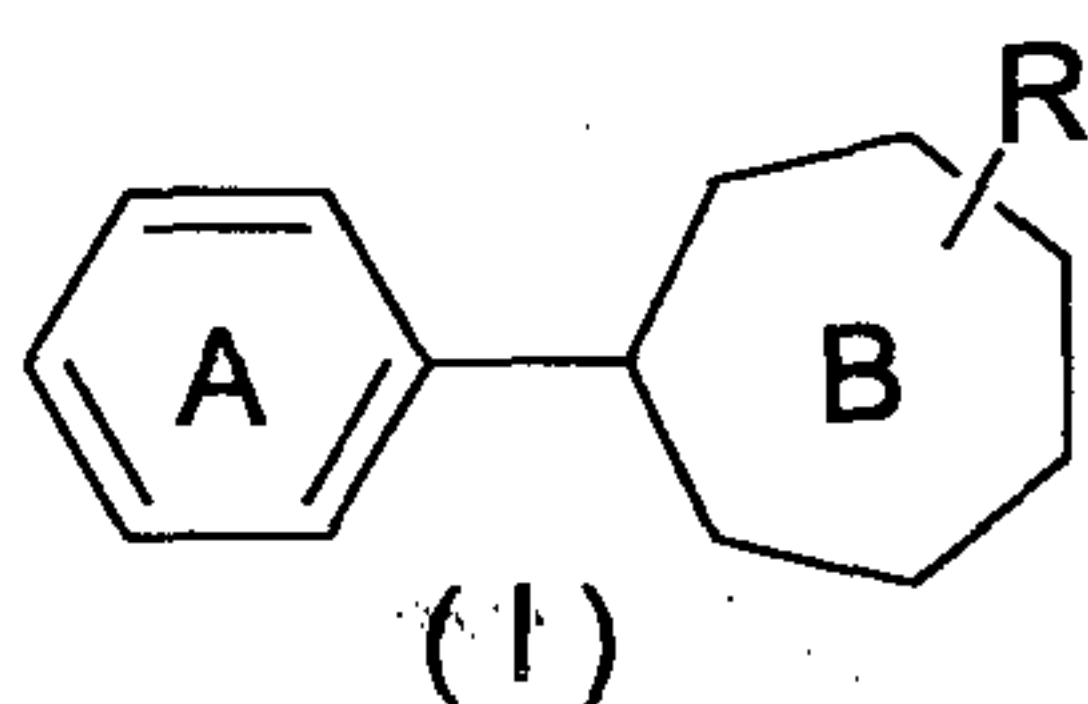
When compound (I) of the present invention has an asymmetric center, isomers such as enantiomer, diastereomer and the like may be present. Such isomers and a mixture thereof are all encompassed in the scope of the present invention. When an isomer due to conformation or tautomerism is present, such isomer and a mixture thereof are also encompassed in compound (I) of the present invention.

35 [0186]

Next, the preparation of compound (I) is explained.

Compound (I) is constituted by the following compounds (Ia)-(If) based on the positions of ring A and substituent R. Hereinafter, the preparation of compounds (Ia)-(If) are explained in the following. The compound used for preparation of compounds (Ia)-(If) may be in the form of a salt, and examples of the salt include those similar to the salts of compound (I).

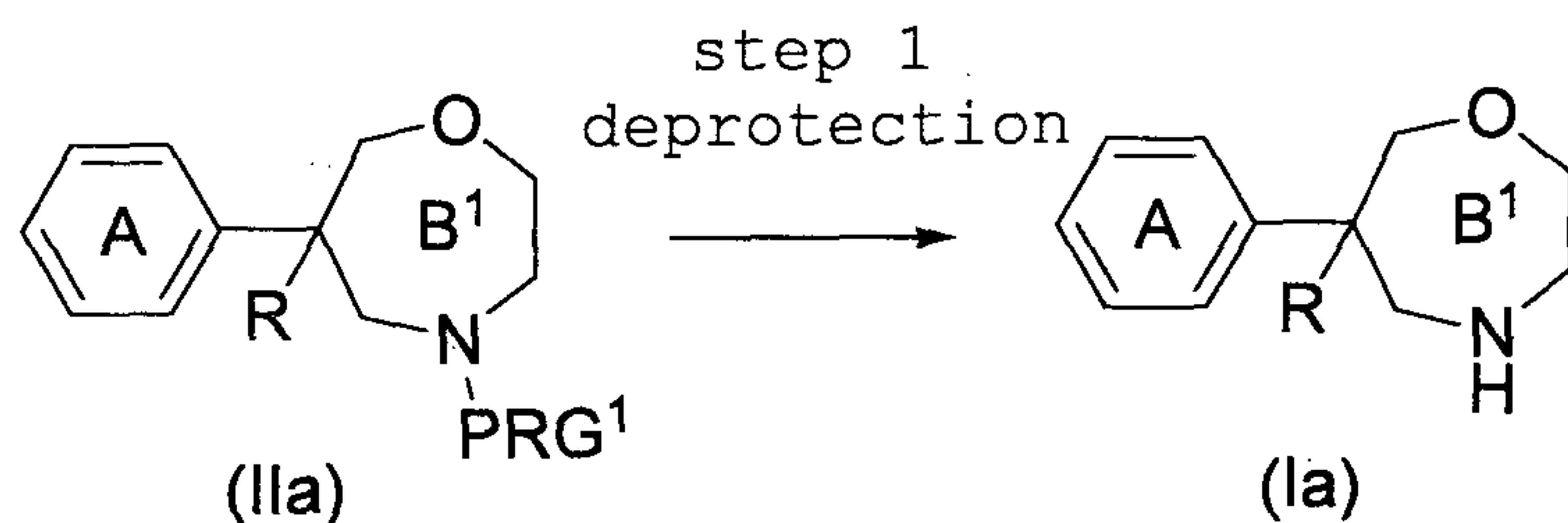
[0187]



[0188]

[Preparation of compound (Ia)]

[0189]



15 [0190]

wherein PRG¹ is a protecting group, and other symbols are each as defined above.

In Step 1, compound (Ia) can be prepared, for example, by

deprotecting compound (IIa). Examples of the "protecting group" for PRG¹ include those described in Greene's protective groups in organic synthesis 4th edition (Wiley-International Publication). Preferred are carbamate protecting groups such as tert-butoxycarbonyl (Boc) group, benzyloxycarbonyl (Cbz) group, 9-fluorenylmethyloxycarbonyl (Fmoc) group and the like; amide protecting groups such as acetyl (Ac) group, trifluoroacetyl group and the like; and alkyl protecting groups such as benzyl (Bzl) group, methyl group and the like.

10 The deprotection of Step 1 is performed, for example, according to the method described in the above-mentioned Greene's protective groups in organic synthesis 4th edition. For example, a treatment with an acid such as hydrochloric acid, trifluoroacetic acid and the like, and the like is

15 preferably employed for a tert-butoxycarbonyl group, and a catalytic reduction using a metal catalyst such as palladium and the like, or a method using an alkyl chloroformate and the like is preferably employed for a benzyl group. When protecting group is a tert-butoxycarbonyl group, the "acid"

20 used for the acid treatment is preferably an organic solvent solution containing hydrogen chloride, hydrochloric acid or trifluoroacetic acid. The "organic solvent" is preferably, for example, an alcohol solvent such as ethanol, methanol and the like, or an ester solvent such as ethyl acetate and the like.

25 The amount of the "acid" to be used is generally 1 equivalent to a solvent amount, preferably 1 equivalent to 100 equivalents, relative to compound (IIa). The reaction solvent is preferably, for example, an alcohol solvent such as ethanol, methanol and the like, or an ester solvent such as

30 ethyl acetate and the like. The reaction temperature is generally -78°C to 200°C, preferably 0°C to 50°C. The reaction time is generally 1 min to 48 hr, preferably 5 min to 24 hr.

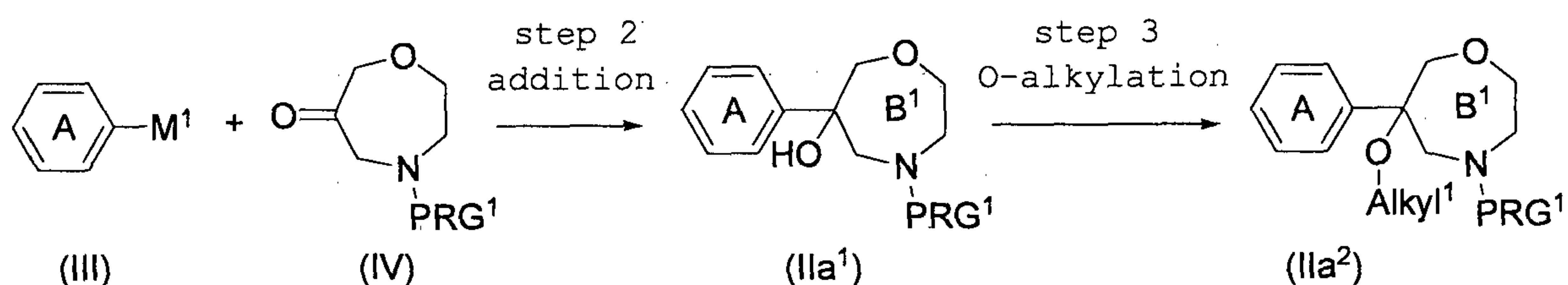
[0191]

Compound (IIa¹) (R is -OH) and compound (IIa²) (R is -O-Alkyl¹) which are encompassed in compound (IIa) can be

35

prepared, for example, according to the following method.

[0192]



[0193]

5 wherein M¹ is a metal or a salt thereof, Alkyl¹ is a C₁₋₆ alkyl group optionally having substituent(s), and other symbols are each as defined above.

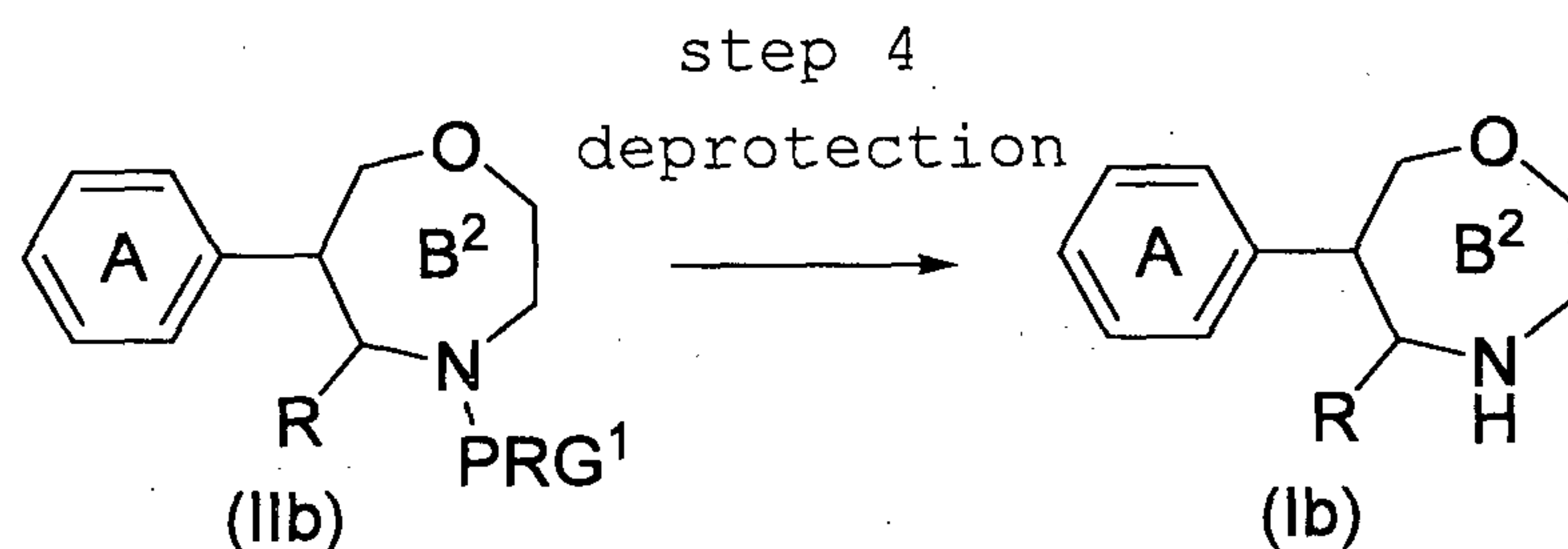
In Step 2, compound (IIa¹) (R is -OH) can be prepared, for example, by subjecting compound (IV) (PRG¹ is -Boc) described in WO 2004/074291 to an addition reaction with
 10 compound (III). "M¹" of compound (III) is preferable an alkali metal, an alkaline earth metal or a salt thereof, more preferable lithium or a halogenated magnesium.

In Step 3, the obtained compound (IIa¹) can be converted
 15 to compound (IIa²) (R is -O-Alkyl¹) by introduction of an alkyl group. The "O-alkylation" can be performed, for example, according to the method described in Tetrahedron Lett., 30, 641 (1989).

[0194]

20 [Preparation of Compound (Ib)]

[0195]



[0196]

wherein each symbol is as defined above.

25 In Step 4, compound (Ib) can be prepared, for example, by deprotecting compound (IIb). Examples of the "protecting group" for PRG¹ include those similar to the protecting group exemplified in Step 1. Among them, tert-butoxycarbonyl (Boc)

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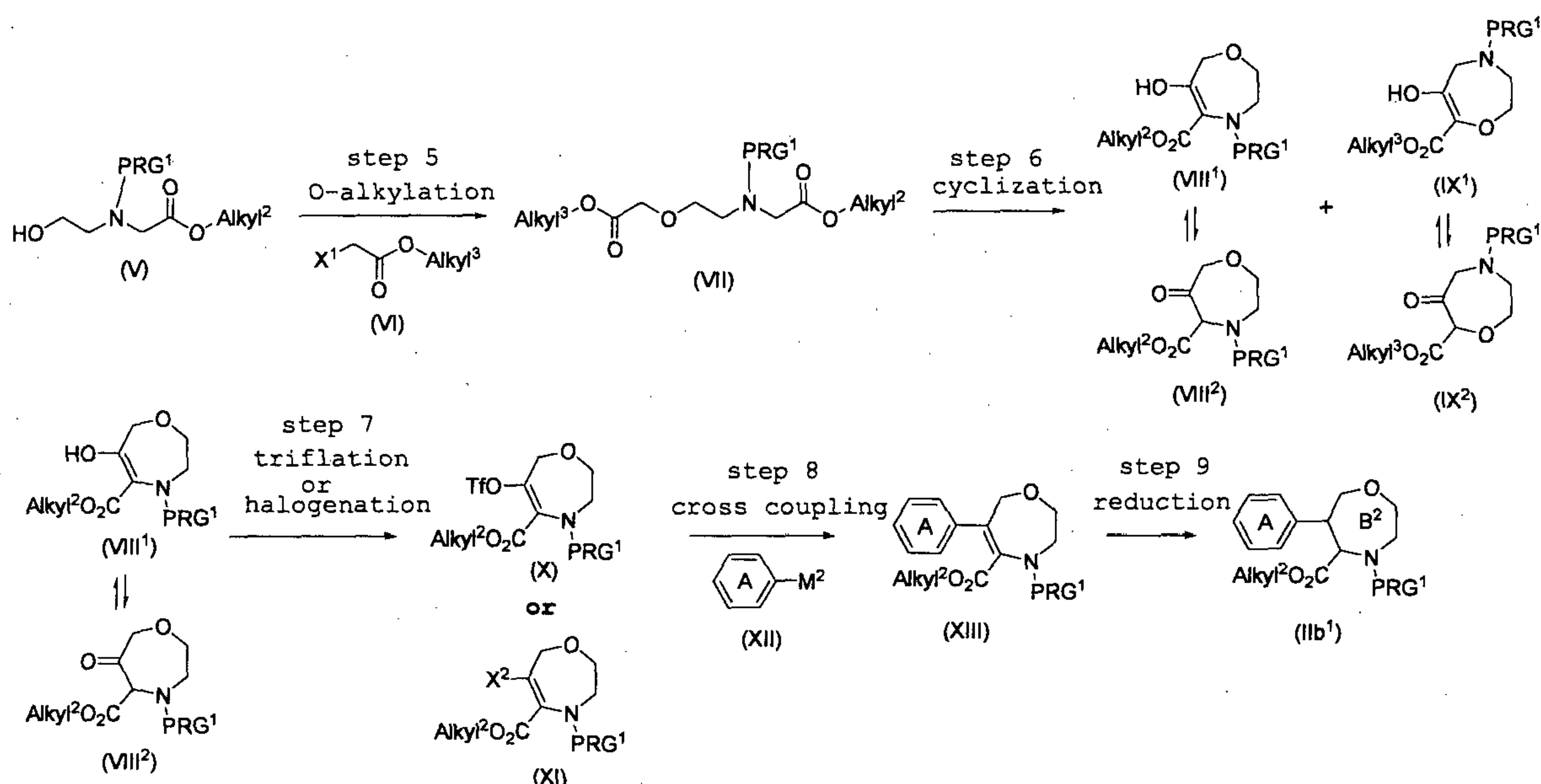
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group and the like are preferable. Step 4 can be performed under the same reaction conditions as in Step 1 or reaction conditions similar thereto.

[0197]

- 5 Compound (IIb¹) (R is -CO₂Alkyl²) encompassed in compound (IIb) can be prepared, for example, according to the following method.

[0198]



10 [0199]

wherein Alkyl² and Alkyl³ are each a C₁₋₆ alkyl group, X¹ and X² are each a halogen atom, Tf is a trifluoromethanesulfonyl group, M² is a metal or a derivative thereof, and other symbols are each as defined above.

15 [0200]

In Step 5, compound (VII) can be prepared by alkylating the hydroxyl group of compound (V) with compound (VI). The step may be performed in the presence of a base. Examples of the "base" include

- 20 1) strong bases such as hydrides of an alkali metal or alkaline earth metal (e.g., lithium hydride, sodium hydride, potassium hydride, calcium hydride and the like), amides of an alkali metal or alkaline earth metal (e.g., lithium amide, sodium amide, lithium diisopropylamide, lithium

dicyclohexylamide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, potassium hexamethyldisilazide and the like), C₁₋₆ alkoxides of an alkali metal or alkaline earth metal (e.g., sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium tert-butoxide and the like) and the like;
2) inorganic bases such as hydroxides of an alkali metal or alkaline earth metal (e.g., sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide and the like), carbonates of an alkali metal or alkaline earth metal (e.g., sodium carbonate, potassium carbonate, cesium carbonate and the like), hydrogencarbonates of an alkali metal or alkaline earth metal (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate and the like) and the like; and
3) organic bases such as amines such as triethylamine, diisopropylethylamine, N-methylmorpholine and the like; amidines such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DBN (1,5-diazabicyclo[4.3.0]non-5-ene) and the like; basic heterocyclic compounds such as pyridine, dimethylaminopyridine, imidazole, 2,6-lutidine and the like, and the like
and the like. Among them, a hydride of an alkali metal or alkaline earth metal (e.g. sodium hydride and the like) is preferable.

[0201]

In Step 6, compounds (VIII¹) and (VIII²) can be prepared by subjecting compound (VII) to cyclization. Compounds (VIII¹) and (VIII²) are in the keto-enol tautomer relationship, and are present in the form of a mixture thereof or isomer of either of them. The step can be performed by a general Dieckmann condensation, for example, the method described in Helvetica Chimica Acta, 90, 1006-1027 (2007). While byproducts (IX¹) and (IX²) (which are also keto-enol tautomers, like the above) may be prepared in this step, they can be removed by a purification method such as silica gel column chromatography, recrystallization and the like.

[0202]

In Step 7, compound (X) or (XI) can be prepared by triflating or halogenating compounds (VIII¹) and (VIII²). The "triflation" can be performed, for example, according to the method described in Comprehensive Organic Functional Group Transformations II (Elsevier Pergamon), vol.2, 633-634. The "halogenation" can be performed, for example, according to the method described in Journal of the American Chemical Society, 65, 2208 (1943). The "halogen" of the "halogenation" is preferably chlorine, bromine or iodine.

[0203]

In Step 8, compound (XIII) can be prepared by subjecting compound (X) or (XI) to cross coupling with compound (XII). The step can be performed, for example, according to the Suzuki-Miyaura coupling reaction described in Tetrahedron, 58, 9633-9695 (2002), the Stille coupling reaction described in for example, Organic Reactions, 50, 1-652 (1997), and the like. Compound (XII) is an organic boronic acid compound ($M^2 = -B(OH)_2$ or an ester thereof) when employing the Suzuki-Miyaura coupling reaction, or an organotin compound ($M^2 =$ trialkylstannyl) when employing the Stille coupling reaction. The step is preferably performed by the Suzuki-Miyaura coupling reaction.

[0204]

In Step 9, compound (IIb¹) can be prepared by reducing compound (XIII). The "reduction" can be performed, for example, according to a method using a metal hydride such as sodium borohydride, lithium borohydride, zinc borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, cyanolithium borohydride, dibutylaluminum hydride, aluminum hydride, lithium aluminum hydride, borane complex (borane-THF complex etc.), catecholborane and the like; a catalytic reduction using a transition metal catalyst such as palladium, platinum, rhodium, Raney-nickel and the like; or a method using a metal such as magnesium and the like. Among them, a

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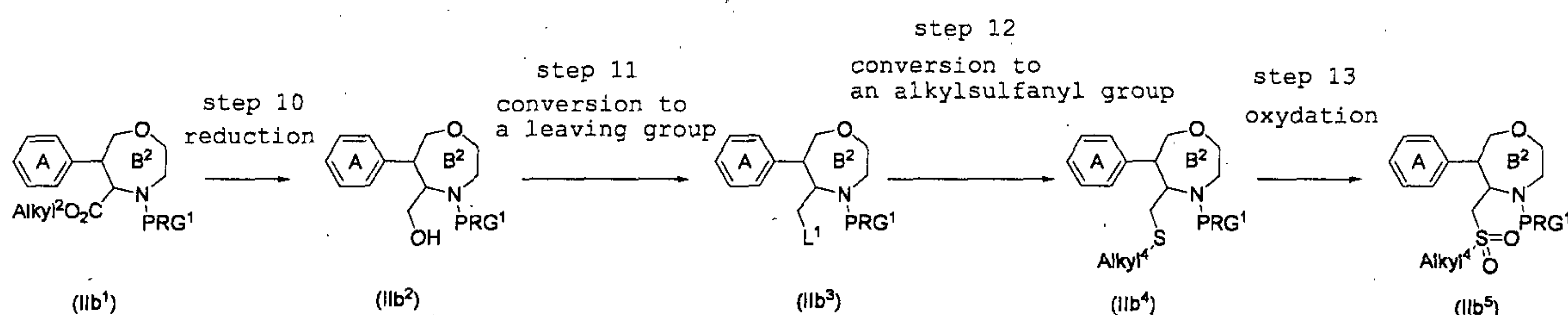
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method using sodium borohydride is preferable. The product obtained in this step may be a diastereomer mixture due to stereoisomerism, and it can be separated and purified by silica gel column chromatography, recrystallization and the like, as necessary.

[0205]

Compounds (IIb²) (R is -CH₂OH), (IIb³) (R is -CH₂L¹), (IIb⁴) (R is -CH₂S-Alkyl⁴) and (IIb⁵) (R is -CH₂SO₂-Alkyl⁴) which are encompassed in compound (IIb) can be prepared, for example, from compound (IIb¹) as shown in the following method.

[0206]



[0207]

wherein L¹ is a leaving group, Alkyl⁴ is a C₁₋₆ alkyl group optionally having substituent(s), and other symbols are each as defined above.

[0208]

In Step 10, compound (IIb²) can be prepared by reducing compound (IIb¹). The "reduction" can be performed in the same manner as in Step 9. Among them, a method using a metal hydride such as sodium borohydride, lithium borohydride, lithium aluminum hydride and the like is preferable.

[0209]

In Step 11, compound (IIb³) can be prepared by converting the hydroxyl group of compound (IIb²) to the leaving group L¹. Examples of the leaving group L¹ include a halogen atom (e.g., a chlorine atom, a bromine atom, an iodine atom), C₁₋₆ alkylsulfonyloxy optionally substituted by halogen atom(s) (e.g., methanesulfonyloxy, ethanesulfonyloxy, trifluoromethanesulfonyloxy), C₆₋₁₀ arylsulfonyloxy optionally substituted by C₁₋₆ alkyl (e.g., benzenesulfonyloxy, p-

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toluenesulfonyloxy) and the like. Among them, a halogen atom and methanesulfonyloxy are preferable. For example, this step is performed according to the method described in Journal of the American Chemical Society, 107, 3950 (1985) when the leaving group L^1 is a halogen atom, and this step is performed according to the method described in Synthesis, 6, 627-629 (1995) when the leaving group L^1 is methanesulfonyloxy.

[0210]

In Step 12, compound (IIb⁴) can be prepared by converting the leaving group L^1 of compound (IIb³) into the alkylsulfanyl group using the corresponding thiol. The step may be performed using a base. Examples of the "base" include those similar to the "base" exemplified in Step 5. Among them, an alkali metal hydride such as sodium hydride and the like is preferable. In addition, an alkali metal salt of the thiol may be used instead of the thiol.

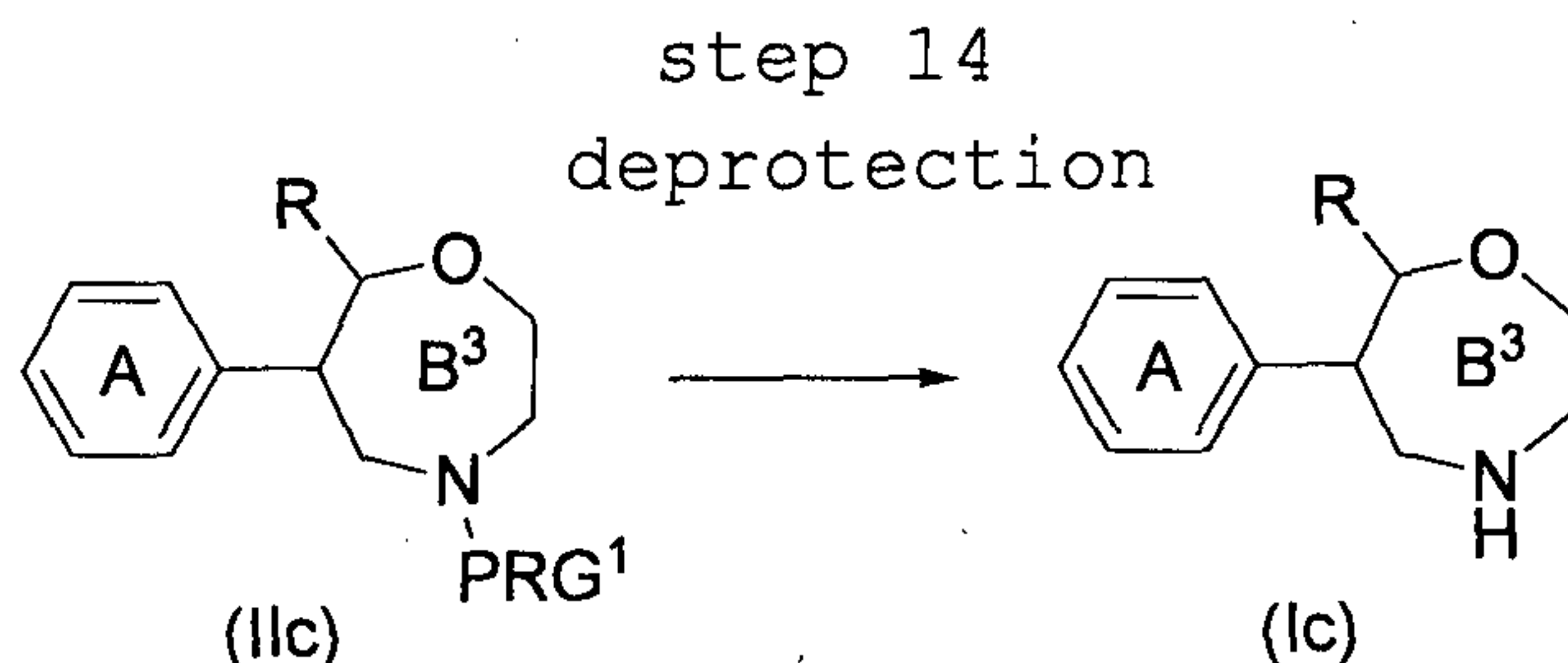
[0211]

In Step 13, compound (IIb⁵) can be prepared by oxidizing compound (IIb⁴). The "oxidation" can be performed, for example, using an oxidant such as 3-chlorophenylperbenzoic acid, sodium periodate, aqueous hydrogen peroxide, peracetic acid, Oxone (registered trade mark) and the like. Among them, 3-chlorophenylperbenzoic acid and the like are preferable. The step can be performed, for example, according to the method described in Journal of Organic Chemistry, 68, 5075-5083 (2003).

[0212]

[Preparation of Compound (Ic)]

[0213]



[0214]

wherein each symbol is as defined above.

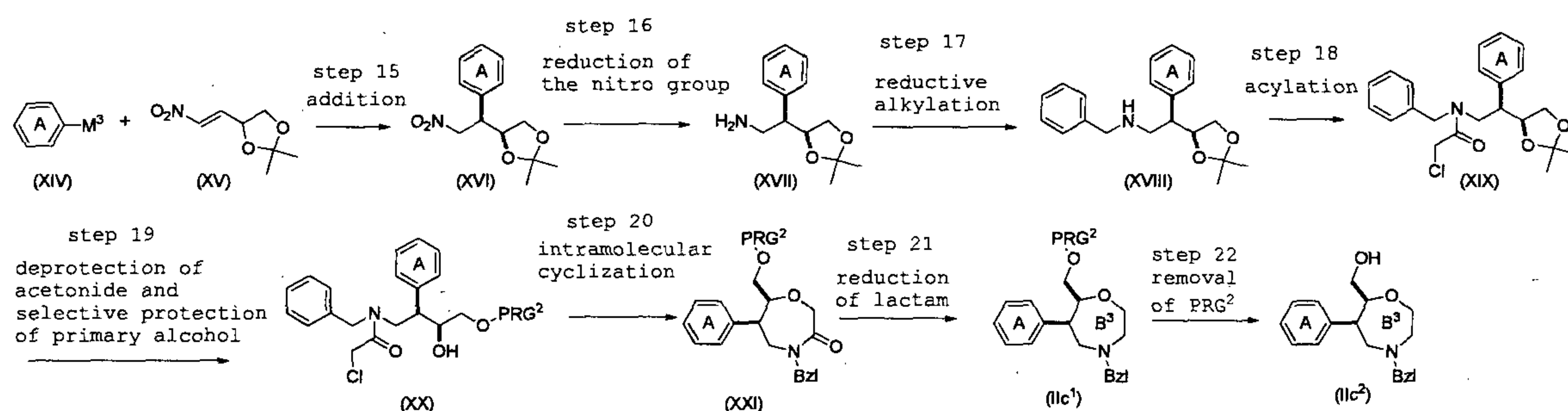
[0215]

In Step 14, compound (Ic) can be prepared, for example, by deprotecting compound (IIc). Examples of the "protecting group" for PRG¹ include those similar to the "protecting group" exemplified in Step 1. Among them, tert-butoxycarbonyl (Boc) group, benzyl (Bzl) group and the like are preferable. Step 14 can be performed under the same reaction conditions as in Step 1 or reaction conditions similar thereto.

10 [0216]

Compound (IIc¹) (R is -CH₂OPRG², and PRG¹ is Bzl) and (IIc²) (R is -CH₂OH, and PRG¹ is Bzl) which are encompassed in compound (IIc) can be prepared, for example, according to the following method.

15 [0217]



[0218]

wherein M³ is a metal or a derivative thereof, PRG² is a protecting group, Bzl is a benzyl group, and other symbols are each as defined above.

[0219]

In Step 15, compound (XVI) can be prepared by subjecting compound (XV) to addition with compound (XIV). Examples of the "M³" of compound (XIV) include an alkali metal, an alkaline earth metal, zinc, copper, boron, silicon, a derivative thereof and the like. Among them, lithium and halogenated magnesium are preferable. The step can be performed, for example, according to the method described in Tetrahedron Letters, 37, 3055-3058 (1996). The product obtained in this step may be a diastereomer mixture due to stereoisomerism, and

it can be separated and purified by silica gel column chromatography, recrystallization and the like, as necessary.
[0220]

In Step 16, compound (XVII) can be prepared by reducing
5 the nitro group of compound (XVI). The "reduction of the nitro group" can be performed, for example, according to a catalytic reduction reaction using a transition metal catalyst such as palladium, platinum, rhodium, Raney-nickel and the like; a method using a metal hydride such as lithium aluminum hydride,
10 sodium borohydride in the presence of divalent nickel chloride and the like; a method using a powder of a metal such as zinc, iron, tin and the like under acidic conditions; and the like. Among them, catalytic reduction is preferable. The step can be performed, for example, according to the method described in
15 Synthesis, 19, 3245-3252 (2005) when using Raney-nickel.
[0221]

In Step 17, compound (XVIII) can be prepared by subjecting compound (XVII) to a reductive alkylation with benzaldehyde. The "reductive alkylation" can be performed, for
20 example, according to the method described in Organic Reactions, 59, 1-714 (2001).
[0222]

In Step 18, compound (XIX) can be prepared by acylating compound (XVIII). The step can be generally performed in the
25 presence of the "base" exemplified in Step 5. The "base" is preferably triethylamine or diisopropylethylamine.
[0223]

In Step 19, compound (XX) can be prepared by deprotecting the acetonide compound (XIX), and then selectively protecting
30 the resulting primary alcohol. The "deprotection of the acetonide" can be performed, for example, according to the method described in Greene's protective groups in organic synthesis 4th edition (Wiley-International Publication). For example, a method using diluted hydrochloric acid, and the
35 like are preferably employed. The "deprotection of the

acetone" can be performed, for example, according to the conditions described in Tetrahedron, 46, 1767-1782 (1990). The "selective protection of the primary alcohol" can be generally performed, for example, by introducing a bulky protecting group such as pivaloyl (Piv) group, tert-butyldimethylsilyl (TBDMS) group, tert-butyldiphenylsilyl (TBDPS) group and the like. tert-Butyldimethylsilyl group is preferably used. The "selective protection of the primary alcohol" can be performed, for example, according to the conditions described in Tetrahedron, 49, 8211-8222 (1993) when using tert-butyldimethylsilyl group as a protecting group. The "deprotection of the acetone" and "selective protection of the primary alcohol" may be performed successively without via an isolation and purification operation.

[0224]

In Step 20, compound (XXI) can be prepared by subjecting compound (XX) to an intramolecular cyclization reaction. The "intramolecular cyclization reaction" can be generally performed in the presence of a base. Examples of the "base" include those similar to the "base" exemplified in Step 5. Among them, sodium tert-butoxide is preferable.

[0225]

In Step 21, compound (IIc¹) can be prepared by reducing the lactam compound (XXI). The "reduction of the lactam" can be performed, for example, using the "reducing agent" exemplified in Step 9. Among them, borane complex (borane-THF complex etc.), catecholborane, aluminum hydride, lithium aluminum hydride and the like are preferable.

[0226]

In Step 22, compound (IIc²) can be prepared by removing the protecting group "PRG²" of compound (IIc¹). The removal can be performed, for example, according to the method selected from the methods described in Greene's protective groups in organic synthesis 4th edition (Wiley-International Publication), depending on the protecting group "PRG²". When

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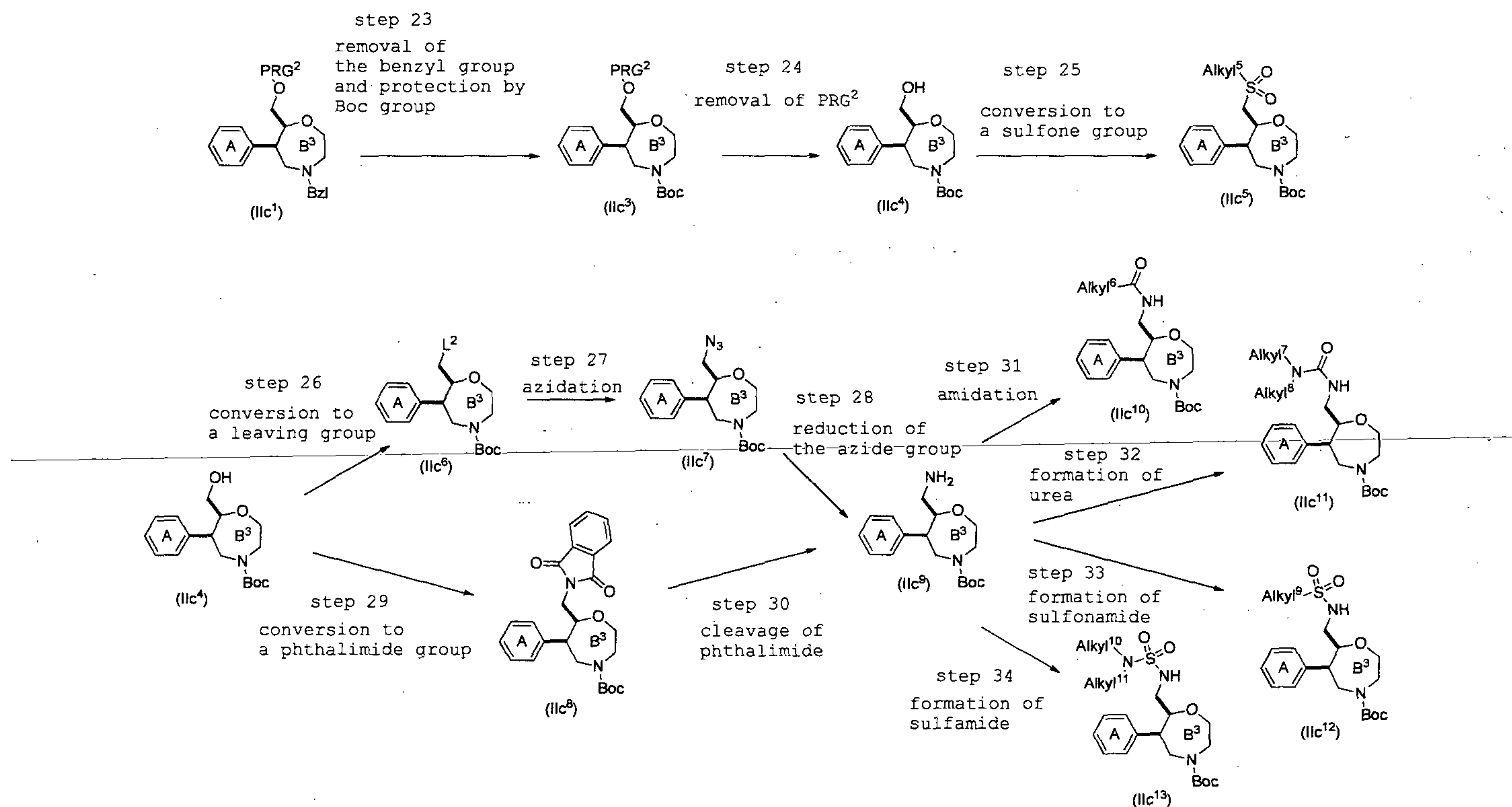
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the removal of "PRG²" proceeds simultaneously in Step 20 or Step 21, this step may be omitted.

[0227]

Compound (IIc³) (R is -CH₂OPRG², and RPG¹ is Boc), (IIc⁴) (R is -CH₂OH, and RPG¹ is Boc), (IIc⁵) (R is -CH₂SO₂-Alkyl⁵, and RPG¹ is Boc), (IIc⁶) (R is -CH₂L², and RPG¹ is Boc), (IIc⁷) (R is -CH₂N₃, and RPG¹ is Boc), (IIc⁸) (R is -CH₂Phthalimide, and RPG¹ is Boc), (IIc⁹) (R is -CH₂NH₂, and RPG¹ is Boc), (IIc¹⁰) (R is -CH₂NHCOAlkyl⁶, and RPG¹ is Boc), (IIc¹¹) (R is -CH₂NHCON(Alkyl⁷)(Alkyl⁸), and RPG¹ is Boc), (IIc¹²) (R is -CH₂NHSO₂Alkyl⁹, and RPG¹ is Boc) and (IIc¹³) (R is -CH₂NHSO₂N(Alkyl¹⁰)(Alkyl¹¹), and RPG¹ is Boc) which are encompassed in compound (IIc) can be prepared, for example, from compound (IIc¹) according to the following method.

15 [0228]



[0229]

wherein L² is a leaving group, Alkyl⁵, Alkyl⁶ and Alkyl⁹ are each a C₁₋₆ alkyl group optionally having substituent(s), Alkyl⁷, Alkyl⁸, Alkyl¹⁰ and Alkyl¹¹ are each a hydrogen atom or a C₁₋₆ alkyl group optionally having substituent(s), and other

symbols are each as defined above.

[0230]

In Step 23, compound (IIc³) can be prepared by removing the N-benzyl group of compound (IIc¹), and then subjecting the resulting compound to protection by Boc group. The "removal of the benzyl group" and "protection by Boc group" can be performed, for example, according to the method selected from the methods described in Greene's protective groups in organic synthesis 4th edition (Wiley-International Publication).

10 [0231]

In Step 24, compound (IIc⁴) can be prepared by removing PRG² of compound (IIc³). The "removal of PRG²" can be performed, for example, according to the method selected from the methods described in the aforementioned "Greene's protective groups in organic synthesis 4th edition". When the removal of "PRG²" proceeds simultaneously in Step 23, this step may be omitted.

[0232]

In Step 25, compound (IIc⁵) can be prepared by converting the hydroxyl group presented in the side chain of compound (IIc⁴) to a sulfone group. The "conversion to the sulfone group" can be performed, for example, in the same manner as in the aforementioned Steps 11-13.

[0233]

25 Compound (IIc⁹) can be prepared, for example, from the azide derivative (IIc⁷) or the phthalimide derivative (IIc⁸).

[0234]

The "azide derivative (IIc⁷)" can be prepared by, in Step 26, converting the hydroxyl group presented in the side chain of compound (IIc⁴) to a leaving group L², and then, in Step 27, subjecting the resulting compound to azidation. Examples of the leaving group L² include those similar to the aforementioned L¹, and a methanesulfonyloxy group, a chlorine atom and the like are preferable. The "azidation" is performed using an azidating agent such as sodium azide,

35

trimethylsilylazide and the like.

[0235]

In Step 29, the "phthalimide derivative (IIc⁸)" can be prepared, for example, according to the Mitsunobu reaction described in Bioorganic and Medicinal Chemistry Letters, 19 (8), 2244-2248 (2009). The "phthalimide derivative (IIc⁸)" can also be prepared, for example, by reacting compound (IIc⁶) with potassium phthalimide.

[0236]

10 In Step 28, Compound (IIc⁹) can be prepared by reducing the azide group of the azide derivative (IIc⁷). The "reduction of the azide group" can be performed, for example, in the same reaction conditions as in Step 9, or according to the Staudinger reaction described in Tetrahedron, 48, 1353-1406 (1992). In Step 30, compound (IIc⁹) can also be prepared by
15 subjecting the phthalimide derivative (IIc⁸) to cleavage. The step can be performed, for example, according to the method described in Journal of Organic Chemistry, 43, 2320 (1978).

[0237]

20 In Step 31, compound (IIc¹⁰) can be prepared by subjecting compound (IIc⁹) to amidation. The "amidation" can be performed according to a method known per se, for example, a method using a reactive derivative such as an acid halide, an acid azide, an acid anhydride and the like; condensation of
25 a carboxylic acid in the presence of a condensing agent such as dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, carbonyldiimidazole and the like, and the like.

[0238]

30 In Step 32, compound (IIc¹¹) can be prepared by subjecting compound (IIc⁹) to formation of urea. The "formation of urea" can be performed according to a method known per se, for example, a reaction with an alkylisocyanate; the method via a phenylcarbamate, which is described in
35 Journal of Medicinal Chemistry, 36, 2984-2997, (1993); and the

like. Among them, for the preparation of a terminal-unsubstituted urea, trimethylsilyl isocyanate is preferably used.

[0239]

5 In Step 33, compound (IIc¹²) can be prepared by subjecting compound (IIc⁹) to formation of sulfonamide. The "formation of sulfonamide" can be performed according to a method known per se, for example, the reaction with sulfonyl chloride in the presence of a base. Examples of the "base" 10 include those similar to the base exemplified in Step 5. Among them, a tertiary amine such as triethylamine and the like is preferable.

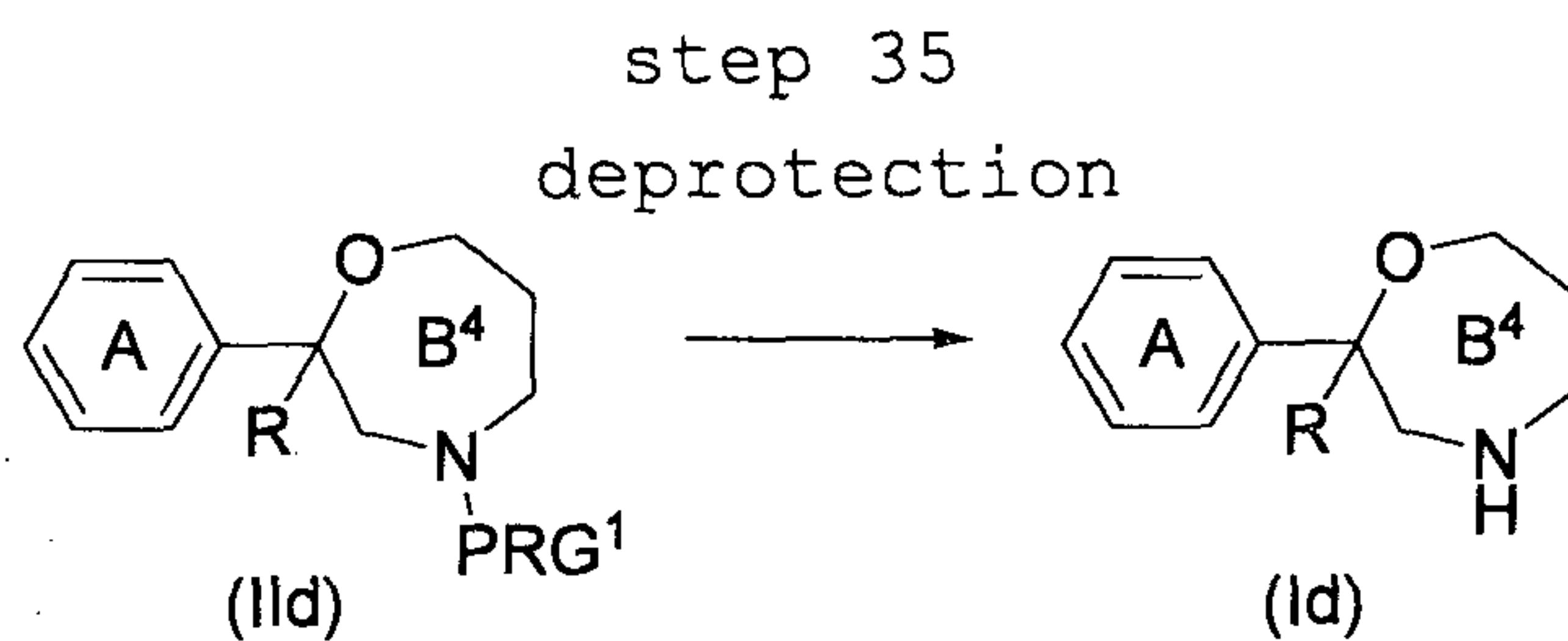
[0240]

In Step 34, compound (IIc¹³) can be prepared by 15 subjecting compound (IIc⁹) to formation of sulfamide. The "formation of sulfamide" can be performed, for example, according to the condensation with sulfamoyl chloride, which is described in WO 2007/049041; the method using N-(tert-butoxycarbonyl)-N-[4-(dimethylazaniumylidene)-1,4- 20 dihydropyridin-1-ylsulfonyl]azanide, which is described in Organic Letters, 3 (14), 2241-2243 (2001); and the like.

[0241]

[Preparation of Compound (Id)]

[0242]



[0243]

wherein each symbol is as defined above.

[0244]

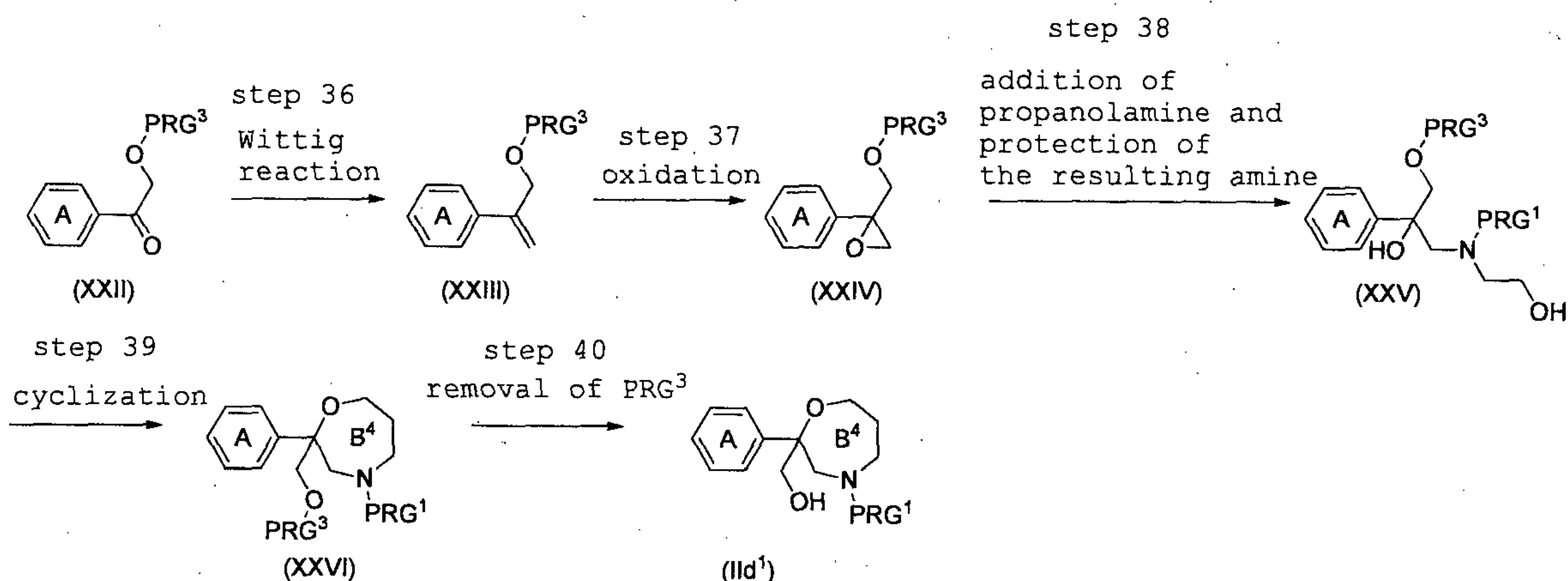
30 In Step 35, compound (Id) can be prepared, for example, by deprotecting compound (IIId). Examples of the "protecting group" for PRG¹ include those similar to the protecting group

exemplified in Step 1. Among them, tert-butoxycarbonyl (Boc) group and the like are preferable. Step 35 can be performed under the same reaction conditions as in Step 1 or reaction conditions similar thereto.

5 [0245]

Compound (IIId¹) (R is -CH₂OH) which is encompassed in compound (IIId) can be prepared, for example, according to the following method.

[0246]



10

[0247]

wherein PRG³ is a protecting group, and other symbols are each as defined above.

[0248]

15 In Step 36, compound (XXIII) can be prepared by subjecting compound (XXII) to the Wittig reaction. The "Wittig reaction" can be performed according to a method known per se, for example, the method described in Tetrahedron, 62 (17), 4120-4127 (2006).

20 [0249]

In Step 37, compound (XXIV) can be prepared by oxidizing compound (XXIII). The "oxidation" can be performed using a known oxidant, for example, an organic peroxide such as aqueous hydrogen peroxide, tert-butylhydroperoxide and the like, a peracid such as peracetic acid, m-chloroperbenzoic acid and the like, and the like. For example, when m-chloroperbenzoic acid is used, the "oxidation" can be

performed according to the conditions described in European Journal of Organic Chemistry, 2, 489-497 (2006).

[0250]

In Step 38, compound (XXV) can be prepared by subjecting
5 compound (XXIV) to addition of propanolamine, and then
protecting the resulting amine. The "addition of
propanolamine" can be performed, for example, according to the
conditions described in Tetrahedron: Asymmetry, 16, 2249-2256
(2005). Examples of the protecting group and introduction
10 method used for the "protection of the resulting amine"
include those exemplified in Step 1.

[0251]

In Step 39, compound (XXVI) can be prepared by subjecting
compound (XXV) to an intramolecular cyclization reaction. This
15 reaction is generally performed under dehydrating conditions.
Examples of the conditions include a condition in the presence
of a mineral acid such as sulfuric acid, phosphoric acid and
the like; a condition in the presence of a dehydrating reagent
such as thionyl chloride, phosphorus oxychloride and the like;
20 or the condition employed in the Mitsunobu reaction. Among
them, the condition employed in the Mitsunobu reaction is
preferable. The "Mitsunobu reaction" can be performed, for
example, according to the method described in Organic
Reactions, 42, 335-656(1992). Examples of the reagent to be
25 used include those described in the aforementioned "Organic
Reactions". Among them, cyanomethylenetriethylphosphorane,
which is known as the Tsunoda reagent, is preferable.

[0252]

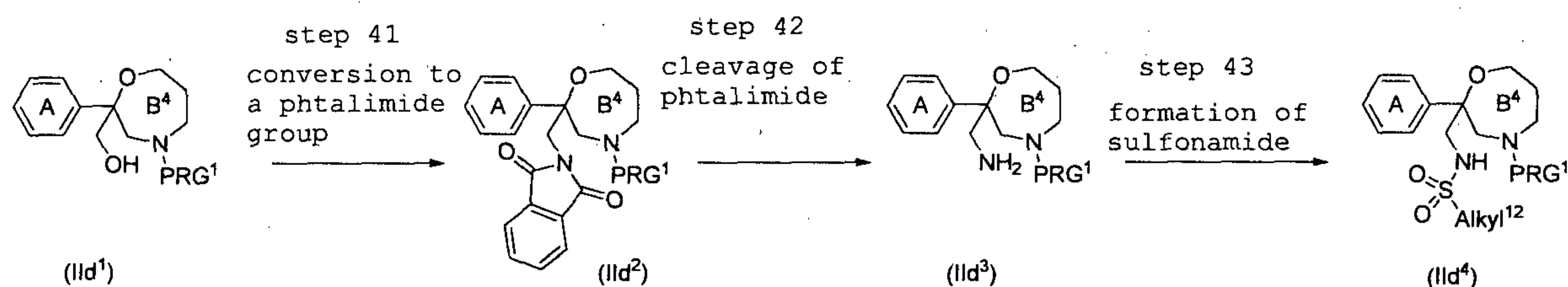
In Step 40, compound (IIId¹) can be prepared by removing
30 "PRG³" of compound (XXVI). Examples of "PRG³" and deprotection
thereof include the hydroxyl-protecting group and deprotection
thereof, which are described in Greene's protective groups in
organic synthesis 4th edition (Wiley-International
Publication). Preferred is deprotection that does not
35 adversely influence the co-presenting "PRG¹". For example,

when "PRG¹" is a Boc group, and "PRG³" is a p-methoxyphenyl group or a p-methoxybenzyl group, "PRG³" can be removed using a reagent such as cerium ammonium nitrate, and the reagent does not adversely influence the "Boc group" that is co-present.

5 [0253]

Compounds (IIId²) (R is -CH₂Phthalimide), (IIId³) (R is -CH₂NH₂) and (IIId⁴) (R is -CH₂NHSO₂Alkyl¹²) which are encompassed in compound (IIId) can be prepared, for example, from compound (IIId¹) according to the following method.

10 [0254]



[0255]

wherein Alkyl¹² is a C₁₋₆ alkyl group optionally having substituent(s), and other symbols are each as defined above.

15 [0256]

In Step 41, compound (IIId²) can be prepared by converting the hydroxyl group of compound (IIId¹) to a phthalimide group. The step can be performed, for example, in the same manner as in the aforementioned Step 29.

20 [0257]

In Step 42, compound (IIId³) can be prepared by subjecting the phthalimide of compound (IIId²) to cleavage. The step can be performed, for example, in the same manner as in the aforementioned Step 30.

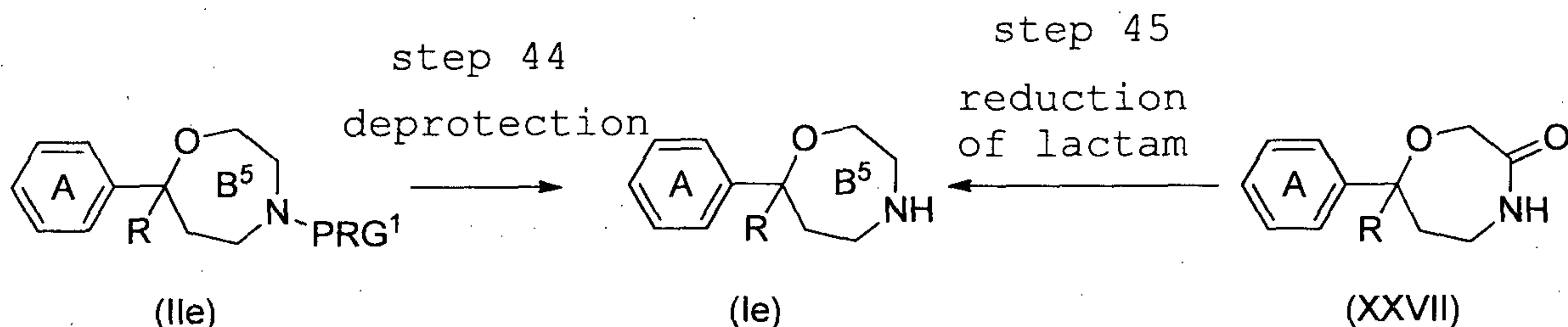
25 [0258]

In Step 43, compound (IIId⁴) can be prepared by subjecting compound (IIId³) to formation of sulfonamide. The step can be performed, for example, in the same manner as in the aforementioned Step 33.

30 [0259]

[Preparation of Compound (Ie)]

[0260]



[0261]

wherein each symbol is as defined above.

5 [0262]

In Step 44, compound (Ie) can be prepared, for example, by deprotecting compound (IIe). Examples of the "protecting group" for PRG¹ include those similar to the protecting group exemplified in Step 1. Among them, tert-butoxycarbonyl (Boc) group and the like are preferable. Step 44 can be performed under the same reaction conditions as in Step 1 or reaction conditions similar thereto.

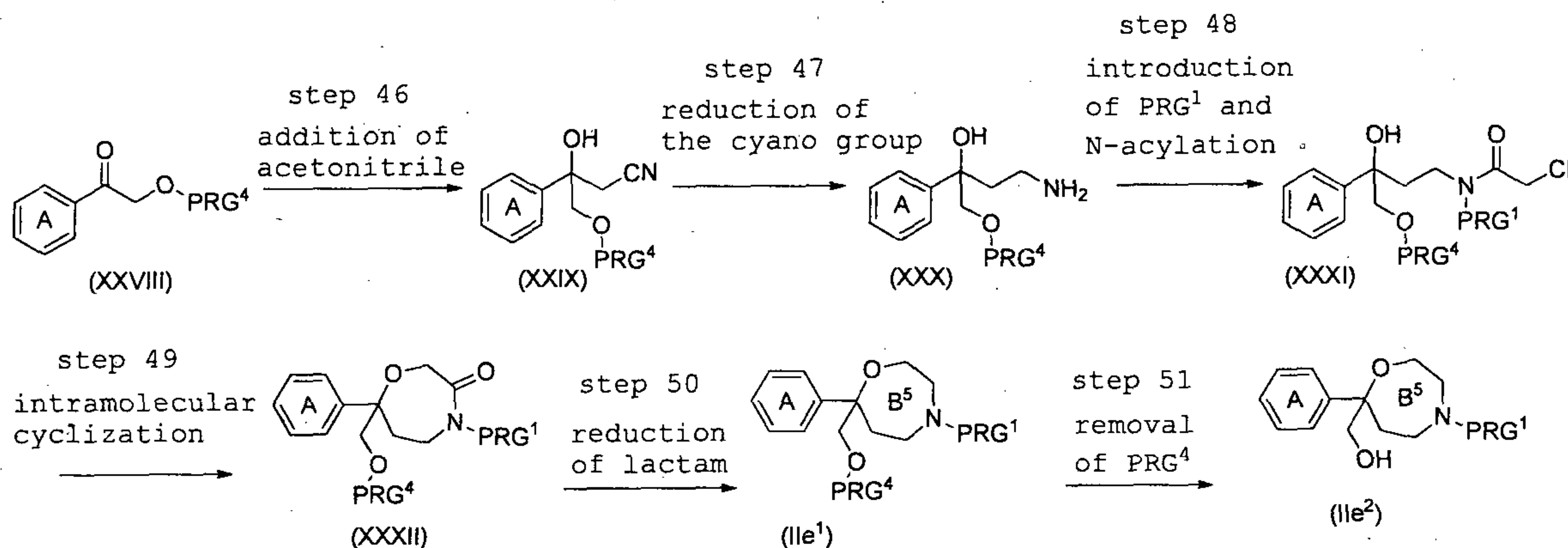
[0263]

In Step 45, compound (Ie) can also be prepared, for example, by reducing the lactam compound (XXVII). The "reduction of the lactam" can be performed, for example, using a reducing agent exemplified in the aforementioned Step 9. Among them, the method using a borane complex (borane-THF complex etc.), catecholborane, aluminum hydride, lithium aluminum hydride or the like is preferable. For example, the "reduction of the lactam" can be performed, for example, according to the conditions described in Journal of Medicinal Chemistry, 39, 3539-3546 (1996) when borane-THF complex is used.

25 [0264]

Compounds (IIe¹) (R is -CH₂OPRG⁴) and (IIe²) (R is -CH₂OH) which are encompassed in compound (IIe) can be prepared according to the method described in US4499087, for example, according to the following method.

30 [0265]



[0266]

wherein PRG⁴ is a protecting group, and other symbols are each as defined above.

In Step 46, compound (XXIX) can be prepared, for example, by subjecting compound (XXVIII) to addition with acetonitrile. The step can be performed according to the method described in the aforementioned US4499087. Examples of "PRG⁴" include the hydroxyl-protecting group described in Greene's protective groups in organic synthesis 4th edition (Wiley-International Publication). Among them, an optionally substituted benzyl group, an optionally substituted phenyl group, silicon protecting groups such as a tert-butyldimethylsilyl group and the like, a methyl group, and the like are preferable.

[0267]

In Step 47, compound (XXX) can be prepared, for example, by reducing the cyano group of compound (XXIX). The step can be performed according to a method known per se, for example, using the reducing agent exemplified in the aforementioned Step 9. Among them, the method using a borane complex (borane-THF complex etc.), catecholborane, aluminum hydride, lithium aluminum hydride, Raney-nickel or the like is preferable.

[0268]

In Step 48, compound (XXXI) can be prepared, for example, by subjecting compound (XXX) to introduction of PRG¹ and N-acylation. Examples of "PRG¹" include those similar to the protecting group exemplified in Step 1. Among them, preferred is a protecting group that maintains basicity of the nitrogen

atom after protection. To be specific, a benzyl group, a methyl group and the like are preferable. The "introduction of PRG¹" can be performed according to a method known per se. For example, when PRG¹ is a benzyl group, the "introduction of PRG¹" can be performed by subjecting compound (XXX) to reductive alkylation with benzaldehyde, or subjecting compound (XXX) to benzoylation and the reduction of the aminobenzoyl group. The "N-acylation" can be performed, for example, by subjecting the amine after the introduction of PRG¹ to condensation with chloroacetyl chloride. The step can be performed in the presence of a "base" exemplified in the aforementioned Step 5. The "base" is preferably an organic tertiary amine such as triethylamine and the like.

[0269]

In Step 49, compound (XXXII) can be prepared, for example, by subjecting compound (XXXI) to intramolecular cyclization. The step can be performed, for example, in the same manner as in the aforementioned Step 20.

[0270]

In Step 50, compound (IIe¹) can be prepared, for example, by reducing the lactam compound (XXXII). The step can be performed in the same manner as in the aforementioned Step 45, for example, by using the reducing agent exemplified in the aforementioned Step 9. Among them, the method using a borane complex (borane-THF complex etc.), catecholborane, aluminum hydride, lithium aluminum hydride or the like is preferable.

[0271]

In Step 51, compound (IIe²) can be prepared, for example, by removing the protecting group PRG⁴ of compound (IIe¹). The step can be performed, for example, according to the method selected from the methods described in the aforementioned "Greene's protective groups in organic synthesis 4th edition". For example, when PRG⁴ is a p-methoxyphenyl group, PRG⁴ can be removed, for example, using cerium ammonium nitrate. The step can be performed, for example, according to the conditions

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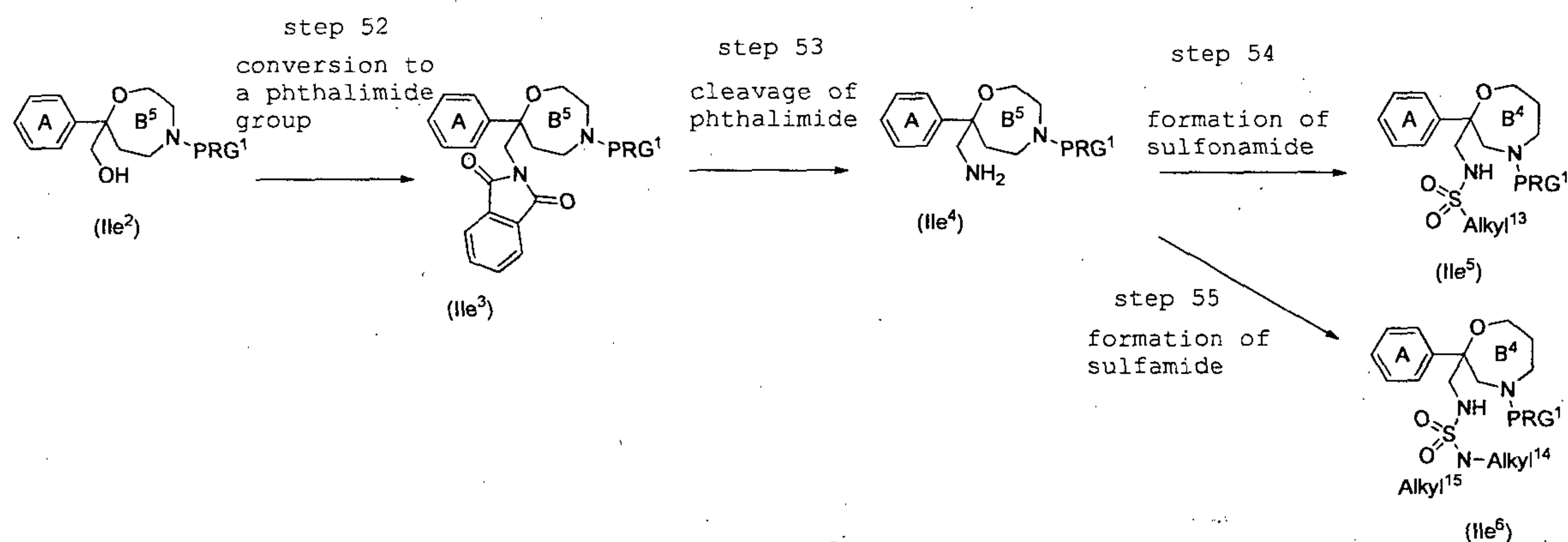
described in Journal of Medicinal Chemistry, 46, 2790-2793

(2003).

[0272]

Compounds (IIe⁵) (R is -CH₂NHSO₂Alkyl¹³) and (IIe⁶) (R is -
 5 CH₂NHSO₂N(Alkyl¹⁴)(Alkyl¹⁵)) which are encompassed in compound
 (IIe) can be prepared, for example, from compound (IIe²)
 according to the following method.

[0273]



10 [0274]

wherein Alkyl¹³ is a C₁₋₆ alkyl group optionally having
 substituent(s), Alkyl¹⁴ and Alkyl¹⁵ are each a hydrogen atom or
 a C₁₋₆ alkyl group optionally having substituent(s), and other
 symbols are each as defined above.

15 [0275]

Compound (IIe⁵) can be prepared, for example, from
 compound (IIe²) via compounds (IIe³) and (IIe⁴) according to
 Steps 52, 53 and 54 successively in this order. The "Steps 52,
 53 and 54" can be performed in the same manner as in the
 20 aforementioned Steps 29, 30 and 33.

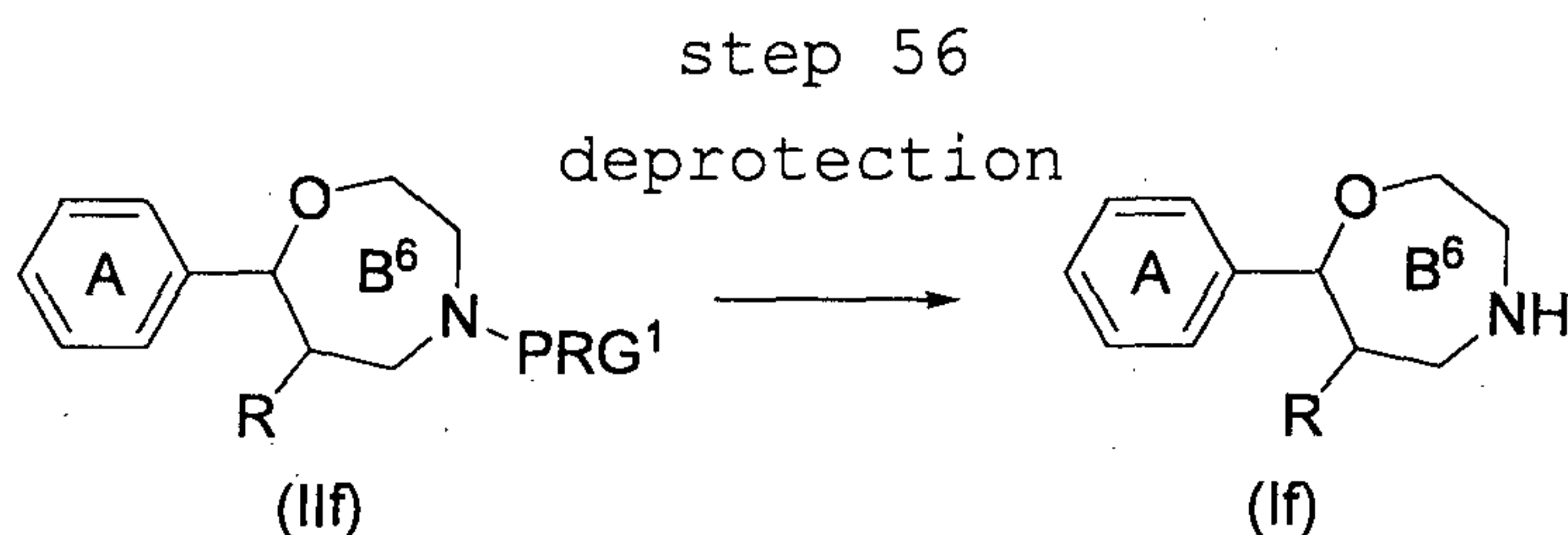
[0276]

In Step 55, compound (IIe⁶) can be prepared, for example,
 by subjecting compound (IIe⁴) to formation of sulfamide. The
 step can be performed in the same manner as in the
 25 aforementioned Step 34.

[0277]

[Preparation of Compound (If)]

[0278]



[0279]

wherein each symbol is as defined above.

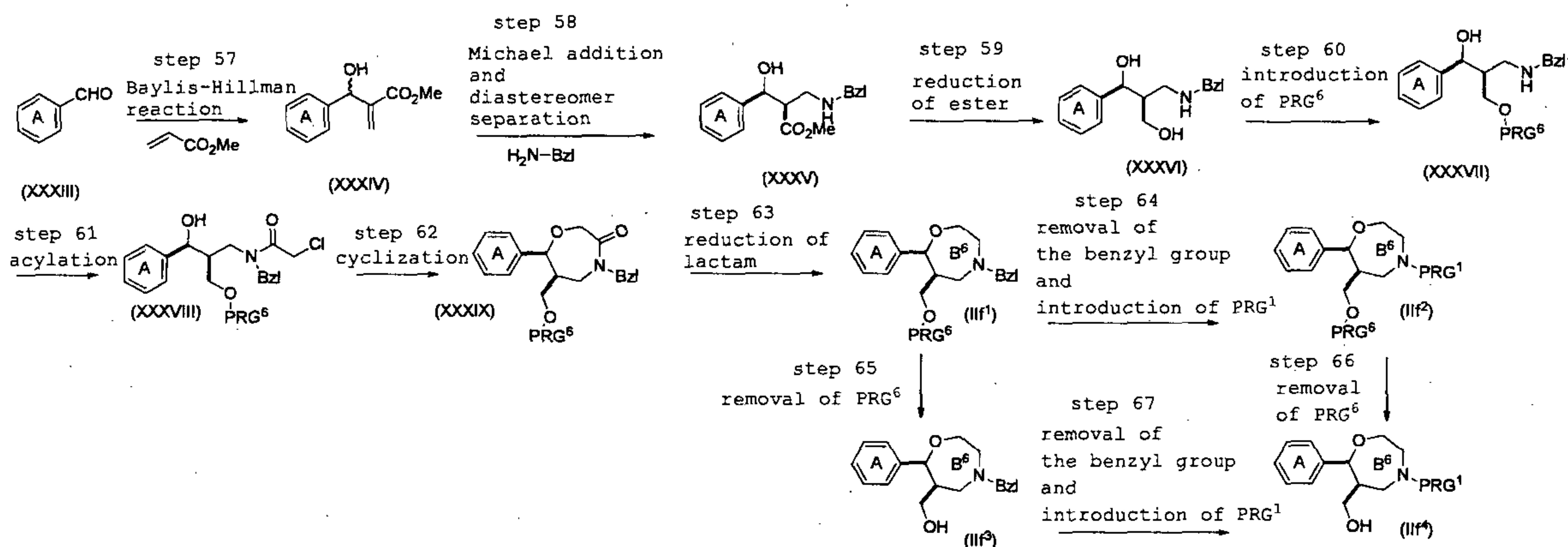
[0280]

5 In Step 56, compound (If) can be prepared, for example, by deprotecting compound (IIf). Examples of the "protecting group" for PRG¹ include those similar to the protecting group exemplified in Step 1. Among them, a tert-butoxycarbonyl (Boc) group and the like are preferable. Step 56 can be performed
10 under the same reaction conditions as in Step 1 or reaction conditions similar thereto.

[0281]

Compounds (IIf¹) (PRG¹ is Bzl, and R is -CH₂OPRG⁶), (IIf²) (R is -CH₂OPRG⁶), (IIf³) (PRG¹ is Bzl, and R is -CH₂OH) and
15 (IIf⁴) (R is -CH₂OH) which are encompassed in compound (IIf) can be prepared, for example, according to the following method.

[0282]



20 [0283]

wherein PRG⁶ is a protecting group, and other symbols are each as defined above.

[0284]

In Step 57, compound (XXXIV) can be prepared, for

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example, by subjecting compound (XXXIII) to the Baylis-Hillman reaction. The step can be performed, for example, according to the method described in Organic Reactions, 51, 201-350 (1997).

[0285]

5 In Step 58, compound (XXXV) can be prepared, for example, by subjecting compound (XXXIV) to the Michael addition with benzylamine, and then subjecting the resulting compound to diastereomer separation. The "Michael addition with benzylamine" can be performed, for example, according to the
10 method described in Synthesis, 6, 911-917 (2007) and the like. Other primary amine (capable of removing the alkyl moiety in the later step, for example, methylamine, (diphenylmethyl)amine, dibenzosuberylamine etc.) can also be used instead of benzylamine. The compound obtained in this
15 step may be in the form of a mixture with the below-mentioned compound (XL). These are in the diastereomer relationship, and can be separated by an appropriate method. The "diastereomer separation" can be performed, for example, by purification method such as silica gel column chromatography and the like,
20 recrystallization and the like. The "diastereomer separation" may be performed not only in this step but also in the below-mentioned Steps 59-67.

[0286]

In Step 59, compound (XXXVI) can be prepared, for
25 example, by reducing the ester moiety of compound (XXXV). The step can be performed, for example, using the reducing agent exemplified in Step 9. Among them, the method using a reducing agent such as lithium aluminum hydride, lithium borohydride or the like is preferable.

30 [0287]

In Step 60, compound (XXXVII) can be prepared, for example, by introducing the protecting group PRG⁶ into the hydroxyl group of compound (XXXVI). Examples of "PRG⁶" include the hydroxyl-protecting group described in Greene's protective
35 groups in organic synthesis 4th edition (Wiley-International

Publication). Among them, an optionally substituted benzyl group, an optionally substituted phenyl group, silicon protecting groups such as a tert-butyldimethylsilyl group and the like, a methyl group and the like are preferable. The
5 introduction of a protecting group can be performed according to the method selected from the methods described in the above-mentioned "Greene's protective groups in organic synthesis 4th edition". For example, when "PRG⁶" is a tert-butyldimethylsilyl group, the introduction can be performed,
10 for example, according to the method described in Journal of Organic Chemistry, 71, 9628-9636 (2006).

[0288]

In Step 61, compound (XXXVIII) can be prepared by subjecting compound (XXXVII) to acylation. The step can be
15 generally performed in the presence of a "base" exemplified in Step 5, according to a method known per se. Among them, triethylamine and diisopropylethylamine are preferable.

[0289]

In Step 62, compound (XXXIX) can be prepared by
20 subjecting compound (XXXVIII) to cyclization. The step can be generally performed in the same manner as in the aforementioned Step 20, and also performed in the presence of a "base" exemplified in Step 5. As the "base", among them, sodium tert-butoxide, sodium hydride, sodium hydroxide and the
25 like are preferable.

[0290]

In Step 63, compound (IIIf¹) can be prepared, for example, by reducing the lactam compound (XXXIX). The step can be performed, for example, using a reducing agent exemplified in
30 the aforementioned Step 9. Among them, the method using a borane complex (borane-THF complex etc.), catecholborane, aluminum hydride, lithium aluminum hydride or the like is preferable.

[0291]

35 In Step 64, compound (IIIf²) can be prepared, for example,

by removing the benzyl group of compound (II^f¹), and then introducing the protecting group PRG¹. The "removal of the benzyl group" can be performed, for example, by hydrogenation using a transition metal catalyst, which is described in
5 Journal of Medicinal Chemistry, 51, 875-896 (2008) and the like; or the method using a chlorocarbonate described in Chemical and Pharmaceutical Bulletin, 54 (11), 1535-1544 (2006) and the like, and the like. The "introduction of the protecting group PRG¹" can be performed according to the method
10 selected from the methods described in the aforementioned "Greene's protective groups in organic synthesis 4th edition". For example, when "PRG¹" is a tert-butoxycarbonyl (Boc) group, the introduction can be performed according to the method described in Journal of Medicinal Chemistry, 48, 2100-2107
15 (2005) and the like.

[0292]

In Step 65, compound (II^f³) can be prepared, for example, by removing the protecting group PRG⁶ of compound (II^f¹). The "removal of the protecting group PRG⁶" can be performed
20 according to the method selected from the methods described in the aforementioned "Greene's protective groups in organic synthesis 4th edition". For example, when "PRG⁶" is a tert-butyldimethylsilyl group, the removal can be performed according to the method described in Journal of Organic
25 Chemistry, 71, 9628-9636 (2006).

[0293]

In Step 66, compound (II^f⁴) can be prepared, for example, by removing the protecting group PRG⁶ of compound (II^f²). The step can be performed in the same manner as in the
30 aforementioned Step 65.

[0294]

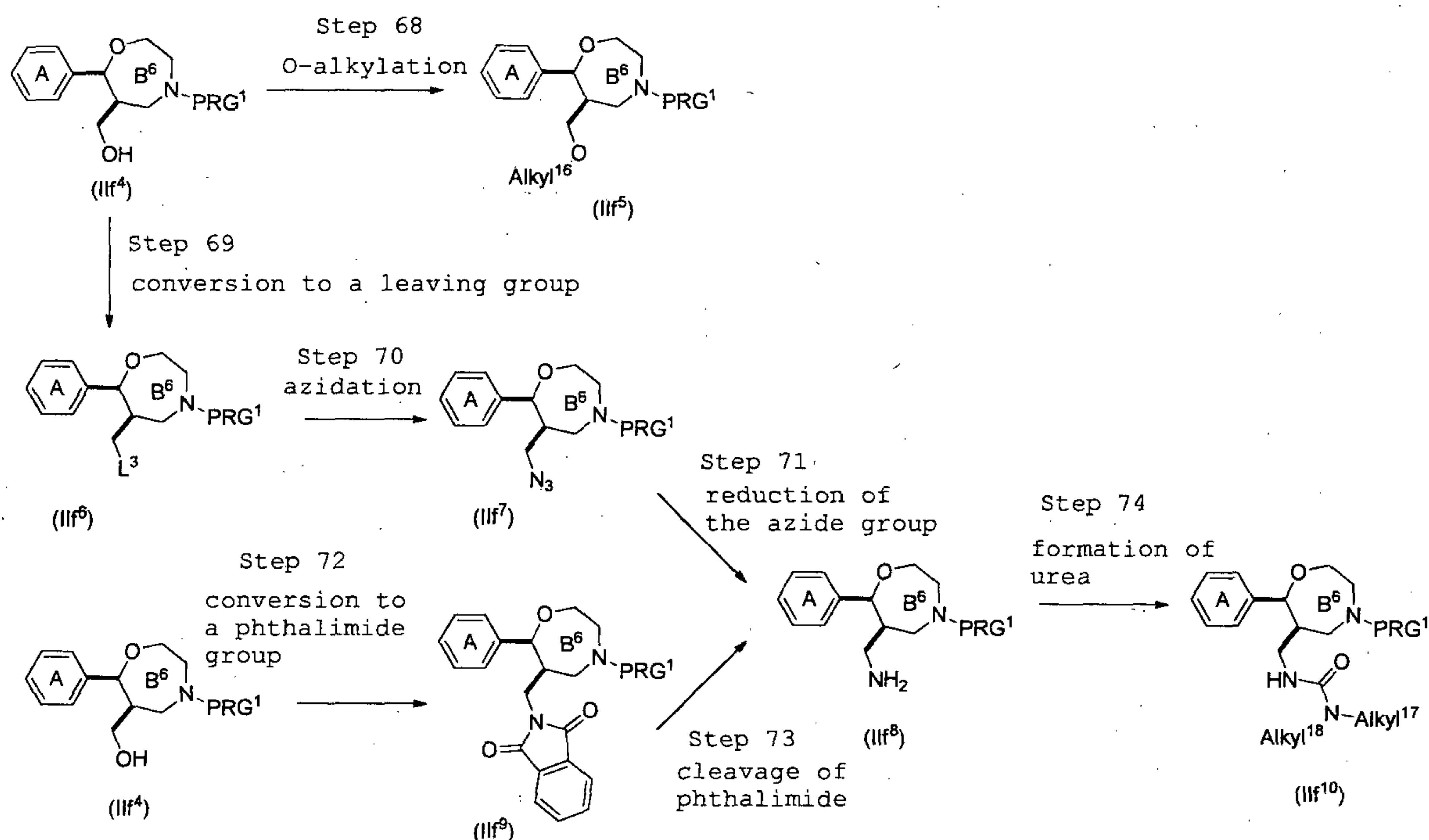
In Step 67, compound (II^f⁴) can also be prepared, for example, by removing the benzyl group of compound (II^f³), and then introducing the protecting group PRG¹. The step can be
35 performed in the same manner as in the aforementioned Step 64.

[0295]

Compounds (II^{f5}) (R is -CH₂OAlkyl¹⁶), (II^{f6}) (R is -CH₂L³), (II^{f7}) (R is -CH₂N₃), (II^{f8}) (R is -CH₂NH₂), (II^{f9}) (R is -CH₂Phthalimide) and (II^{f10}) (R is -CH₂NHCON(Alkyl¹⁷)(Alkyl¹⁸))

5 which are encompassed in compound (II^f) can be prepared, for example, from compound (II^{f4}) according to the following method.

[0296]



10 [0297]

wherein Alkyl¹⁶ is a C₁₋₆ alkyl group optionally having substituent(s), Alkyl¹⁷ and Alkyl¹⁸ are each a hydrogen atom or a C₁₋₆ alkyl group optionally having substituent(s), L³ is a leaving group, and other symbols are each as defined above.

15 [0298]

Steps 68, 69, 70, 71, 72, 73 and 74 shown here can be performed in the same manner as in the aforementioned Steps 3, 26, 27, 28, 29, 30 and 32.

[0299]

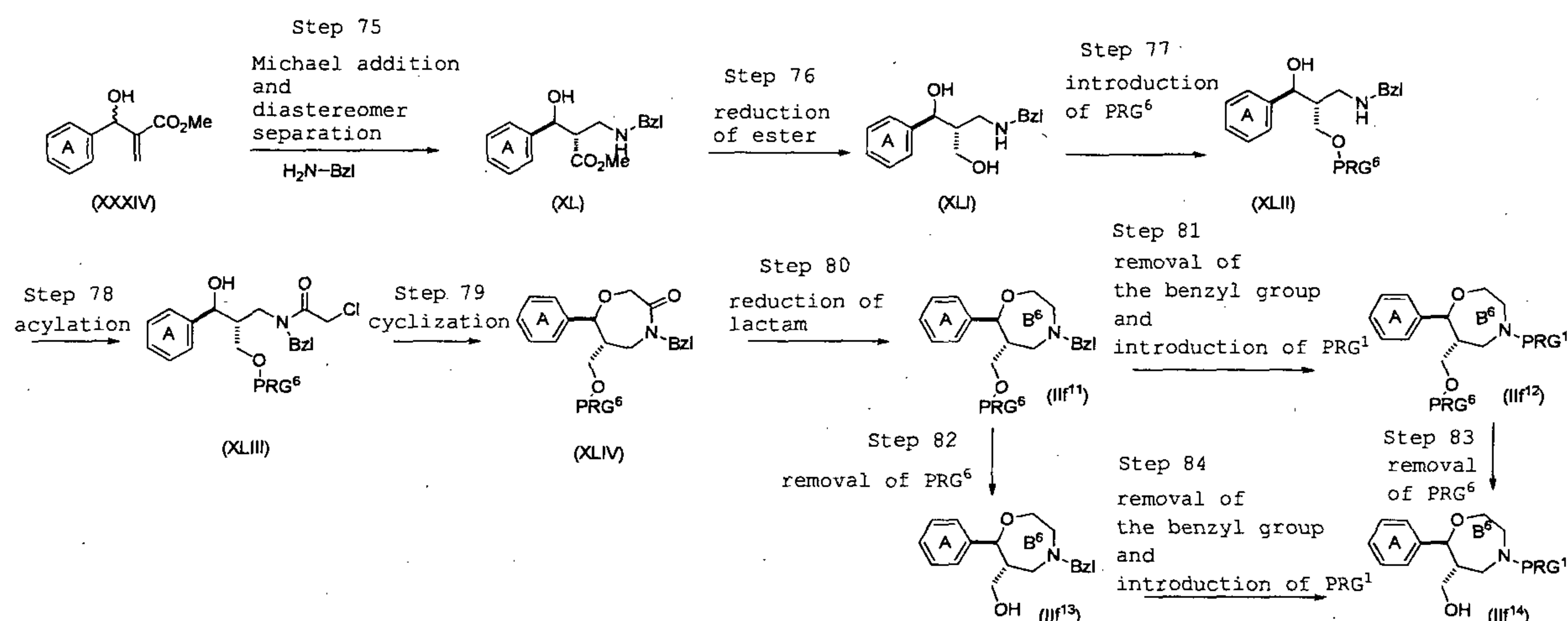
20

Compounds (II^{f11}) (PRG¹ is Bzl, and R is -CH₂OPRG⁶), (II^{f12}) (R is -CH₂OPRG⁶), (II^{f13}) (PRG¹ is Bzl, and R is -CH₂OH) and (II^{f14}) (R is -CH₂OH) which are encompassed in compound (II^f) can be prepared, for example, according to the following

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method.

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[0300]



[0301]

5 wherein each symbol is as defined above.

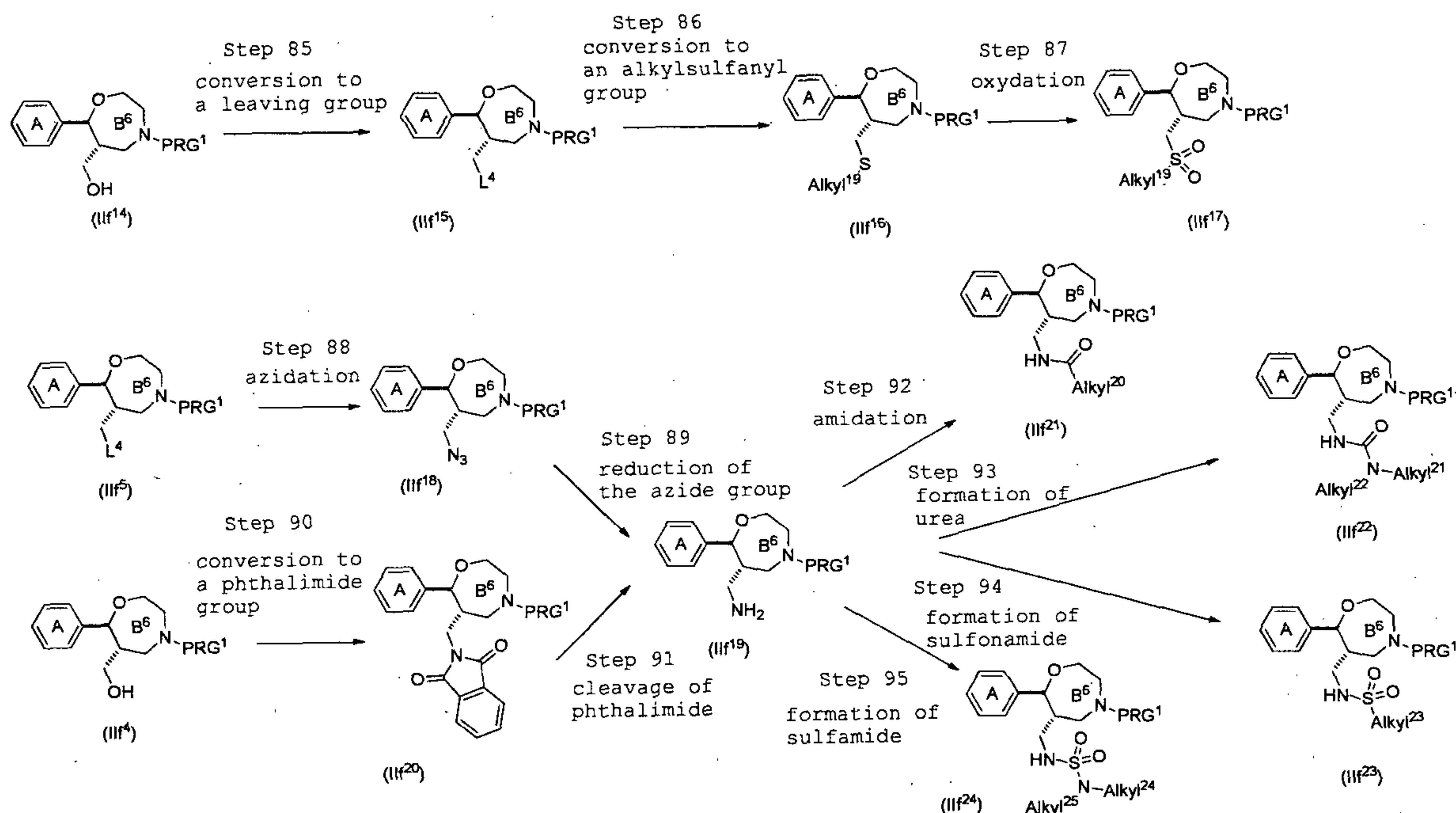
[0302]

Steps 75, 76, 77, 78, 79, 80, 81, 82, 83 and 84 shown here can be performed in the same manner as in the aforementioned Steps 58, 59, 60, 61, 62, 63, 64, 65, 66 and 10 67. The compound obtained in Step 75 may be in the form of a mixture with the aforementioned compound (XXXV). These are in the diastereomer relationship, and can be separated by an appropriate method. The "diastereomer separation" may be performed not only in step 75 but also in the below-mentioned 15 Steps 76-84.

[0303]

Compounds (IIIf¹⁵) (R is $-\text{CH}_2\text{L}^4$), (IIIf¹⁶) (R is $-\text{CH}_2\text{S-}$ Alkyl¹⁹), (IIIf¹⁷) (R is $-\text{CH}_2\text{SO}_2\text{-Alkyl}^{19}$), (IIIf¹⁸) (R is $-\text{CH}_2\text{N}_3$), (IIIf¹⁹) (R is $-\text{CH}_2\text{NH}_2$), (IIIf²⁰) (R is $-\text{CH}_2\text{Phthalimide}$), (IIIf²¹) (R is $-\text{CH}_2\text{NHCO(Alkyl}^{20})$), (IIIf²²) (R is $-\text{CH}_2\text{NHCON(Alkyl}^{21})(\text{Alkyl}^{22})$), 20 (IIIf²³) (R is $-\text{CH}_2\text{NHSO}_2(\text{Alkyl}^{23})$) and (IIIf²⁴) (R is $-\text{CH}_2\text{NHSO}_2\text{N(Alkyl}^{24})(\text{Alkyl}^{25})$) which are encompassed in compound (IIIf) can be prepared, for example, from compound (IIIf¹⁴) according to the following method.

25 [0304]



[0305]

wherein Alkyl¹⁹, Alkyl²⁰ and Alkyl²³ are each a C₁₋₆ alkyl group optionally having substituent(s), Alkyl²¹, Alkyl²², Alkyl²⁴ and Alkyl²⁵ are each a hydrogen atom or a C₁₋₆ alkyl group optionally having substituent(s), L⁴ is a leaving group, and other symbols are each as defined above.

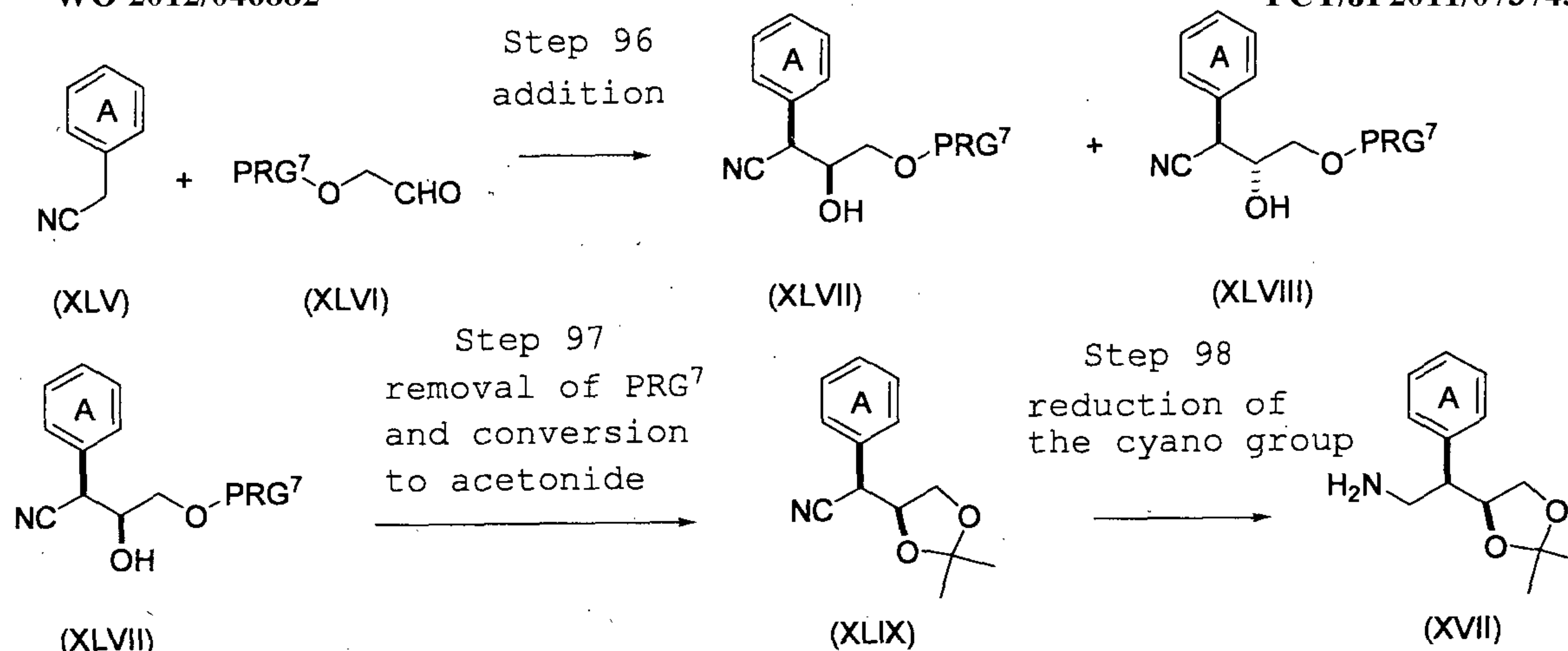
[0306]

Steps 85, 86, 87, 88, 89, 90, 91, 92, 93, 94 and 95 shown here can be performed in the same manner as in the aforementioned Steps 26, 12, 13, 27, 28, 29, 30, 31, 32, 33 and 34.

[0307]

[Alternative Preparation Method of Compound (XVII)]

15 [0308]



[0309]

wherein PRG^7 is a protecting group, and other symbols are each as defined above.

5 Compound (XVII) can also be prepared, for example, according to Steps 96, 97 and 98 instead of Steps 15 and 16. Examples of the "protecting group" for PRG^7 include those similar to the protecting group exemplified in Step 1. Among them, a tert-butyldimethylsilyl (TBDMS) group, tert-
 10 butyldiphenylsilyl (TBDPS) group and the like are preferable.

In Step 96, compound (XLVII) can be prepared, for example, according to the method described in Journal of Organic Chemistry, 59, 4053-4055 (1994). The "addition" can be performed in the presence of a base. Examples of the "base"
 15 include those similar to the "base" exemplified in Step 5, and, for example, an alkali metal alkylate or alkaline earth metal alkylate (e.g., n-butyllithium, isopropylmagnesium bromide and the like) and an alkali metal arylate or alkaline earth metal arylate (e.g., phenyllithium, phenylmagnesium
 20 bromide and the like). The base to be used in Step 96 is preferably lithium diisopropylamide, lithium hexamethyldisilazide, n-butyllithium or the like. In the step, the corresponding diastereomer compound (XLVIII) may be prepared besides compound (XLVII), and it can be separated and
 25 purified by column chromatography or crystallization. Compound (XLVIII) obtained in the step can be used for the below-mentioned Step 99. The "separation and purification of the

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diastereomer" may be performed in Step 17, 18, 19, 20, 21 or 22, or the below-mentioned Step 97 or 98 instead of this step.

In Step 97, compound (XLIX) can be prepared by removing PRG⁷ and then converting the resulting compound to the corresponding acetonide. The "removal of PRG⁷" can be performed according to the method described in Greene's protective groups in organic synthesis 4th edition (Wiley-International Publication). For example, the removal is preferably performed in the presence of p-toluenesulfonic acid, boron trifluoride, tetrabutylammonium fluoride or the like. The "conversion to the acetonide" can be performed according to the method described in the above-mentioned Greene's protective groups in organic synthesis 4th edition (Wiley-International Publication). As a reagent, for example, acetone, 2,2-dimethoxypropane, 2-methoxy-1-propene and the like are preferably used. The "removal of PRG⁷" and "conversion to the acetonide" may be performed successively in stepwisely or simultaneously in a single system.

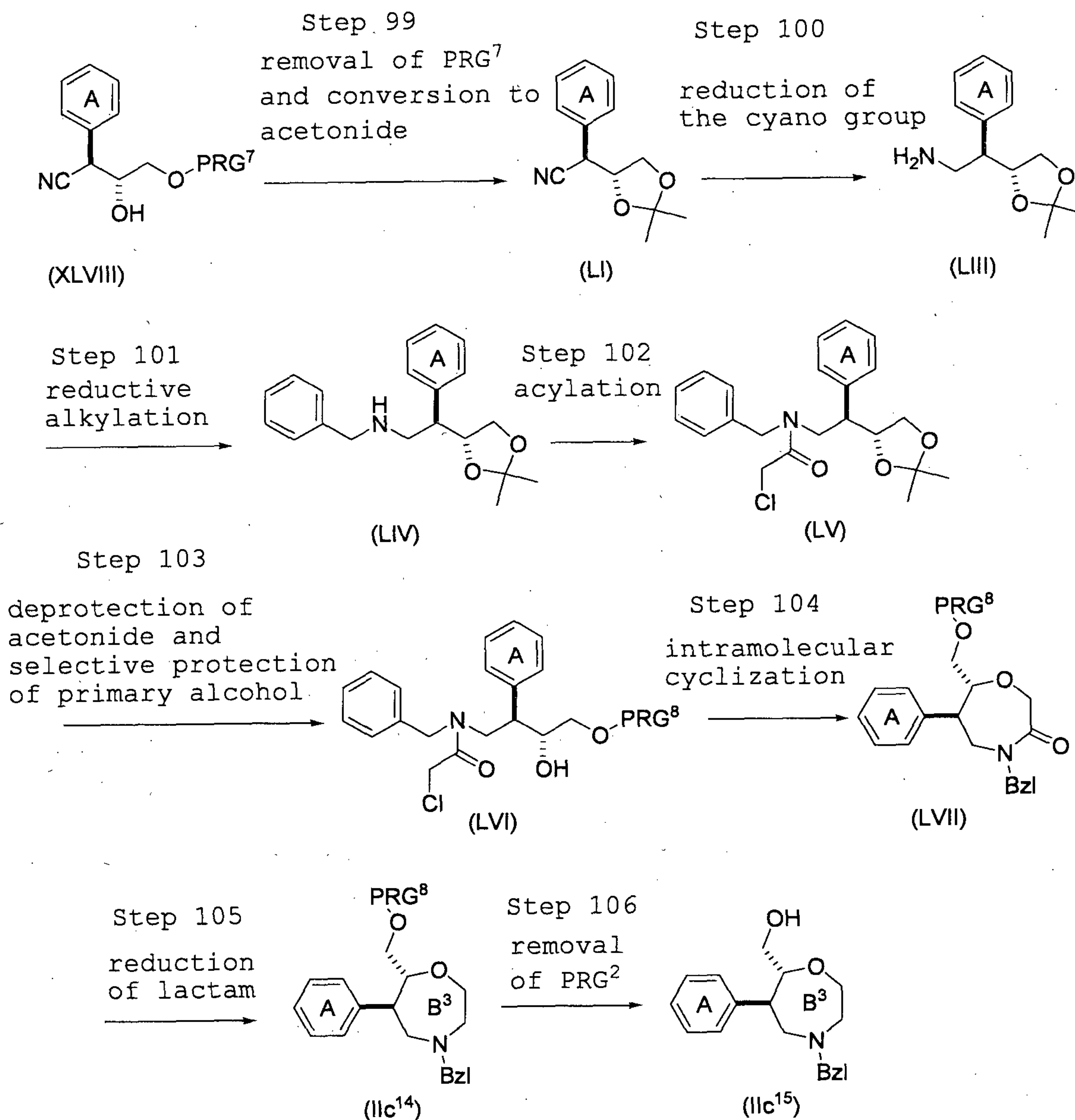
In Step 98, compound (XVII) can be prepared by reducing the cyano group of compound (XLIX). The step can be performed in the same manner as in the aforementioned Step 47. The reagent to be used is preferably, for example, diisobutylaluminum hydride (DIBAL-H) or borane-THF complex.

[0310]

[Preparation of Compounds (IIc¹⁴) and (IIc¹⁵), and Derivative Thereof]

Compound (IIc¹⁴) (R is -CH₂OPRG², and PRG¹ is Bzl) and compound (IIc¹⁵) (R is -CH₂OH, and PRG¹ is Bzl) which are encompassed in compound (IIc) can be prepared, for example, according to the following method.

[0311]



[0312]

wherein PRG⁸ is a protecting group, and other symbols are each as defined above.

- 5 Compound (IIc¹⁴) can be prepared, for example, according to Steps 99, 100, 101, 102, 103, 104 and 105 successively in this order. The above-mentioned steps can be performed in the same manner as in the aforementioned Steps 97, 98, 17, 18, 10, 20 and 21. As compound (XLVIII), the compound obtained in the
- 10 aforementioned Step 96 can be used. Examples of the "protecting group" for PRG⁸ include those similar to the protecting group exemplified in Step 1. Among them, a tert-butyldimethylsilyl (TBDMS) group, tert-butyldiphenylsilyl

(TBDPS) group and the like are preferable.

In Step 106, compound (IIc¹⁵) can be prepared by removing PRG⁸. The step can be performed in the same manner as in the aforementioned Step 22.

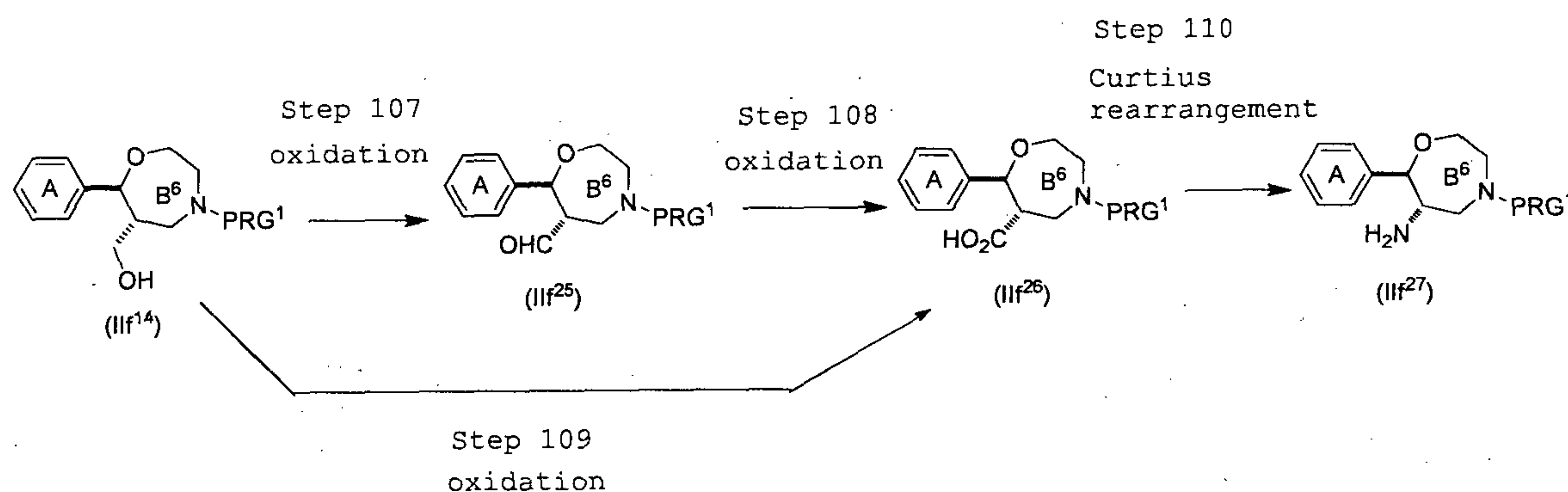
5 The compound (IIc¹⁵) thus prepared can be converted to various derivatives by appropriately combining, for example, the methods analogous to the aforementioned Steps 23-34.

[0313]

[Preparation of Compounds (IIf²⁵), (I IIf²⁶) and (I IIf²⁷), and
10 Derivative Thereof]

Compound (IIf²⁵) (R is -CHO), compound (IIf²⁶) (R is -CO₂H) and compound (IIf²⁷) (R is -NH₂) which are encompassed in compound (IIf) can be prepared, for example, according to the following method.

15 [0314]



[0315]

wherein each symbol is as defined above.

In Step 107, compound (IIIf²⁵) can be prepared by
20 oxidizing compound (IIIf¹⁴). The step can be performed, for example, according to the DMSO oxidation described in Tetrahedron, 34, 1651-1660 (1978) or the Dess-Martin oxidation described in Synthesis, 1271-1287 (1999).

In Step 108, compound (IIIf²⁶) can be prepared by
25 oxidizing compound (IIIf²⁵). The step can be performed, for example, according to the method described in Journal of Medicinal Chemistry, 35, 3135-3141 (1992).

In Step 109, compound (IIIf²⁶) can also be prepared by directly oxidizing compound (IIIf¹⁴) without via compound

(IIIf²⁵). The step can be performed, for example, according to the method using ruthenium oxide, which is described in Tetrahedron, 40, 2365-2380 (1948); or the method using chromic acid, which is described in Comprehensive Organic Synthesis, 5 7, 251-289 (Pergamon Press, 1991).

In Step 110, compound (IIIf²⁷) can be prepared by subjecting compound (IIIf²⁶) to the Curtius rearrangement. The step can be performed, for example, according to the method described in Organic Reactions, 337-349 (1946), Journal of 10 Organic Chemistry, 69, 6184-6201 (2004), or Chemical Communication, 514 (1979).

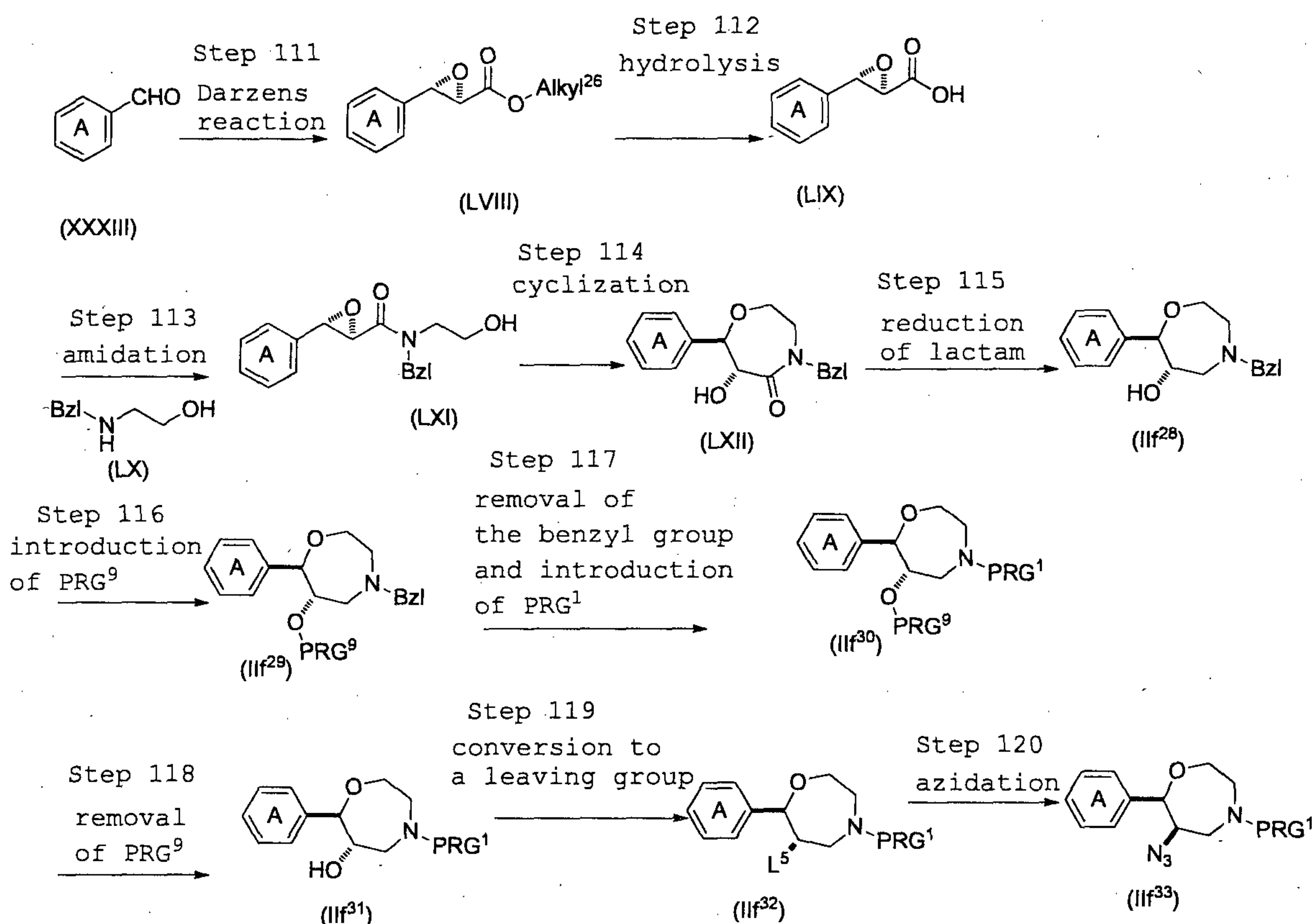
Compound (IIIf²⁷) obtained in the step can be subjected to amidation, or formation of urea, sulfonamide or sulfamide in the same manner as in Steps 31, 32, 33 or 34.

15 [0316]

[Preparation of Compounds (IIIf²⁸), (IIIf²⁹), (IIIf³⁰), (IIIf³¹), (IIIf³²) and (IIIf³³), and Derivative Thereof]

Compound (IIIf²⁸) (R is -OH, and PRG¹ is Bzl), compound (IIIf²⁹) (R is -OPRG⁹, and PRG¹ is Bzl), compound (IIIf³⁰) (R is - 20 OPRG⁹), compound (IIIf³¹) (R is -OH), compound (IIIf³²) (R is -L⁵) and compound (IIIf³³) (R is -N₃) which are encompassed in compound (IIIf) can be prepared, for example, according to the following method.

[0317]



[0318]

wherein Alkyl²⁶ is a C₁₋₆ alkyl group, PRG⁹ is a protecting group, L⁵ is a leaving group, and other symbols are each as defined above.

Compound (LXII) can be produced, for example, from compound (XXXIII) via compounds (LVIII), (LIX) and (LXI) according to Steps 111, 112, 113 and 114 successively in this order. These steps can be performed, for example, according to the method described in Synthesis, 15, 2549-2561 (2005).

Amidation in Step 113 can be also performed, for example, according to the method described in [Fundamentals and Experiments of Peptide Synthesis] (Nobuo Izumiya et al.; Maruzen Co., Ltd.). As a condensation agent to be used in the step, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) described in Tetrahedron, 57, 1551 (2001) can be used.

In Step 115, compound (IIIf²⁸) can be prepared by reducing the lactam compound (LXII). The step can be performed in the same manner as in the aforementioned Step 21.

In Step 116, compound (IIIf²⁹) can be prepared by introducing the protecting group PRG⁹. Examples of the "protecting group" for PRG⁹ include those similar to the protecting group exemplified in Step 1. Among them, a tert-butyldimethylsilyl (TBDMS) group, tert-butyldiphenylsilyl (TBDPS) group and the like are preferable. The step can be performed in the same manner as in the aforementioned Step 60.

In Step 117, compound (IIIf³⁰) can be prepared by removing the benzyl group, and then introducing PRG¹. The step can be performed in the same manner as in the aforementioned Step 64.

In Step 118, compound (IIIf³¹) can be prepared by removing PRG⁹. The step can be performed in the same manner as in the aforementioned Step 65. Compound (IIIf³¹) obtained in the step can be subjected to inversion of configuration on the carbon atom which the hydroxyl group is bonded to, according to the method described in Organic Reactions, 42, 335-656 (1992), and the resulting inverted compound may be used for Step 120. Compound (IIIf³¹) and the resulting inverted compound thereof can also be, for example, converted to the corresponding ether in the same manner as in the aforementioned Step 3.

In Step 119, compound (IIIf³²) can be prepared by converting the hydroxy group of compound (IIIf³¹) to a leaving group. The step can be performed in the same manner as in the aforementioned Step 11.

In Step 120, compound (IIIf³³) can be prepared by subjecting compound (IIIf³²) to azidation. The step can be performed in the same manner as in the aforementioned Step 27. In the step, the configuration on the reaction center is known to be generally inverted due to the substitution of the azide group. Compound (IIIf³³) obtained in the step can also be converted to the corresponding amine, amide, urea, sulfonamide or sulfamide in the same manner as in the aforementioned Steps 28, 31, 32, 33 or 34.

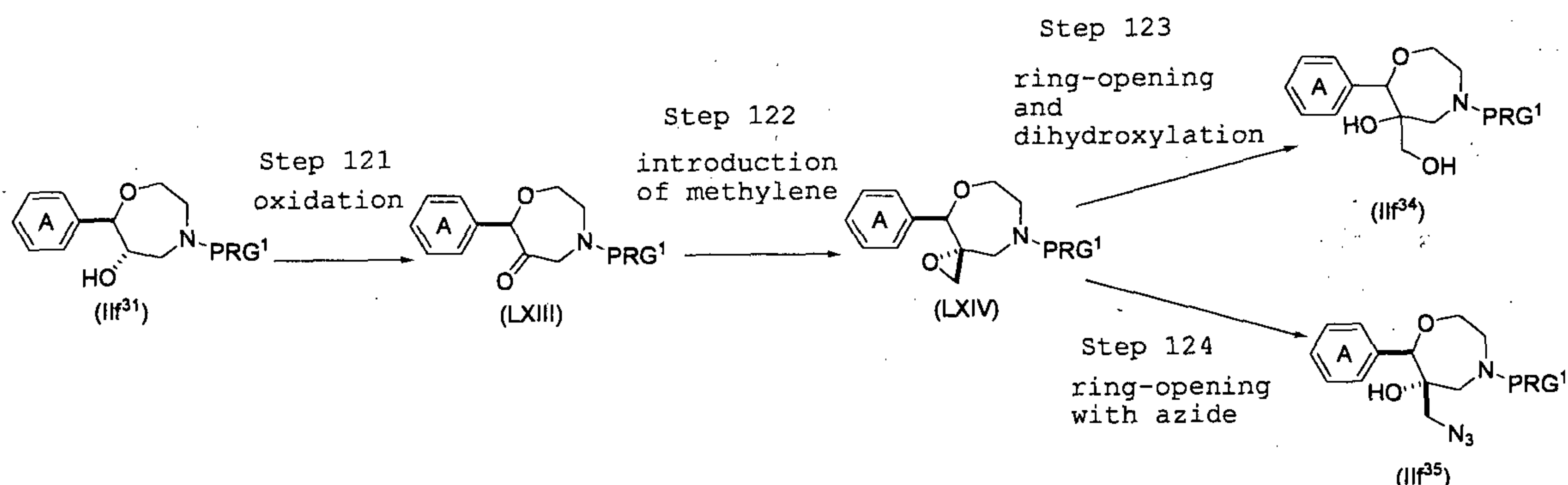
[0319]

[Preparation of Compounds (IIIf³⁴), (IIIf³⁵) and Derivative

Thereof]

Compound (IIIf³⁴) (R is -CH₂OH, ring B⁶ further has a hydroxy group on the 6-position), and compound (IIIf³⁵) (R is -CH₂N₃, and ring B⁶ further has a hydroxy group on the 6-position) which are encompassed in compound (IIIf) can be prepared, for example, according to the following method.

[0320]



[0321]

wherein each symbol is as defined above.

In Step 121, compound (LXIII) can be prepared by oxidizing the hydroxyl group of compound (IIIf³¹). The step can be performed in the same manner as in the aforementioned Step 107.

In Step 122, compound (LXIV) can be prepared by introducing methylene into the carbonyl group of compound (LXIII). The step can be performed, for example, according to the method described in Tetrahedron, 57, 8983-8988 (2001) or Chemical Reviews, 97, 2341-2372 (1997).

In Step 123, compound (IIIf³⁴) can be prepared by subjecting the epoxy group of compound (LXIV) to a ring-opening reaction and dihydroxylation. The step can be performed, for example, according to the method described in Angewandte Chemie International Edition, 44, 734-737 (2005).

In Step 124, compound (IIIf³⁵) can be prepared by subjecting the epoxy group of compound (LXIV) to a ring-opening reaction with an azide. The step can be performed, for example, according to the method described in Synthesis, 19, 3108-3120 (2008). Compound (IIIf³⁵) obtained in the step can be

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converted to the corresponding amine, amide, urea, sulfonamide or sulfamide in the same manner as in the aforementioned Step 28, 31, 32, 33 or 34.

[0322]

- 5 [Conversion of R group in Compound (Ia), (Ib), (Ic), (Id), (Ie) and (If) to alcohol, amine, azide, ether, thioether, sulfone, amide, urea, sulfonamide, sulfamide, ester or carboxylic acid]

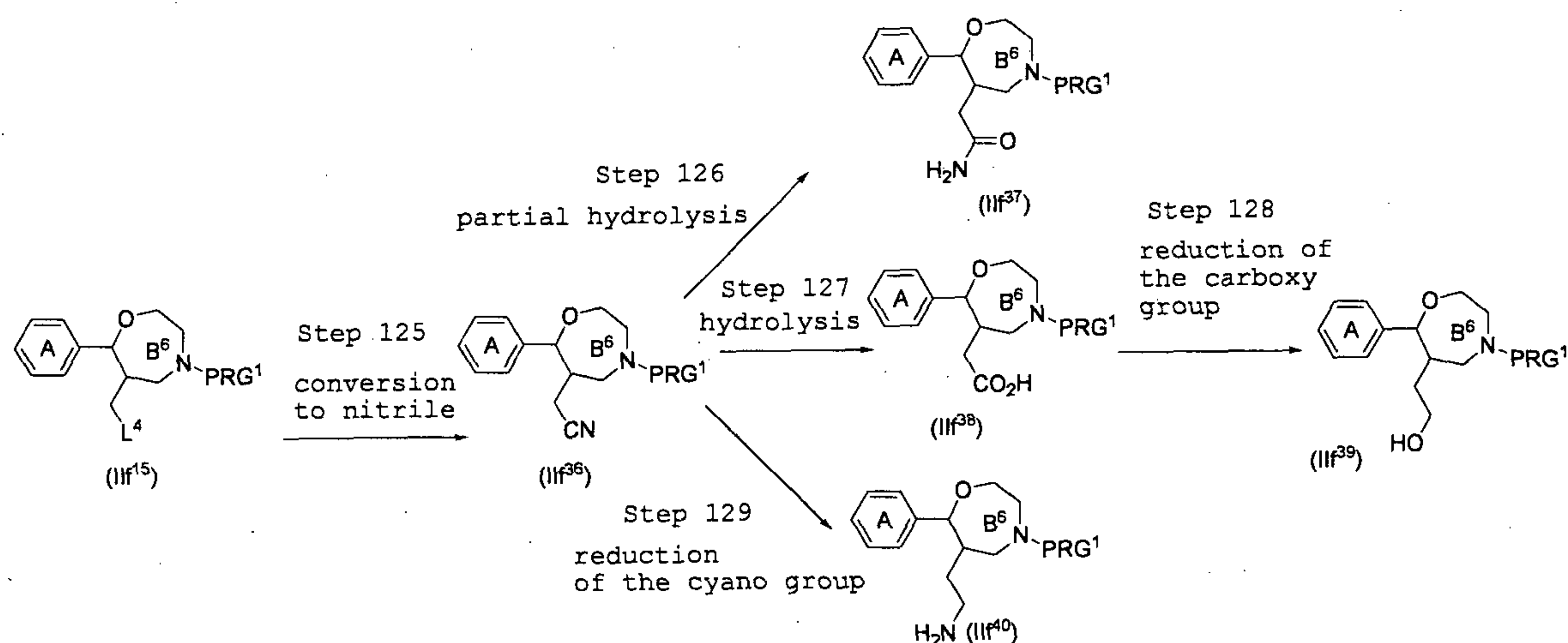
The construction method of each R group shown in the preparation of the above-mentioned compounds (IIa)-(IIf) can also be applied to construction of any R group of compounds (IIa)-(IIf), as long as it is chemically acceptable. That is, the method of conversion of each R group shown in the preparation of the above-mentioned compounds (IIa)-(IIf) to the corresponding alcohol, amine, azide, ether, thioether, sulfone, amide, urea, sulfonamide, sulfamide, ester or carboxylic acid can be used for any of the preparation of compounds (IIa)-(IIf).

After obtaining the corresponding compounds (IIa)-(IIf), the object compounds (Ia)-(If) can be prepared, respectively, according to the aforementioned Steps 1, 4, 14, 35, 44 and 56.

[0323]

[Addition of one carbon to R group in compounds (Ia), (Ib), (Ic), (Id), (Ie) and (If)]

25 [0324]



[0325]

wherein each symbol is as defined above.

In Step 125, addition of one carbon to R group can be performed, for example, by converting compound (IIIf¹⁵) to the corresponding nitrile. The step can be performed, for example,
5 according to the method described in Journal of Organic Chemistry, 25, 257 (1960).

In Step 126, the obtained compound (IIIf³⁶) can be converted to the amide compound (IIIf³⁷) by partial hydrolysis of the cyano group of compound (IIIf³⁶). The step can be
10 performed, for example, according to the method described in Journal of Organic Chemistry, 57, 4441-4444 (1992).

In Step 127, compound (IIIf³⁶) can be converted to the carboxylic acid compound (IIIf³⁸) by hydrolysis of the cyano group of compound (IIIf³⁶). The step can be performed, for
15 example, according to the method described in Journal of the American Chemical Society, 107, 7967 (1985).

In Step 128, compound (IIIf³⁸) can be converted to the alcohol compound (IIIf³⁹) by reduction of the carboxy group of compound (IIIf³⁸). The step can be performed, for example,
20 according to the method described in Organic Synthesis, 64, 104 (1985) or Organic Reactions, 6, 469 (1951).

In Step 129, compound (IIIf³⁶) can be converted to the amine compound (IIIf⁴⁰) by reduction of the cyano group of compound (IIIf³⁶). The step can be performed in the same manner
25 as in the aforementioned Step 9. Among them, the method described in Journal of Organic Chemistry, 51, 4856 (1986) or Journal of the American Chemical Society, 72, 876 (1950) is preferable.

The obtained carboxylic acid compound (IIIf³⁸), alcohol
30 compound (IIIf³⁹), amine compound (IIIf⁴⁰) can be converted according to the method described in the present specification.

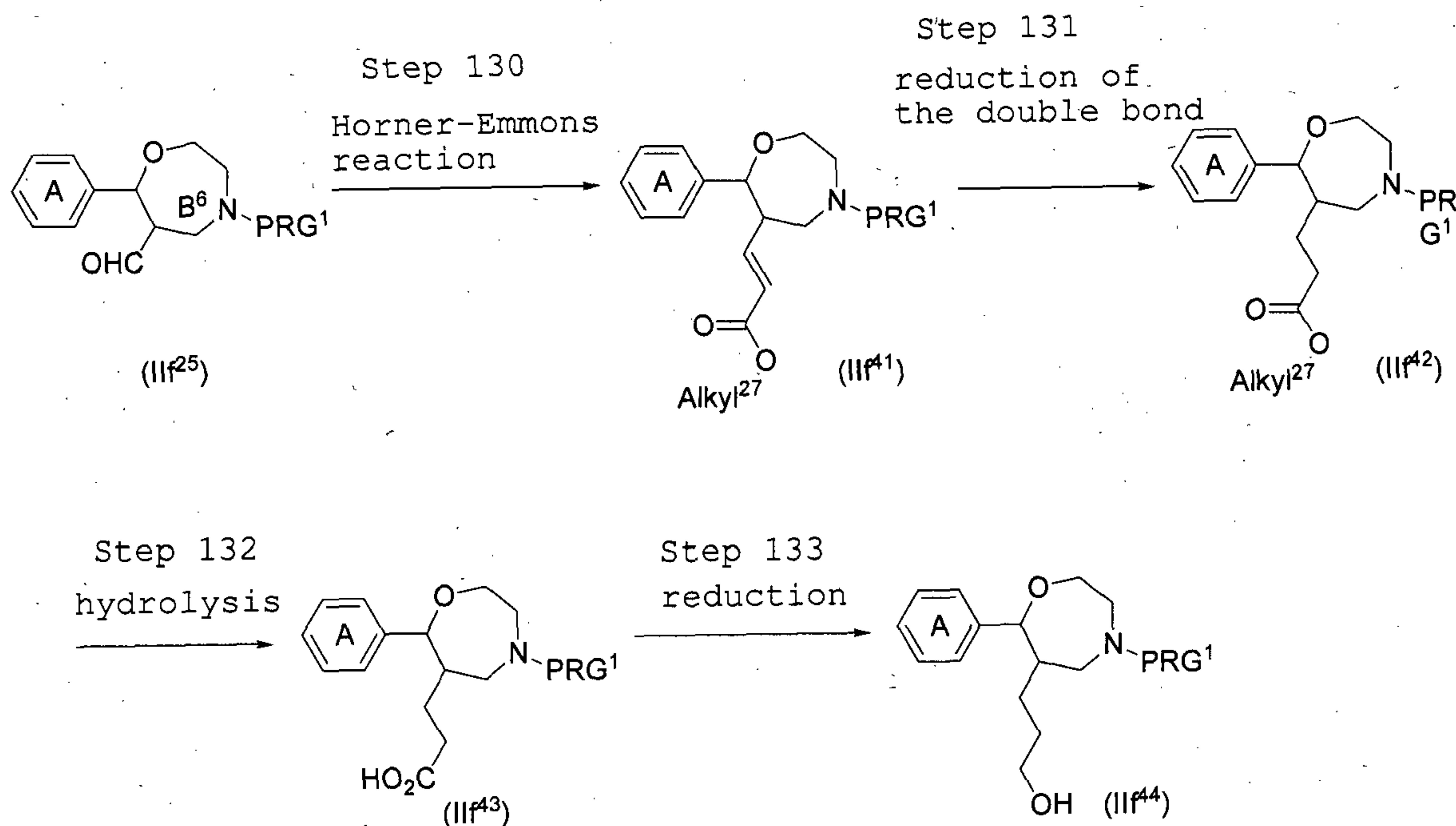
The above-mentioned addition of one carbon to R group can be applied not only to compound (IIIf) but also to any of
35 compounds (IIa)-(IIe), as long as it is chemically acceptable.

After obtaining the corresponding compounds (IIa)-(IIf), the object compounds (Ia)-(If) can be prepared, respectively, according to the aforementioned Steps 1, 4, 14, 35, 44 and 56.

[0326]

- 5 [Addition of two carbons to R group in Compounds (Ia), (Ib), (Ic), (Id), (Ie) and (If)]

[0327]



[0328]

- 10 wherein Alkyl²⁷ is a C₁₋₆ alkyl group, and other symbols are each as defined above.

In Step 130, addition of two carbons to R group can be performed, for example, by subjecting compound (IIIf²⁵) to the Horner-Emmons reaction. The step can be performed, for example, according to the method described in Chemical Reviews, 89, 863-927 (1989).

In Step 131, the obtained compound (IIIf⁴¹) can be converted to the ester compound (IIIf⁴²) by reduction of the double bond of compound (IIIf⁴¹). The step can be performed, for example, according to the method described in Journal of Medicinal Chemistry, 35, 3135-3141 (1992) or Journal of Medicinal Chemistry, 50, 2651-2966 (2007).

In Step 132, compound (IIIf⁴²) can be converted to the

carboxylic acid compound (IIIf⁴³) by hydrolysis. The step can be performed, for example, according to the method described in Journal of Organic Chemistry, 50, 2128 (1985).

In Step 133, compound (IIIf⁴³) can be converted to the alcohol compound (IIIf⁴⁴) by reduction. The step can be performed in the same manner as in the aforementioned Step 128.

Compound (IIIf⁴²) can also be directly converted to the alcohol compound (IIIf⁴⁴) by reduction without via compound (IIIf⁴³). The "reduction of the ester" can be performed in the same manner as in the aforementioned Step 9.

The obtained carboxylic acid compound (IIIf⁴³) and alcohol compound (IIIf⁴⁴) can be converted according to the method described in the present specification.

The above-mentioned addition of two carbons to R group can be applied not only to compound (IIIf) but also to any of compounds (IIa)-(IIe), as long as it is chemically acceptable.

After obtaining the corresponding compounds (IIa)-(IIf), the object compounds (Ia)-(If) can be prepared, respectively, according to the aforementioned Steps 1, 4, 14, 35, 44 and 56.

[0329]

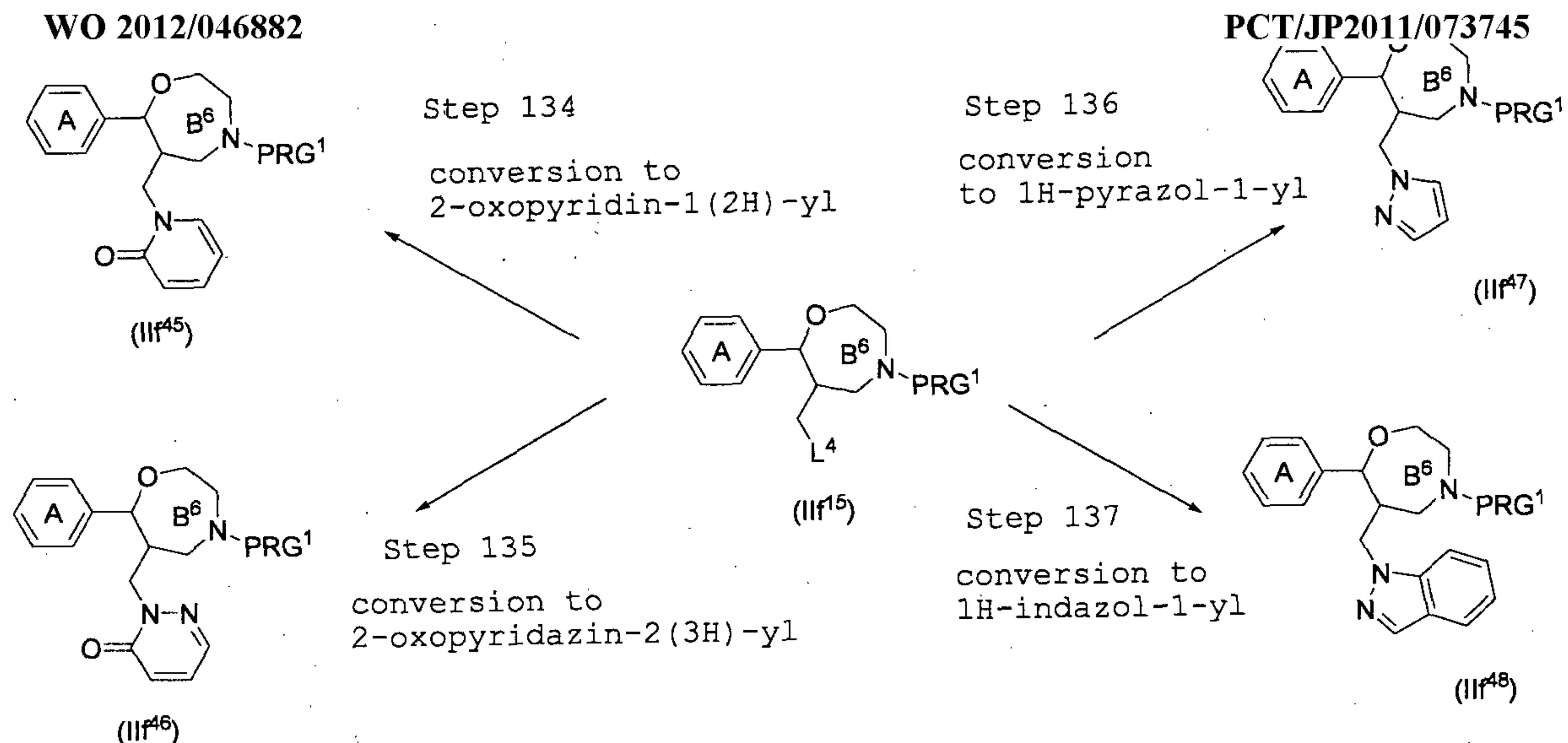
[Various modification method of R group in compounds (Ia), (Ib), (Ic), (Id), (Ie) and (If)]

[0330]

(1) Conversion to 2-oxopyridin-1(2H)-yl, 2-oxopyridazin-2(3H)-yl, 1H-pyrazol-1-yl or 1H-indazol-1-yl

[0331]

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[0332]

wherein each symbol is as defined above.

In Step 134, compound (IIIf⁴⁵) can be prepared by
 5 converting the leaving group of compound (IIIf¹⁵) to 2-oxopyridin-1(2H)-yl. The "2-oxopyridin-1(2H)-yl" optionally has additional substituent(s). The step can be performed, for example, according to the method described in Journal of Organic Chemistry, 64, 950-953 (1999), Tetrahedron, 57, 607-
 10 616 (2001). In addition, Step 134 can be performed, for example, according to the Mitsunobu reaction described in Organic Reactions, 42, 335-656 (1992).

In Step 135, compound (IIIf⁴⁶) can be prepared by
 converting the leaving group of compound (IIIf¹⁵) to 2-oxopyridazin-2(3H)-yl. The "2-oxopyridazin-2(3H)-yl"
 15 optionally has additional substituent(s). The step can be performed in the same manner as in the aforementioned Step 134.

In Step 136, compound (IIIf⁴⁷) can be prepared by
 20 converting the leaving group of compound (IIIf¹⁵) to 1H-pyrazol-1-yl. The "1H-pyrazol-1-yl" optionally has additional substituent(s). The step can be performed in the same manner as in the aforementioned Step 134.

In Step 137, compound (IIIf⁴⁸) can be prepared by
 25 converting the leaving group of compound (IIIf¹⁵) to 1H-indazol-1-yl. The "1H-indazol-1-yl" optionally has additional

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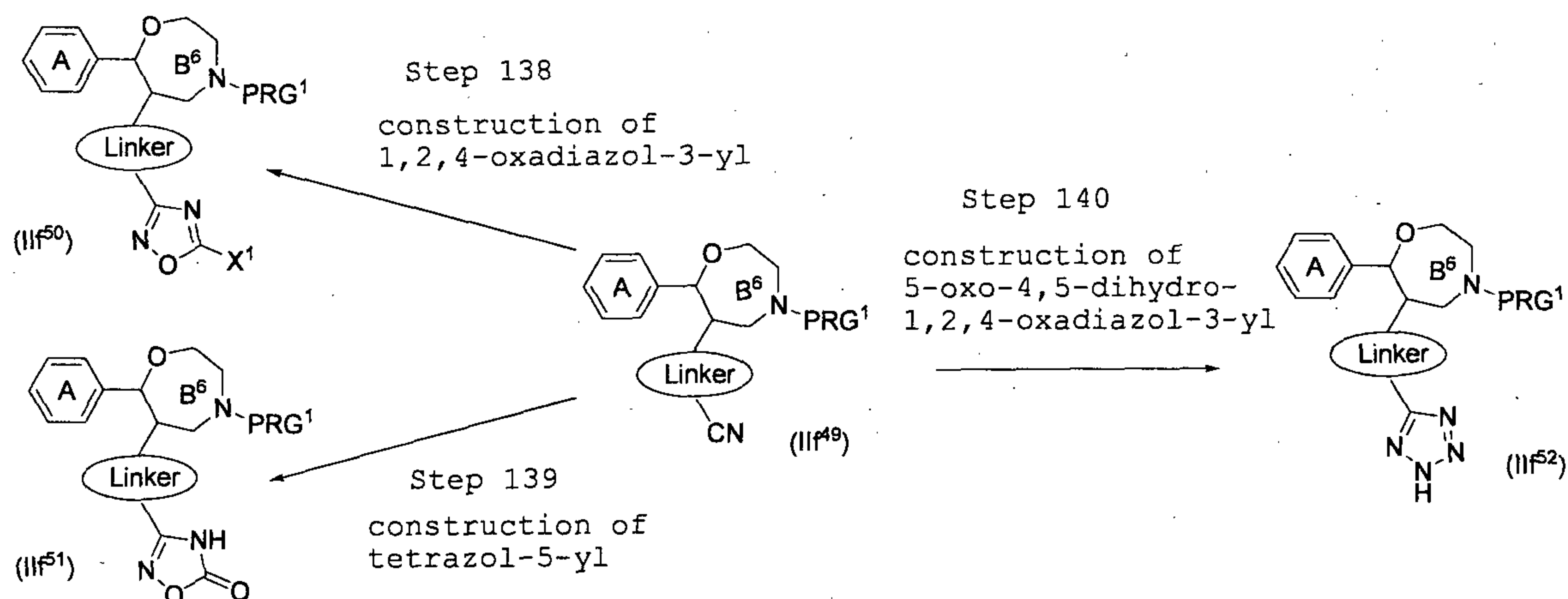
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substituent(s). The step can be performed in the same manner as in the aforementioned Step 134.

[0333]

(2) Construction of 1,2,4-oxadiazol-3-yl, 5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl or tetrazol-5-yl

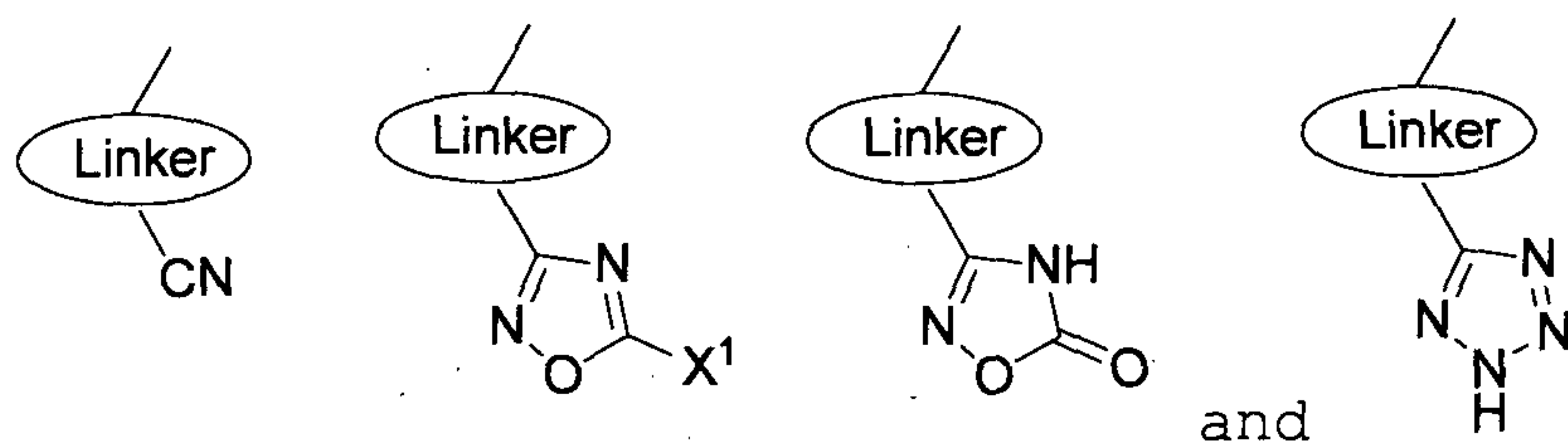
[0334]



[0335]

wherein Linker is not particularly limited as long as

10 [0336]



[0337]

are encompassed in R, X¹ is a hydrogen atom, a C₁₋₆ alkyl group optionally having substituent(s), an aryl group optionally having substituent(s), an amide group or a carboxyl group, and other symbols are each as defined above.

In Step 138, compound (IIIf⁵⁰) can be prepared by converting the cyano group of compound (IIIf⁴⁹) to 1,2,4-oxadiazol-3-yl having X¹ on the 5-position. The step can be performed, for example, according to the method described in Bioorganic and Medicinal Chemistry, 12, 2815-2824 (2004).

In Step 139, compound (IIIf⁵¹) can be prepared by converting the cyano group of compound (IIIf⁴⁹) to 5-oxo-4,5-

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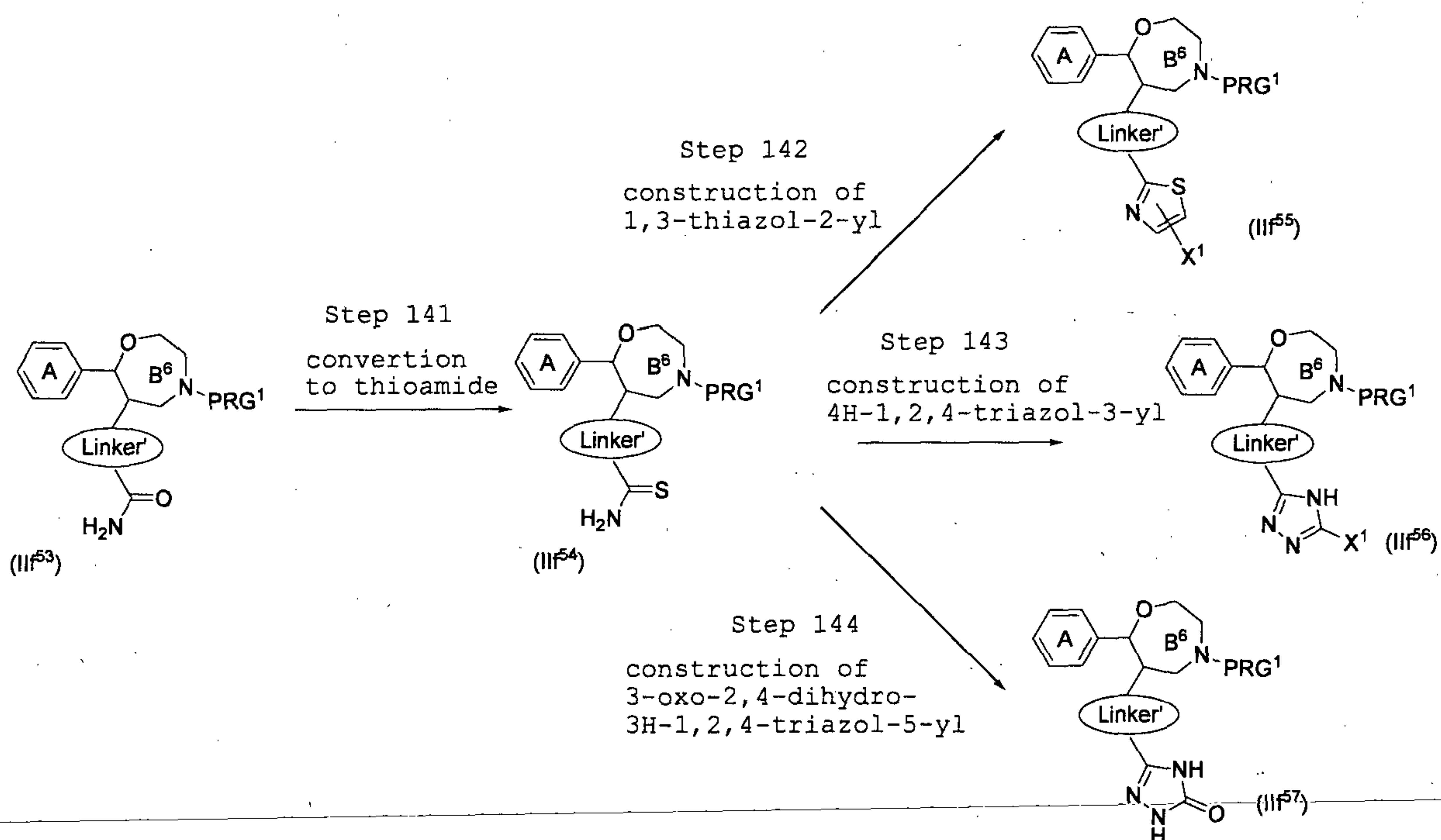
dihydro-1,2,4-oxadiazol-3-yl. The step can be performed, for example, according to the method described in WO 2008-62905.

In Step 140, compound (II^{f52}) can be prepared by converting the cyano group of compound (II^{f49}) to tetrazol-5-yl. The step can be performed, for example, according to the method described in Advances in Heterocyclic Chemistry, 21, 323-435 (1977).

[0338]

(3) Construction of 1,3-thiazol-2-yl, 4H-1,2,4-triazol-3-yl or 3-oxo-2,4-dihydro-3H-1,2,4-triazol-5-yl

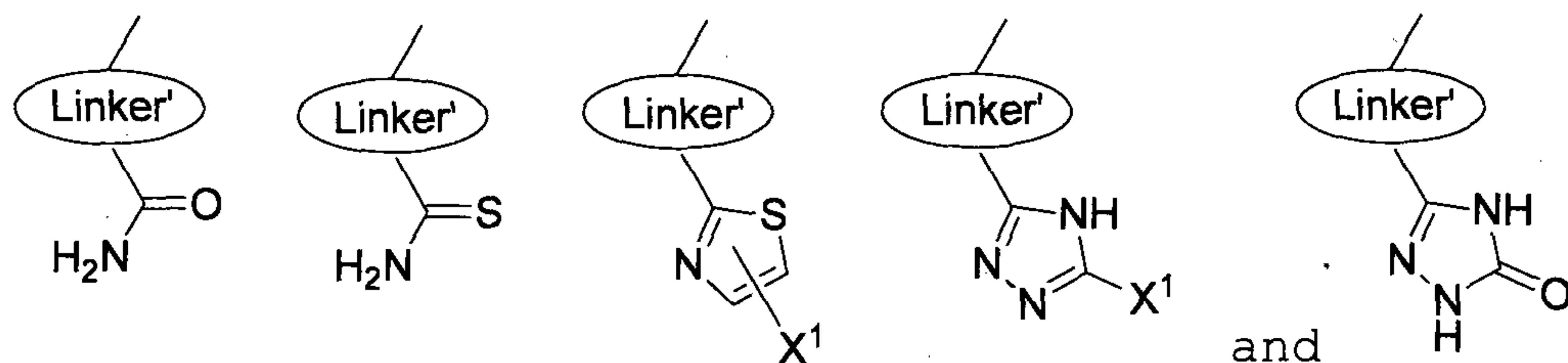
[0339]



[0340]

wherein Linker' is not particularly limited as long as

15 [0341]



[0342]

are encompassed in R, and other symbols are each as defined above.

Both 1,3-thiazol-2-yl, 4H-1,2,4-triazol-3-yl and 3-oxo-2,4-dihydro-3H-1,2,4-triazol-5-yl can be induced from thioamide.

In Step 141, compound (II^{f54}) can be prepared by converting the amide group of compound (II^{f53}) to a thioamide group. The step can be performed, for example, according to the method described in Journal of Organic Chemistry, 66, 3459-3466 (2001).

In Step 142, compound (II^{f55}) can be prepared by converting the thioamide group of compound (II^{f54}) to 1,3-thiazol-2-yl. The step can be performed, for example, according to the method described in Bioorganic and Medicinal Chemistry, 15, 6574-6595 (2007).

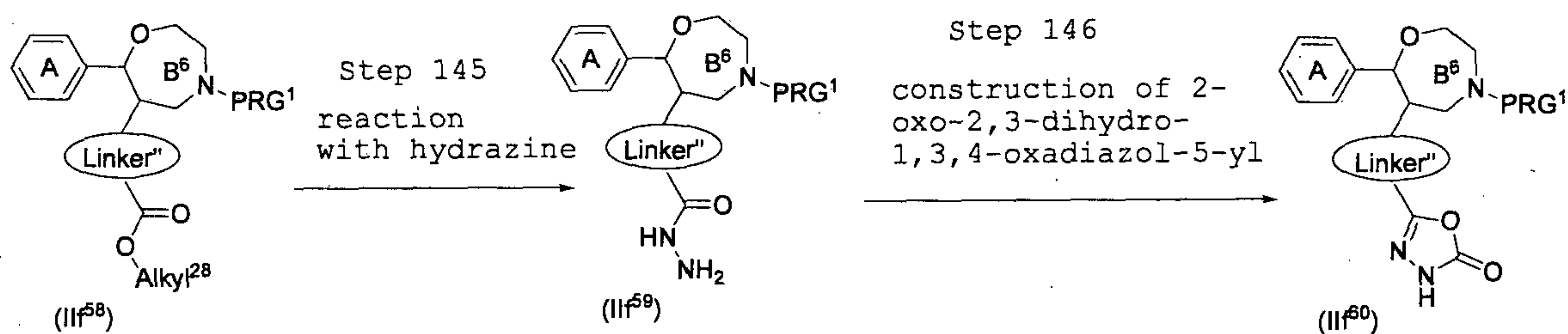
In Step 143, compound (II^{f56}) can be prepared by converting the thioamide group of compound (II^{f54}) to 4H-1,2,4-triazol-3-yl. The step can be performed, for example, according to the method described in Bioorganic and Medicinal Chemistry Letters, 14, 817-821 (2004).

In Step 144, compound (II^{f57}) can be prepared by converting the thioamide group of compound (II^{f54}) to 3-oxo-2,4-dihydro-3H-1,2,4-triazol-5-yl. The step can be performed, for example, according to the method described in Journal of Heterocyclic Chemistry, 18, 79-83 (1981).

[0343]

(4) Construction of 2-oxo-2,3-dihydro-1,3,4-oxadiazol-5-yl

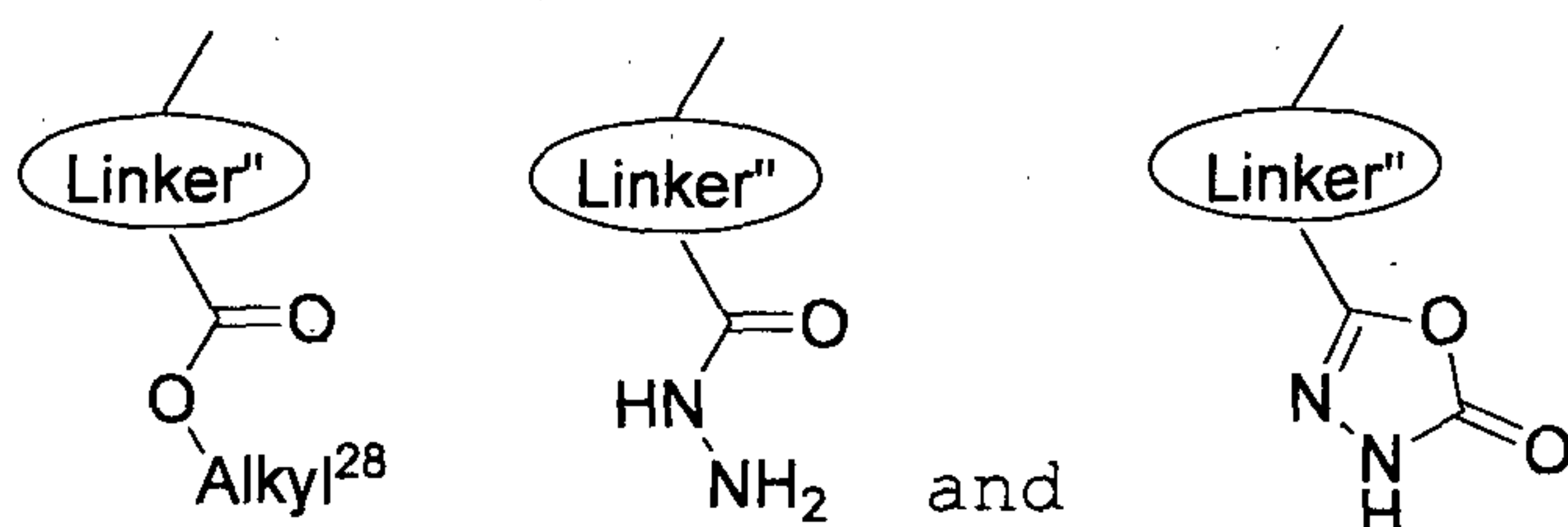
[0344]



[0345]

wherein Linker'' is not particularly limited as long as

[0346]



[0347]

are encompassed in R, Alkyl²⁸ is a C₁₋₆ alkyl group, and other symbols are each as defined above.

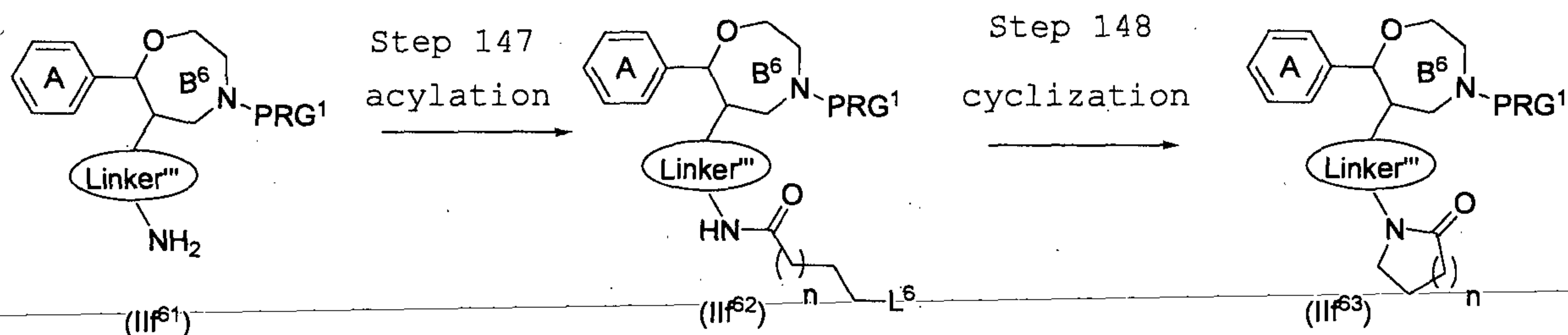
- 5 In Step 145, compound (IIIf⁵⁹) can be prepared by reacting compound (IIIf⁵⁸) with hydrazine. The step can be performed, for example, according to the method described in Bioorganic and Medicinal Chemistry, 18, 5007-5015 (2010).

- 10 In Step 146, compound (IIIf⁶⁰) can be prepared by subjecting compound (IIIf⁵⁹) to cyclization. The step can be performed, for example, according to the method described in Organic Letters, 10, 1755-1758 (2008).

[0348]

(5) Construction of lactam ring

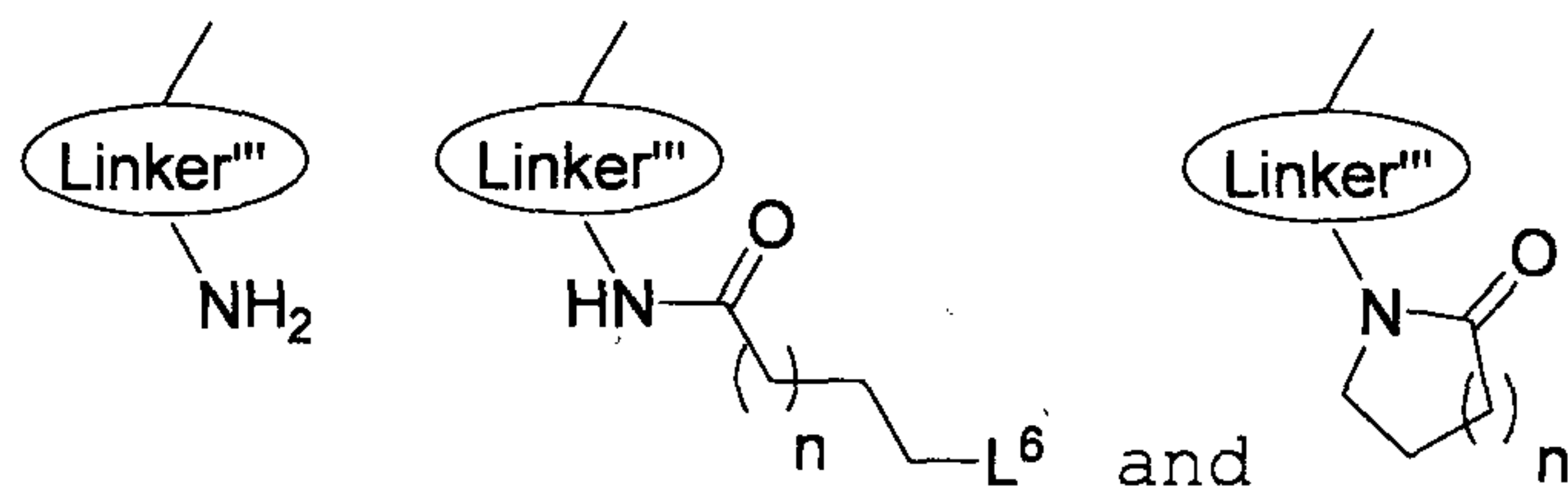
- 15 [0349]



[0350]

wherein Linker''' is not particularly limited as long as

[0351]



20

[0352]

are encompassed in R, L⁶ is a leaving group, n is any integer of 1 to 5, and other symbols are each as defined above.

In Step 147, compound (IIIf⁶²) can be prepared by

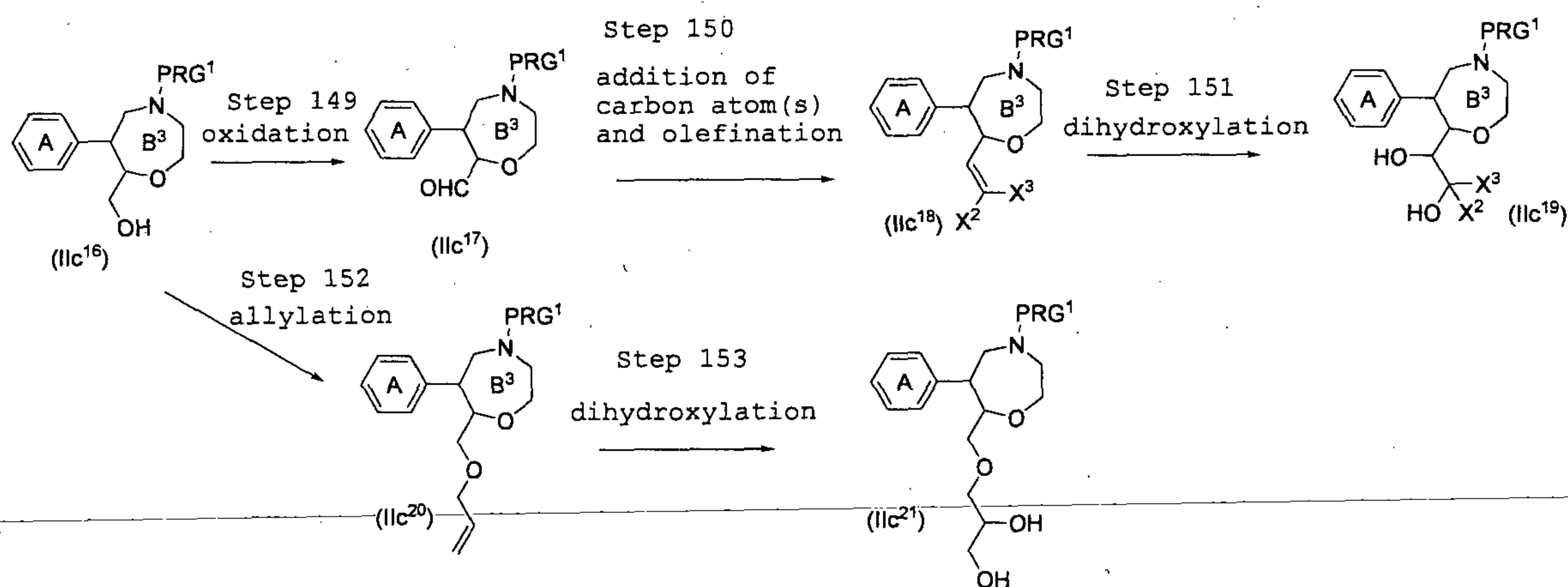
subjecting compound (IIIf⁶¹) to acylation. The step can be performed in the same manner as in the aforementioned Step 18. For the "acylation", an acyl group having a leaving group L⁶ at the terminal is selected. Examples of the "leaving group L⁶" include those similar to the leaving group exemplified in the aforementioned Step 11. Among them, a chlorine atom and a bromine atom are preferable.

In Step 148, compound (IIIf⁶³) can be prepared by subjecting compound (IIIf⁶²) to cyclization. The step can be generally performed in the presence of a base. Examples of the "base" include those similar to the base exemplified in the aforementioned Step 5. Among them, sodium hydride, sodium tert-butoxide and sodium hydroxide are preferable.

[0353]

(6) Conversion to 1,2-diol

[0354]



[0355]

wherein X² and X³ are each a hydrogen atom, a C₁₋₆ alkyl group optionally having substituent(s), an aryl group, a 5-membered or 6-membered aromatic heterocyclic group, and other symbols are each as defined above.

In Step 149, compound (IIc¹⁷) can be prepared by oxidizing the hydroxyl group of compound (IIc¹⁶). The step can be performed, for example, by DMSO oxidation such as the Swern oxidation, the Moffat oxidation, the Corey-Kim oxidation and the like, the Ley oxidation using tetrapropylammonium

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perruthenate (TPAP), or the oxidation using Dess-Martin reagent, and the like. The step can be performed, for example, according to the method described in Organic Reactions, 39, 297-572 (1990) for the Swern oxidation, Aldrichimica Acta, 23, 13-19 (1990) for the Ley oxidation, Journal of the American Chemical Society, 126, 320-328 (2004) for the Dess-Martin oxidation, and the like.

In Step 150, compound (IIc¹⁸) can be prepared by subjecting compound (IIc¹⁷) to addition of carbon(s) and olefination. The step can be performed, for example, according to the Wittig reaction, Horner-Emmons reaction, Peterson reaction and the like. The Wittig reaction can be performed, for example, according to the method described in Organic Reactions, 14, 270-490 (1965) and the like.

In Step 151, compound (IIc¹⁹) can be prepared by subjecting compound (IIc¹⁸) to dihydroxylation. The step can be performed, for example, according to the method using osmium tetroxide, which is described in the Chemical Reviews, 80, 187-213 (1980). Osmium tetroxide supported by a polymer which is described in Synthesis 45 (1989) and the like may be used as a catalyst. In addition, the asymmetric dihydroxylation described in Tetrahedron: Asymmetry 3, 1317-1349 (1992) and the like may be performed.

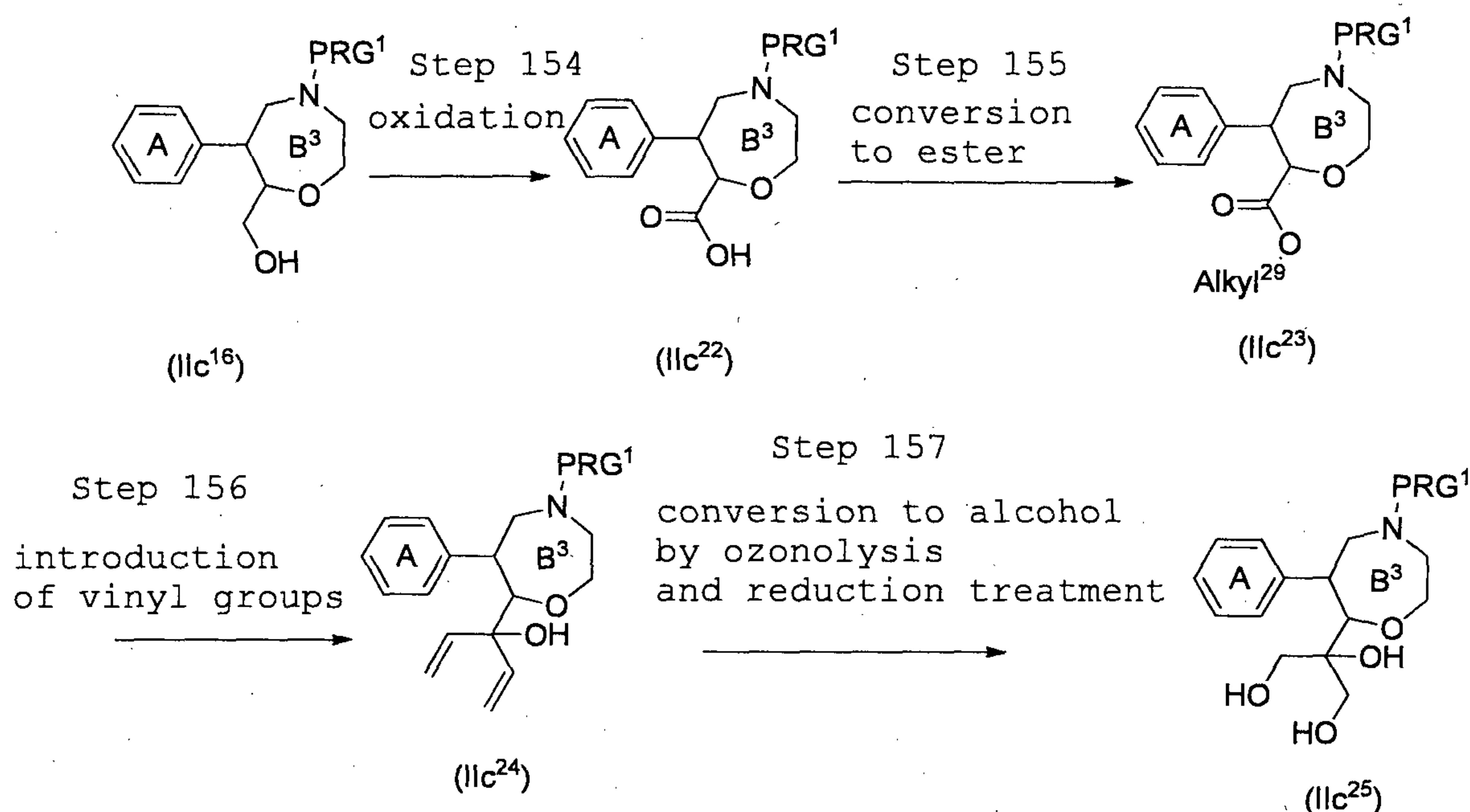
In Step 152, compound (IIc²⁰) can be prepared by subjecting compound (IIc¹⁶) to allylation. The step can be performed, for example, according to the method described in Tetrahedron, 53, 17501-17512 (1997).

In Step 153, compound (IIc²¹) can be prepared by subjecting compound (IIc²⁰) to dihydroxylation. The step can be performed in the same manner as in the aforementioned Step 151.

[0356]

(7) Conversion to 1,2,3-triol

[0357]



[0358]

wherein Alkyl²⁹ is a C₁₋₆ alkyl group, and other symbols are each as defined above.

5 In Step 154, compound (IIc²²) can be prepared by oxidizing compound (II¹⁶). The step can be performed, for example, according to a conventional oxidation of carboxylic acid, such as Jones oxidation and the like. Among them, the method using ruthenium catalyst, which is described in
 10 Tetrahedron Letters 33, 2307-2310 (1992) or the like is preferable. The step can be performed in the same manner as in the aforementioned Steps 107-108.

In Step 155, compound (IIc²³) can be prepared by converting the carboxylic acid moiety of compound (II²²) to an
 15 ester moiety. The step can be performed, for example, according to the Fischer esterification reaction described in Organic Synthesis Collective Volume 1, 241 (1941) and the like, the alkylation using an alkyl halide which is described in the Journal of Organic Chemistry, 50, 2668 (1985) and the
 20 like, or the methylation using diazomethane which is described in Journal of Organic Chemistry, 50, 2323 (1985).

In Step 156, compound (IIc²⁴) can be prepared by introducing two vinyl groups into the ester group of compound

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(II²³). The step can be performed by adding reacting 2 or more equivalents of a vinyl metal compound to compound (II²³). The vinyl metal compound to be used is preferably a Grignard reagent such as vinylmagnesium bromide and the like, or
5 vinyl lithium. The step can be performed, for example, according to the method described in Journal of Organic Chemistry, 65, 5817-5822 (2000) and the like. The reaction may be performed in the presence of cerium(III) chloride which is described in Organic Letters, 3, 671-674 (2001).

10 In Step 157, compound (IIc²⁵) can be prepared by subjecting compound (II²⁴) to ozonolysis, and then treating the resulting compound with a reducing agent. The step may be performed by isolating the aldehyde intermediate produced by the ozonolysis, and then reducing the aldehyde intermediate.
15 However, the step is preferably performed by reducing the aldehyde intermediate without isolation in the same system. Examples of the "reducing agent" include those similar to the reducing agent exemplified in Step 9. Among them, sodium borohydride is preferable. The step can be performed, for
20 example, according to the method described in Journal of Organic Chemistry, 61, 3999-4006 (1996).

[0359]

The various modification methods of R group shown in the above-mentioned (1)-(7) can also be applied to the
25 modification of R group in each of the compounds (IIa), (IIb), (IIc), (IId), (IIe) and (IIf).

After obtaining the corresponding compounds (IIa)-(IIf), the object compounds (Ia)-(If) can be prepared, respectively, according to the aforementioned Steps 1, 4, 14, 35, 44 and 56.

30 [0360]

When compound (I) is obtained as a free compound, it can be converted to the object salt by a method known per se or a method analogous thereto. When it is obtained as a salt, it can be converted to the object other salt by a method known
35 per se or a method analogous thereto.

Compound (I) prepared by such method can be isolated and purified by a conventional separation means such as recrystallization, distillation, chromatography and the like.

5 When compound (I) contains an optical isomer, a stereoisomer, a positional isomer or a rotamer, these are also encompassed in compound (I), and each of them can be obtained as a single produce by a synthesis method and a separation method (e.g., concentration, solvent extraction, column
10 chromatography, recrystallization etc.) known per se. For example, when compound (I) contains an optical isomer, the optical isomer resolved from the compound is also encompassed in compound (I).

[0362]

15 The optical isomer can be prepared by a method known per se. To be specific, an optically active synthetic intermediate is used, or the final racemate product is subjected to optical resolution according to a conventional method to give an optical isomer.

20 The method of optical resolution may be a method known per se, such as a fractional recrystallization method, a chiral column method, a diastereomer method, etc.

[0363]

1) Fractional recrystallization method

25 A method wherein a salt of a racemate with an optically active compound (e.g., (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine, etc.) is formed, which is separated by a fractional
30 recrystallization method, and if desired, a free optical isomer is obtained by a neutralization step.

[0364]

2) Chiral column method

A method wherein a racemate or a salt thereof is applied
35 to a column for separation of an optical isomer (a chiral

column) to allow separation. In the case of a liquid chromatography, for example, a mixture of the optical isomers is applied to a chiral column such as ENANTIO-OVM (manufactured by Tosoh Corporation), CHIRAL series (manufactured by Daicel Chemical Industries, Ltd.) and the like, and developed with water, various buffers (e.g., phosphate buffer, etc.) and organic solvents (e.g., ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, etc.) solely or in admixture to separate the optical isomer. In the case of a gas chromatography, for example, a chiral column such as CP-Chirasil-DeX CB (manufactured by GL Sciences Inc.) and the like is used to allow separation.

[0365]

3) Diastereomer method

A method wherein a racemic mixture is prepared into a diastereomeric mixture by chemical reaction with an optically active reagent, which is made into a single substance by a typical separation method (e.g., a fractional recrystallization method, a chromatography method, etc.) and the like, and is subjected to a chemical treatment such as hydrolysis and the like to separate an optically active reagent moiety, whereby an optical isomer is obtained. For example, when compound (I) contains hydroxy, or primary or secondary amino in a molecule, the compound and an optically active organic acid (e.g., MTPA [α -methoxy- α -(trifluoromethyl)phenylacetic acid], (-)-menthoxyacetic acid, etc.) and the like are subjected to condensation reaction to give diastereomers in the ester form or in the amide form, respectively. When compound (I) has a carboxylic acid group, this compound and an optically active amine or alcohol reagent are subjected to condensation reaction to give diastereomers in the amide form or in the ester form, respectively. The separated diastereomer is converted to an optical isomer of the original compound by acid hydrolysis or base hydrolysis.

[0366]

The compound (I) may be a crystal. The compound (I) may be a single crystal, or a mixture of plural crystal forms. Moreover, compound (I) may be a cocrystal.

The crystal of the compound (I) can be prepared by
5 crystallization of compound (I) according to crystallization methods known *per se*.

Examples of the crystallization method include a method of crystallization from a solution, a method of crystallization from vapor, a method of crystallization from the melts and the
10 like.

[0367]

The "crystallization from a solution" is typically a method of shifting a non-saturated state to supersaturated state by varying factors involved in solubility of compounds (solvent
15 composition, pH, temperature, ionic strength, redox state, etc.) or the amount of solvent. Specific examples thereof include a concentration method, a slow cooling method, a reaction method (a diffusion method, an electrolysis method), a hydrothermal growth method, a flux method and the like. Examples of the
20 solvent to be used include aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, etc.), saturated hydrocarbons (e.g., hexane, heptane, cyclohexane, etc.), ethers (e.g., diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane,
25 etc.), nitriles (e.g., acetonitrile, etc.), ketones (e.g., acetone, etc.), sulfoxides (e.g., dimethyl sulfoxide, etc.), acid amides (e.g., N,N-dimethylformamide, etc.), esters (e.g., ethyl acetate, etc.), alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), water and the like. These solvents are
30 used alone or in a combination of two or more at a suitable ratio (e.g., 1:1 to 1:100 (a volume ratio)). Where necessary, a seed crystal can be used.

[0368]

Examples of the "crystallization from vapor" include a
35 vaporization method (a sealed tube method, a gas stream method),

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a gas phase reaction method, a chemical transportation method and the like.

[0369]

Examples of the "crystallization from the melts" include a normal freezing method (a Czockralski method, a temperature gradient method and a Bridgman method, etc.), a zone melting method (a zone leveling method and a floating zone method, etc.), a special growth method (a VLS method and a liquid phase epitaxy method, etc.) and the like.

10 [0370]

Preferable examples of the crystallization method include a method of dissolving compound (I) in a suitable solvent (e.g., alcohols such as methanol, ethanol, etc., and the like) at a temperature of 20 to 120°C, and cooling the resulting solution to a temperature not higher than the temperature of dissolution (e.g., 0 to 50°C, preferably 0 to 20°C) and the like.

The thus obtained crystals of compound (I) can be isolated, for example, by filtration and the like.

An analysis method of the obtained crystal is generally a method of crystal analysis by powder X-ray diffraction. As a method of determining crystal orientation, a mechanical method or an optical method and the like can also be used.

The compound (I) may be a pharmaceutically acceptable cocrystal or cocrystalline salt. Here, the cocrystal or cocrystalline salt means a crystalline substance constituted by two or more kinds of specific solids at room temperature, each of which has different physical properties (e.g., structure, melting point, melting heat, hygroscopicity, solubility, stability etc.). The cocrystal or cocrystalline salt can be prepared by a cocrystallization method known per se.

[0371]

The crystal of compound (I) obtained by the above-mentioned preparation has high purity, high quality, and low hygroscopicity, is not denatured even after a long-term

preservation under general conditions, and is extremely superior in the stability. In addition, it is also superior in the biological properties (e.g., pharmacokinetics (absorption, distribution, metabolism, excretion), efficacy expression etc.) and is extremely useful as a pharmaceutical agent.

[0372]

In the present specification, the specific rotation ($[\alpha]_D$) means, for example, a specific rotation measured using a polarimeter (JASCO, P-1030 polarimeter (No. AP-2)) and the like.

In the present specification, the melting point means a melting point measured using, for example, a micro melting point apparatus (YANACO, MP-500D), a DSC (differential scanning calorimetry) apparatus (SEIKO, EXSTAR6000) and the like.

[0373]

A prodrug of compound (I) means a compound which is converted to compound (I) with a reaction due to an enzyme, an gastric acid, etc. under the physiological condition in the living body, that is, a compound which is converted to compound (I) with oxidation, reduction, hydrolysis, etc. according to an enzyme; and a compound which is converted to compound (I) by hydrolysis etc. due to gastric acid, etc. A prodrug for compound (I) may be a compound obtained by subjecting an amino group in compound (I) to an acylation, alkylation or phosphorylation [e.g., a compound obtained by subjecting an amino group in compound (I) to an eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation or tert-butylation, etc.]; a compound obtained by subjecting a hydroxy group in compound (I) to an acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting a hydroxy group in compound (I) to an acetylation, palmitoylation, propanoylation, pivaloylation, succinylation,

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fumarylation, alanylation or dimethylaminomethylcarbonylation, etc.); a compound obtained by subjecting a carboxy group in compound (I) to an esterification or amidation [e.g., a compound obtained by subjecting a carboxy group in compound (I) to an ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification or methylamidation, etc.] and the like. These compounds can be prepared from compound (I) by a method known *per se*.

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

[0374]

The compound (I) of the present invention or a salt thereof or a prodrug thereof (hereinafter sometimes to be abbreviated as the compound of the present invention) has a superior monoamine (serotonin, norepinephrine, dopamine etc.) reuptake inhibitory activity.

In addition, the compound of the present invention is low toxic and safe. Particularly, it is useful since it does not show phototoxicity.

Compound (I) or a salt thereof can also be used as a tracer in positron emission tomography (PET) once it is labeled with a positron-emitting radionuclide such as ^{11}C , ^{18}F , ^{15}O , ^{13}N and the like.

[0375]

Therefore, the compound of the present invention acts as a substance having an monoamine neurotransmitter (serotonin, norepinephrine, dopamine etc.) reuptake inhibitory activity in a mammal (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine,

sheep, monkey, human and the like), inhibits reuptake of monoamine neurotransmitter, and improves the symptoms of psychoneurotic diseases such as depression, anxiety and the like.

5 In addition, the compound of the present invention acts as a substance having a monoamine (serotonin, norepinephrine, dopamine etc.) reuptake inhibitory activity in a mammal (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey, human and the like), inhibits reuptake of monoamines, and
10 improves the symptoms of lower urinary tract symptoms such as stress urinary incontinence and the like.

[0376]

Since the compound of the present invention has superior properties as a pharmaceutical product, such as low toxicity,
15 a few side effects and the like, it is useful for, for example, the prophylaxis or treatment of the following diseases.

(1) central neurological diseases

(a) psychoneurotic diseases [e.g., depression (e.g., major
20 depression, cerebrovascular disease depression, seasonal depression, depression caused by medicament, HIV depression etc.), anxiety (e.g., generalized anxiety disorder, social anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder etc.), attention
25 deficit hyperactivity disorder (ADHD), bipolar disorder, mania, repetitive depression, sustained mood affective disorders (e.g., cyclothymia, dysthymia etc.), depressive neurosis, sleep disorder, circadian rhythm disorder, eating disorder, drug addiction, premenstrual syndrome, autism, mood
30 disorder due to menopause, senile dementia, mild cognitive dysfunction, narcolepsy, psychophysiologic disorder, manic depression, posttraumatic stress disorder (PTSD), schizophrenia, anxiety neurosis, obsessive neurosis, mood disorder and movement disorder associated with cerebral
35 apoplexy or cerebrovascular disorder etc.]

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(b) neurodegenerative diseases (e.g., muscle fibrosis, Alzheimer's disease, Parkinson's disease, mood disorder associated with neurodegenerative disease etc.)

5 (2) various pains (e.g., neuropathic pain, inflammatory pain, fibromyalgia etc.)

(3) lower urinary tract symptoms (e.g., overactive bladder, stress urinary incontinence, mixed urinary incontinence, pelvic organ pain, urination disorders such as lower urinary tract symptom associated with interstitial cystitis and the
10 like, male lower urinary tract symptom etc.)

(4) pelvic organ prolapse (anterior vaginal wall prolapse, posterior vaginal wall prolapse, uterine prolapse, apical vaginal prolapse, rectal prolapse (rectocele), enterocele, cystocele, urethrocele etc.)

15 (5) other diseases [for example, climacteric disorder, diabetes, obesity, irritable bowel syndrome (IBS), restless legs syndrome (RLS), chronic fatigue syndrome, premenstrual syndrome (PMS), functional dyspepsia (FD), fecal incontinence, digestive system disease, smoking cessation, various
20 dependences]

[0377]

The compound of the present invention is useful as a monoamine reuptake inhibitor, and particularly useful as a prophylactic or therapeutic drug for depression, anxiety,
25 attention deficit hyperactivity disorder, stress urinary incontinence or mixed urinary incontinence. Since the compound of the present invention has a reuptake inhibitory activity against serotonin, norepinephrine and dopamine, it is useful as a triple reuptake inhibitor. Since the compound (I') of the
30 present invention has a norepinephrine reuptake inhibitory activity, it is useful as a norepinephrine reuptake inhibitor.

[0378]

In the present invention, the "monoamine reuptake inhibitor" means a reuptake inhibitor of at least one
35 monoamine selected from serotonin, norepinephrine and

dopamine, which are neurotransmitters. Examples of the "monoamine reuptake inhibitor" include serotonin reuptake inhibitor, norepinephrine reuptake inhibitor, dopamine reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor, norepinephrine-dopamine reuptake inhibitor, serotonin-dopamine reuptake inhibitor, and serotonin-norepinephrine-dopamine reuptake inhibitor.

[0379]

A medicament containing the compound of the present invention can be used singly or in the form of a pharmaceutical composition prepared according to a method known per se as a production method of pharmaceutical preparations (e.g., the method described in the Japanese Pharmacopoeia etc.) by mixing the compound and pharmacologically acceptable carriers to give, for example, tablet (including sugar-coated tablet, film-coated tablet, sublingual tablet, orally disintegrable tablet, buccal tablet and the like), pill, powder, granule, capsule (including soft capsule, microcapsule), troche, syrup, liquid, emulsion, suspension, controlled release preparation (e.g., immediate-release preparation, sustained-release preparation, sustained-release microcapsule), aerosol, film (e.g., orally disintegrable film, oral mucosal adhesive film), injection (e.g., subcutaneous injection, intravenous injection, intramuscular injection, intraperitoneal injection), drip infusion, transdermal absorption type preparation, ointment, lotion, adhesive preparation, suppository (e.g., rectal suppository, vaginal suppository), pellet, nasal preparation, pulmonary preparation (inhalant), eye drop and the like. A sustained-release preparation can be produced according to the method described in JP-A-H9-263545.

The medicament containing the compound of the present invention can be safely administered orally or parenterally (e.g., intravenous, intramuscular, subcutaneous, intraorgan, intranasal, intradermal, instillation, intracerebral, rectal,

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vaginal, intraperitoneal, intratumor, tumor proximal administration, direct administration to a lesion and the like).

[0380]

5 In the preparations of the present invention, the content of the compound of the present invention varies depending on the forms of the preparations, but is generally in the order of 0.01 to 100 % by weight, preferably 0.1 to 50 % by weight, more preferably 0.5 to 20 % by weight, as the content of the
10 compound of the present invention relative to the total weight of each preparation.

[0381]

While the dose varies depending on the kind of the compound of the present invention, administration route,
15 symptom, age of patients and the like, it is, for example, about 0.005 - 50 mg, preferably about 0.05 - 10 mg, more preferably about 0.2 - 4 mg, as the compound of the present invention per 1 kg body weight per day for oral administration to an adult patient with depression, anxiety, attention
20 deficit hyperactivity disorder, climacteric disorder, pain, stress urinary incontinence or mixed urinary incontinence, which may be administered in 1 to 3 divided portions.

[0382]

When the pharmaceutical composition of the present
25 invention is a sustained-release preparation, the dose thereof varies depending on the kind and content of the compound of the present invention, dosage form, sustained duration of drug release, administration subject animal (e.g., mammals such as human, rat, mouse, cat, dog, rabbit, bovine, swine and the
30 like), and administration object. For application by parenteral administration, for example, about 0.1 - about 100 mg of the compound of the present invention only needs to be released from the administered preparation in one week.

[0383]

35 Examples of the aforementioned pharmacologically

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acceptable carrier include excipients (e.g., starch, lactose, sucrose, calcium carbonate, calcium phosphate and the like), binders (e.g., starch, gum arabic, carboxymethylcellulose, hydroxypropylcellulose, crystalline cellulose, alginic acid, 5 gelatin, polyvinylpyrrolidone and the like), lubricants (e.g., stearic acid, magnesium stearate, calcium stearate, talc and the like), disintegrants (e.g., calcium carboxymethylcellulose, talc and the like), diluents (e.g., water for injection, saline and the like), additives (e.g., 10 stabilizer, preservative, colorant, flavor, dissolution aid, emulsifier, buffering agent, isotonicity agent and the like) and the like.

[0384]

For formulation into an injection, for example, the 15 compound of the present invention is formulated into an aqueous suspension with a dispersing agent (e.g., surfactant such as Tween 80, HCO-60 and the like, polysaccharides such as carboxymethylcellulose, sodium alginate, hyaluronic acid and the like, polysorbate etc.), preservative (e.g., 20 methylparaben, propylparaben etc.), isotonic agent (e.g., sodium chloride, mannitol, sorbitol, glucose etc.), buffer (e.g., calcium carbonate etc.), pH adjuster (e.g., sodium phosphate, potassium phosphate etc.) and the like to give an injection to be actually used. In addition, an oily suspension 25 can be obtained by dispersing the compound of the present invention together with vegetable oil such as sesame oil, corn oil and the like or a mixture thereof with a phospholipid such as lecithin and the like, or medium-chain triglyceride (e.g., miglyol 812 etc.) to give an injection to be actually used.

30 [0385]

The prophylactic or therapeutic drug of the present invention can also be used together with other medicament.

Examples of the drug that can be blended or used with the compound of the present invention (hereinafter to be 35 abbreviated as concomitant drug) include the following.

(1) Prophylactic or therapeutic drug for other central neurological diseases

Therapeutic drugs for depression, therapeutic drugs for anxiety (e.g., benzodiazepines such as chlordiazepoxide, diazepam, potassium clorazepate, lorazepam, clonazepam, alprazolam and the like), mood-stabilizing drugs (e.g., lithium carbonate etc.), 5-HT₂ antagonists (e.g., nefazodone etc.), 5-HT_{1A} agonists (e.g., tandospirone, buspirone, gepiron etc.), CRF antagonists (e.g., pexacerfont etc.), β ₃ agonists (e.g., amibegron etc.), melatonin agonists (e.g., ramelteon, agomelatine etc.), α ₂ antagonists (e.g., mirtazapine, setiptiline etc.), NK₂ antagonists (e.g., saredutant etc.), GR antagonists (e.g., mifepristone etc.), NK-1 antagonists (e.g., casopitant, orvepitant etc.), therapeutic drugs for schizophrenia (e.g., chlorpromazine, haloperidol, sulpiride, clozapine, aripiprazole, quetiapine, olanzapine, risperidone etc.), acetylcholinesterase inhibitors (e.g., donepezil, rivastigmine, galanthamine, zanapezil etc.), NMDA antagonists (e.g., memantine etc.), inhibitors of production, secretion, accumulation, coagulation and/or deposition of β amyloid protein [β secretase inhibitor, γ secretase inhibitory action agent, inhibitory action agents of β amyloid protein coagulation (e.g., PTI-00703, ALZHEMED (NC-531), PPI-368 (JP-A-H11-514333), PPI-558 (JP-A-2001-500852), SKF-74652 (Biochem. J. (1999), 340(1), 283-289)), β amyloid vaccine, β amyloid degrading enzyme etc.], activation drugs of brain function (e.g., aniracetam, nicergoline etc.), therapeutic drugs for Parkinson's disease [e.g., dopamine receptor agonists (e.g., L-DOPA, bromocriptine, pergolide, talipexole, pramipexole, cabergoline, amantadine etc.), COMT inhibitors (e.g., entacapone etc.)], therapeutic drugs for attention deficit hyperactivity disorder (e.g., modafinil etc.), therapeutic drugs for amyotrophic lateral sclerosis (e.g., riluzole, neurotrophic factor etc.), therapeutic drugs for insomnia (e.g., etizolam, zopiclone, triazolam, zolpidem, indiplon

etc.), therapeutic drugs for narcolepsy (e.g., modafinil etc.), anti-cytokine drugs (TNF inhibitor, MAP kinase inhibitor etc.), steroid drugs (e.g., dexamethasone, hexestrol, cortisone acetate etc.) and the like.

5 [0386]

(2) Prophylactic or therapeutic drug for other stress urinary incontinence

Adrenaline α 1 receptor agonists (e.g., ephedrine hydrochloride, midodrine hydrochloride etc.), adrenaline β 2
10 receptor agonists (e.g., clenbuterol etc.), norepinephrine reuptake inhibitory substance, norepinephrine and serotonin reuptake inhibitory substances (e.g., duloxetine etc.), tricyclic antidepressants (e.g., imipramine hydrochloride etc.), anticholinergic drugs or stimulants of smooth muscle
15 (e.g., oxybutynin hydrochloride, propiverine hydrochloride, celimeverine hydrochloride etc.), female sex hormone drugs (e.g., conjugated estrogen (premarin), estriol etc.) etc.

[0387]

(3) Agent for treating diabetes

20 Insulin preparations [e.g., animal insulin preparations extracted from the bovine or swine pancreas; human insulin preparations synthesized by a genetic engineering technique using *Escherichia coli* or a yeast; insulin zinc; protamine zinc insulin; a fragment or a derivative of insulin (e.g.,
25 INS-1, etc.)], insulin sensitizers (e.g., pioglitazone hydrochloride, troglitazone, rosiglitazone or its maleate, JTT-501, MCC-555, YM-440, GI-262570, KRP-297, FK-614, CS-011, etc.), α -glucosidase inhibitors (e.g., voglibose, acarbose, miglitol, emiglitate, etc.), biguanides (e.g., phenformin,
30 metformin, buformin, etc.), sulfonylureas (e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glimepiride, etc.) and other insulin secretagogues (e.g., repaglinide, senaglinide, mitiglinide or its calcium salt hydrate, GLP-1, nateglinide,
35 etc.), dipeptidylpeptidase IV inhibitors (e.g., vildagliptin,

sitagliptin, saxagliptin, alogliptin, NVP-DPP-728, PT-100, P32/98, etc.), β 3 agonists (e.g., CL-316243, SR-58611-A, UL-TG-307, AJ-9677, AZ40140, etc.), amylin agonists (e.g., pramlintide, etc.), phosphotyrosine phosphatase inhibitors (e.g., vanadic acid, etc.), gluconeogenesis inhibitors (e.g., glycogen phosphorylase inhibitors, glucose-6-phosphatase inhibitors, glucagon antagonists, etc.), SGLT (sodium-glucose cotransporter) inhibitors (e.g., T-1095, etc.) and the like.

[0388]

10 (4) Agent for treating diabetic complications

Aldose reductase inhibitors (e.g., tolrestat, epalrestat, zenarestat, zopolrestat, fidarestat (SNK-860), minalrestat (ARI-509), CT-112, etc.), neurotrophic factors (e.g., NGF, NT-3, etc.), AGE inhibitors (e.g., ALT-945, pimagedine, pyratoxathine, N-phenacylthiazolium bromide (ALT-766), EXO-226, etc.), active oxygen scavengers (e.g., thiocctic acid, etc.), cerebral vasodilators (e.g., tiapride, etc.) and the like.

[0389]

20 (5) Antihyperlipidemic agent

Statin compounds inhibiting cholesterol synthesis (e.g., pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, cerivastatin or their salt (e.g., sodium salt, etc.), etc.), squalene synthase inhibitors or fibrate compounds having triglyceride lowering action (e.g., bezafibrate, clofibrate, simfibrate, clinofibrate, etc.) and the like.

[0390]

(6) Hypotensive agent

30 Angiotensin converting enzyme inhibitors (e.g., captopril, enalapril, delapril, etc.), angiotensin II antagonists (e.g., losartan, candesartan cilexetil, etc.), calcium antagonists (e.g., manidipine, nifedipine, amlodipine, efonidipine, nicardipine, etc.), clonidine, and the like.

35 [0391]

(7) Antiobesity agent

Antiobesity drugs acting on the central nervous system (e.g. dexfenfluramine, fenfluramine, phentermine, sibutramine, amfepramone, dexamphetamine, mazindol, phenylpropanolamine, clobenzorex, etc.), pancreatic lipase inhibitors (e.g. orlistat, etc.), β 3 agonists (e.g. CL-316243, SR-58611-A, UL-TG-307, AJ-9677, AZ40140, etc.), anorectic peptides (e.g. leptin, CNTF (ciliary neurotrophic factor), etc.), cholecystokinin agonists (e.g. lintitript, FPL-15849, etc.), and the like.

[0392]

(8) Diuretic agent

Xanthine derivatives (e.g., theobromine sodium salicylate, theobromine calcium salicylate, etc.), thiazide preparations (e.g., ethiazide, cyclopenthiazide, trichlormethiazide, hydrochlorothiazide, hydroflumethiazide, benzylhydrochlorothiazide, penflutizide, polythiazide, methyclothiazide, etc.), antialdosterone preparations (e.g., spironolactone, triamterene, etc.), carbonic anhydrase inhibitors (e.g., acetazolamide, etc.), chlorobenzenesulfonamide preparations (e.g., chlorthalidone, mefruside, indapamide, etc.), azosemide, isosorbide, ethacrynic acid, piretanide, bumetanide, furosemide, etc.

[0393]

25 (9) Chemotherapeutic agent

Alkylating agents (e.g., cyclophosphamide, ifosamide, etc.), metabolic antagonists (e.g., methotrexate, 5-fluorouracil, etc.), antitumor antibiotics (e.g., mitomycin, adriamycin, etc.), plant-derived antitumor agents (e.g., vincristine, vindesine, taxol, etc.), cisplatin, carboplatin, etoposide, etc. Among these, 5-fluorouracil derivatives such as furtulon and neo-furtulon are preferred.

[0394]

(10) Immunotherapeutic agent

35 Microorganism- or bacterium-derived components (e.g.,

muramyl dipeptide derivatives, picibanil, etc.), immunopotentiator polysaccharides (e.g., lentinan, schizophyllan, krestin, etc.), genetically engineered cytokines (e.g., interferons, interleukins (IL), etc.), colony
5 stimulating factors (e.g., granulocyte colony stimulating factor, erythropoietin, etc.) and the like. Among these, IL-1, IL-2, IL-12, etc. are preferred.

[0395]

(11) Therapeutic agent recognized to ameliorate cachexia in
10 animal models or clinical practice

Progesterone derivatives (e.g., megestrol acetate) [Journal of Clinical Oncology, vol. 12, pp. 213-225, 1994], metoclopramide pharmaceuticals, tetrahydrocannabinol pharmaceuticals (the above references are applied to both),
15 fat metabolism ameliorating agents (e.g., eicosapentaenoic acid) [British Journal of Cancer, vol. 68, pp. 314-318, 1993], growth hormones, IGF-1, and antibodies to the cachexia-inducing factors such as TNF- α , LIF, IL-6 and oncostatin M.
[0396]

20 (12) Antiinflammatory agent

Steroids (e.g., dexamethasone, etc.), sodium hyaluronate, cyclooxygenase inhibitors (e.g., indomethacin, ketoprofen, loxoprofen, meloxicam, ampiroxicam, celecoxib, rofecoxib, etc.) and the like.

25 [0397]

(13) Miscellaneous

Glycosylation inhibitors (e.g., ALT-711, etc.), nerve regeneration promoting drugs (e.g., Y-128, VX853, prosaptide, etc.), drugs acting on the central nervous system (e.g.,
30 antidepressants such as desipramine, amitriptyline, imipramine, fluoxetine, paroxetine, doxepin, etc.), anticonvulsants (e.g., lamotrigine, carbamazepine), antiarrhythmic drugs (e.g., mexiletine), acetylcholine receptor ligands (e.g., ABT-594), endothelin receptor
35 antagonists (e.g., ABT-627), monoamine reuptake inhibitors

(e.g., tramadol), indoleamine reuptake inhibitors (e.g., fluoxetine, paroxetine), narcotic analgesics (e.g., morphine), GABA receptor agonists (e.g., gabapentin), GABA reuptake inhibitors (e.g., tiagabine), α_2 receptor agonists (e.g., clonidine), local analgesics (e.g., capsaicin), protein kinase C inhibitors (e.g., LY-333531), antianxiety drugs (e.g., benzodiazepines), phosphodiesterase inhibitors (e.g., sildenafil), dopamine receptor agonists (e.g., apomorphine), dopamine receptor antagonists (e.g., haloperidol), serotonin receptor agonists (e.g., tandospirone citrate, sumatriptan), serotonin receptor antagonists (e.g., cyproheptadine hydrochloride, ondansetron), serotonin reuptake inhibitors (e.g., fluvoxamine maleate, fluoxetine, paroxetine), hypnotics (e.g., triazolam, zolpidem), anticholinergic agents, α_1 receptor blocking agents (e.g., tamsulosin, silodosin, naftopidil), muscle relaxants (e.g., baclofen), potassium channel openers (e.g., nicorandil), calcium channel blocking agents (e.g., nifedipine), agents for preventing and/or treating Alzheimer's disease (e.g., donepezil, rivastigmine, galanthamine), agents for treating Parkinson's disease (e.g., L-dopa), agents for preventing and/or treating multiple sclerosis (e.g., interferon β -1a), histamine H_1 receptor inhibitors (e.g., promethazine hydrochloride), proton pump inhibitors (e.g., lansoprazole, omeprazole), antithrombotic agents (e.g., aspirin, cilostazol), NK-2 receptor antagonists, agents of treating HIV infection (saquinavir, zidovudine, lamivudine, nevirapine), agents of treating chronic obstructive pulmonary diseases (salmeterol, tiotropium bromide, cilomilast), etc.

30 [0398]

Anticholinergic agents include, for example, atropine, scopolamine, homatropine, tropicamide, cyclopentolate, butylscopolamine bromide, propantheline bromide, methylbenactyzium bromide, mepenzolate bromide, flavoxate, pirenzepine, ipratropium bromide, trihexyphenidyl, oxybutynin,

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propiverine, darifenacin, tolterodine, temiverine, trospium chloride or a salt thereof (e.g., atropine sulfate, scopolamine hydrogen bromide, homatropine hydrogen bromide, cyclopentolate hydrochloride, flavoxate hydrochloride, 5 pirenzepine hydrochloride, trihexyphenidyl hydrochloride, oxybutynin hydrochloride, tolterodine tartrate, etc.), preferably, oxybutynin, propiverine, darifenacin, tolterodine, temiverine, trospium chloride or a salt thereof (e.g., oxybutynin hydrochloride, tolterodine tartrate, etc.). In 10 addition, acetylcholinesterase inhibitors (e.g., distigmine, etc.) and the like can be used.

[0399]

NK-2 receptor antagonists include, for example, piperidine derivatives such as GR159897, GR149861, SR48968 15 (saredutant), SR144190, YM35375, YM38336, ZD7944, L-743986, MDL105212A, ZD6021, MDL105172A, SCH205528, SCH62373, R-113281, etc., perhydroisoindole derivatives such as RPR-106145, etc., quinoline derivatives such as SB-414240, etc., pyrrolopyrimidine derivatives such as ZM-253270, etc., 20 pseudopeptide derivatives such as MEN11420 (nepadutant), SCH217048, L-659877, PD-147714 (CAM-2291), MEN10376, S16474, etc., and others such as GR100679, DNK333, GR94800, UK-224671, MEN10376, MEN10627, or a salt thereof, and the like.

[0400]

25 In combination of the compound of the present invention and the concomitant drug, 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 and the concomitant drug or 30 a pharmaceutical composition thereof can be administered to the administration subject simultaneously, or may be administered at different times. The dosage of the concomitant drug may be determined according to the administration amount clinically used, and can be appropriately selected depending 35 on the administration subject, administration route, disease,

combination and the like.

[0401]

The concomitant administration mode is not particularly restricted, and it is sufficient that the compound of the present invention and the concomitant drug are combined in administration. Examples of such administration mode include the following methods:

(1) The compound of the present invention or a pharmaceutical composition thereof and the concomitant drug are simultaneously produced to give a single preparation which is administered. (2) The compound of the present invention or a pharmaceutical composition thereof and the concomitant drug or a pharmaceutical composition thereof are separately produced to give two kinds of preparations which are administered simultaneously by the same administration route. (3) The compound of the present invention or a pharmaceutical composition thereof and the concomitant drug or a pharmaceutical composition thereof are separately produced to give two kinds of preparations which are administered by the same administration route only at the different times. (4) The compound of the present invention or a pharmaceutical composition thereof and the concomitant drug or a pharmaceutical composition thereof are separately produced to give two kinds of preparations which are administered simultaneously by different administration routes. (5) The compound of the present invention or a pharmaceutical composition thereof and the concomitant drug or a pharmaceutical composition thereof are separately produced to give two kinds of preparations which are administered by different administration routes at different times (for example, the compound of the present invention or a pharmaceutical composition thereof; and the concomitant drug or a pharmaceutical composition thereof are administered in this order, or in the reverse order).

[0402]

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The mixing ratio of the compound of the present invention and a concomitant drug in the combination drug of the present invention can be appropriately determined according to the subject of administration, administration route, disease and
5 the like.

For example, while the content of the compound of the present invention in the combination drug of the present invention varies depending on the form of the preparation, it is generally about 0.01 to about 100 wt%, preferably about 0.1
10 to about 50 wt%, more preferably about 0.5 to about 20 wt%, relative to the whole preparation.

[0403]

While the content of the concomitant drug in the combination drug of the present invention varies depending on
15 the form of the preparation, it is generally about 0.01 to about 100 wt%, preferably about 0.1 to about 50 wt%, more preferably about 0.5 to about 20 wt%, relative to the whole preparation.

While the content of the additive such as a carrier and
20 the like in the combination drug of the present invention varies depending on the form of the preparation, it is generally about 1 to about 99.99 wt%, preferably about 10 to about 90 wt%, relative to the whole preparation.

Similar contents can be employed when the compound of the
25 present invention and the concomitant drug are independently formulated.

[0404]

The dose of the concomitant drug may be set within the range such that it causes no problems of side effects. The
30 daily dose as the concomitant drug varies depending on severity of symptoms, age, sex, weight and sensitivity of the subject to be administered, time and interval of administration, property, formulation and kinds of pharmaceutical preparation, kinds of active ingredients, etc.,
35 and is not particularly limited. In the case of oral

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administration, a daily dosage in terms of drugs is usually in the order of about 0.001 to 2000 mg, preferably about 0.01 to 500 mg, and more preferably about 0.1 to 100 mg, per 1 kg body weight of mammals, which may be administered once a day or in
5 two to four divided portions a day.

[0405]

In administering the combination drug of the present invention, it may be administered at the same time or, the concomitant drug may be administered before administering the
10 compound of the present invention, and vice versa. In case of staggered administration, the time interval varies depending on the active ingredients to be administered, a formulation and an administration route. For example, if the concomitant drug is administered first, the compound of the present
15 invention may be administered 1 minute to 3 days, preferably 10 minutes to 1 day, more preferably 15 minutes to 1 hour after administering the concomitant drug. If the compound of the present invention is administered first, the concomitant drug may be administered 1 minute to 1 day, preferably 10
20 minutes to 6 hours, more preferably 15 minutes to 1 hour after administering the compound of the present invention.

[0406]

The pharmaceutical composition of the present invention shows low toxicity and can be used safely. Particularly, since
25 the Example compounds shown below are superior in the absorption by oral administration, they can be advantageously used for oral preparations. In addition, the composition is also superior in that it does not show phototoxicity.

Examples

30 [0407]

The present invention is explained in detail in the following by referring to Examples, Experimental Examples and Formulation Examples, which are not to be construed as
limitative, and the invention may be changed within the scope
35 of the present invention.

In the following Examples, the "room temperature" generally means about 10°C to about 35°C. The ratios indicated for mixed solvents are volume mixing ratios, unless otherwise specified. % means wt%, unless otherwise specified.

5 In silica gel column chromatography, NH means use of aminopropylsilane-bound silica gel. The ratios of elution solvents are volume mixing ratios, unless otherwise specified.

In the following Examples, the following abbreviations are used.

10 THF: tetrahydrofuran, DMF: dimethylformamide, CDCl₃: deuterated chloroform, DMSO: dimethyl sulfoxide, CDI: carbonyldiimidazole, AcONH₄: ammonium acetate, EtOH: ethanol, mCPBA: methachloroperbenzoic acid, WSC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, HOBt: 1-hydroxybenzotriazole

¹H NMR (proton nuclear magnetic resonance spectrum) was measured by Fourier-transform type NMR. For the analysis, ACD/SpecManager (trade name) and the like were used. Peaks with very mild protons such as hydroxyl group, amino group and
20 the like are not described.

MS (mass spectrum) was measured by LC/MS (liquid chromatography mass spectrometer). As the ionization method, ESI (ElectroSpray Ionization) method, or APCI (Atmospheric Pressure Chemical Ionization) method was used. The data
25 indicates those found. Generally, a molecular ion peak is observed. In the case of a compound having a tert-butoxycarbonyl group (-Boc), a peak after elimination of a tert-butoxycarbonyl group or tert-butyl group may be observed as a fragment ion. In the case of a compound having a hydroxyl
30 group (-OH), a peak after elimination of H₂O may be observed as a fragment ion. In the case of a salt, a molecular ion peak or fragment ion peak of free form is generally observed.

[0408]

Example 1

35 [(6RS,7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methanol

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monohydrochloride

[0409]

A) methyl 2-[(3,4-dichlorophenyl)(hydroxy)methyl]prop-2-enoate

To a solution of 3,4-dichlorobenzaldehyde (17.5 g) and
5 methyl acrylate (8.6 mL) in acetonitrile (100 mL) was added
1,4-diazabicyclo[2.2.2]octane (3.36 g), and the mixture was
stirred at room temperature for 2 days. The reaction mixture
was concentrated under reduced pressure, and the residue was
purified by silica gel chromatography (hexane/ethyl acetate)
10 to give the title compound (18.7 g).

¹H NMR (300 MHz, CDCl₃) δ 3.17 (1H, d, J = 6.0 Hz), 3.75 (3H, s), 5.50 (1H, d, J = 5.7 Hz), 5.85 (1H, s), 6.37 (1H, s), 7.22 (1H, dd, J = 8.3, 1.9 Hz), 7.41 (1H, d, J = 8.3 Hz), 7.48 (1H, d, J = 1.9 Hz).

15 [0410]

B) methyl (2RS,3RS)-2-[(benzylamino)methyl]-3-(3,4-dichlorophenyl)-3-hydroxypropanoate

To a solution of methyl 2-[(3,4-dichlorophenyl)(hydroxy)methyl]prop-2-enoate (13.6 g) and
20 triethylamine (8.74 mL) in methanol (100 mL) was added
benzylamine (6.84 mL), and the mixture was stirred at room
temperature for 3 days. The reaction mixture was concentrated
under reduced pressure, and the residue was purified by silica
gel chromatography (hexane/ethyl acetate) to give the title
25 compound (4.17 g).

¹H NMR (300 MHz, CDCl₃) δ 2.85-2.98 (2H, m), 3.01-3.12 (1H, m), 3.58 (3H, s), 3.71-3.86 (2H, m), 5.12 (1H, d, J = 3.8 Hz), 7.09 (1H, dd, J = 8.3, 1.9 Hz), 7.26-7.45 (7H, m), 2H not detected.

30 [0411]

C) (1RS,2RS)-2-[(benzylamino)methyl]-1-(3,4-dichlorophenyl)propane-1,3-diol

To a solution of lithium aluminum hydride (644 mg) in THF
(40 mL) was added dropwise a solution of (6RS,7RS)-4-benzyl-6-
35 ({[tert-butyl(dimethyl)silyl]oxy)methyl}-7-(3,4-

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dichlorophenyl)-1,4-oxazepan-3-one (4.17 g) in THF (20 mL)

under ice-cooling, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was cooled to -

78°C, a solution of methyl (2R,3S)-2-[(benzylamino)methyl]-3-

5 (3,4-dichlorophenyl)-3-hydroxypropanoate (10.8 g) in THF (80 mL) was added dropwise, and the mixture was stirred at 0°C for 3 hr. The reaction mixture was poured into ice water, and the mixture was stirred for 30 min, and filtered through celite.

The filtrate was extracted twice with ethyl acetate. The

10 organic layer was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give the title compound (3.44 g).

MS (ESI+): [M+H]⁺ 340.1.

[0412]

15 D) (1RS,2RS)-3-(benzylamino)-2-([tert-butyl(dimethyl)silyl]oxy)methyl)-1-(3,4-dichlorophenyl)propan-1-ol

To a solution of (1RS,2RS)-2-[(benzylamino)methyl]-1-(3,4-dichlorophenyl)propane-1,3-diol (3.44 g) in DMF (30 mL)

20 were added tert-butylchlorodimethylsilane (1.68 g) and imidazole (1.03 g) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted solution was washed

25 with distilled water, saturated aqueous sodium hydrogen carbonate and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (2.98 g).

30 MS (ESI+): [M+H]⁺ 454.1.

[0413]

E) N-benzyl-N-[(2RS,3RS)-2-([tert-butyl(dimethyl)silyl]oxy)methyl)-3-(3,4-dichlorophenyl)-3-hydroxypropyl]-2-chloroacetamide

35 To a solution of (1RS,2RS)-3-(benzylamino)-2-([tert-

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butyl(dimethyl)silyl]oxy)methyl)-1-(3,4-dichlorophenyl)propan-
1-ol (2.98 g) and triethylamine (1.10 mL) in THF (30 mL) was
added chloroacetyl chloride (0.526 mL) under ice-cooling, and
the mixture was stirred at 0°C for 4 hr. The reaction mixture
5 was concentrated under reduced pressure, and the residue was
diluted with ethyl acetate. The diluted solution was washed
with distilled water and brine, and dried over anhydrous
magnesium sulfate. The solvent was evaporated under reduced
pressure. The residue was purified by silica gel
10 chromatography (hexane/ethyl acetate) to give the title
compound (2.95 g).

MS (ESI+): [M-OH+H]⁺ 514.1.

[0414]

F) (6RS,7RS)-4-benzyl-6-([tert-
15 butyl(dimethyl)silyl]oxy)methyl)-7-(3,4-dichlorophenyl)-1,4-
oxazepan-3-one

To a solution of N-benzyl-N-[(2RS,3RS)-2-([tert-
butyl(dimethyl)silyl]oxy)methyl)-3-(3,4-dichlorophenyl)-3-
hydroxypropyl]-2-chloroacetamide (2.72 g) in THF (100 mL) was
20 added sodium tert-butoxide (621 mg) under ice-cooling, and the
mixture was stirred at room temperature for 2 hr. The reaction
mixture was concentrated under reduced pressure, and the
residue was diluted with ethyl acetate. The diluted solution
was washed with distilled water and brine, dried over
25 anhydrous magnesium sulfate and concentrated under reduced
pressure to give the title compound (2.51 g).

MS (ESI+): [M+H]⁺ 494.2.

[0415]

G) (6RS,7RS)-4-benzyl-6-([tert-
30 butyl(dimethyl)silyl]oxy)methyl)-7-(3,4-dichlorophenyl)-1,4-
oxazepane

To a solution of lithium aluminum hydride (347 mg) in
diethyl ether (30 mL) was added, under a nitrogen stream,
aluminum(III) chloride (406 mg) at room temperature, and the
35 mixture was stirred at room temperature for 30 min. The

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reaction mixture was cooled to -78°C , a solution of (6RS,7RS)-4-benzyl-6-([tert-butyl(dimethyl)silyl]oxy)methyl)-7-(3,4-dichlorophenyl)-1,4-oxazepan-3-one (2.51 g) in THF (20 mL) was added dropwise, and the mixture was stirred at 0°C for 3 hr.

5 To the reaction mixture was added 1 N aqueous sodium hydroxide solution (5 mL) at -78°C , and the mixture was stirred at room temperature for 2 hr, and filtered through celite. The filtrate was concentrated under reduced pressure to give the title compound (2.42 g).

10 ^1H NMR (300 MHz, CDCl_3) δ -0.16 - -0.06 (6H, m), 0.79 (9H, s), 2.35-2.50 (1H, m), 2.56-2.74 (2H, m), 2.74-2.85 (2H, m), 3.18-3.27 (1H, m), 3.31-3.40 (1H, m), 3.62-3.73 (2H, m), 3.73-3.78 (1H, m), 3.84-3.96 (1H, m), 4.96-5.02 (1H, m), 7.18 (1H, dd, $J = 8.3, 1.5$ Hz), 7.24-7.42 (6H, m), 7.49 (1H, d, $J = 1.9$ Hz).

15 [0416]

H) tert-butyl (6RS,7RS)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate

To a solution of (6RS,7RS)-4-benzyl-6-([tert-butyl(dimethyl)silyl]oxy)methyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane (2.42 g) in acetonitrile (25 mL) was added 1-chloroethyl chloroformate (0.652 mL), and the mixture was stirred at room temperature for 20 min. The reaction mixture was concentrated under reduced pressure, the residue was diluted with methanol (25 mL), and 2 N hydrogen chloride-ethanol solution (3 mL) was added. The reaction mixture was stirred at 80°C for 1 hr, and ice-cooled, and triethylamine (1.05 mL) and di-tert-butyl dicarbonate (1.16 mL) were added. The reaction mixture was stirred at room temperature for 18 hr, and concentrated under reduced pressure, and the residue

20
25
30 was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (997 mg).

35 ^1H NMR (300 MHz, CDCl_3) δ 1.43-1.56 (9H, m), 2.21-2.40 (1H, m),

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3.15 (1H, td, $J = 11.2, 3.8$ Hz), 3.24-3.56 (3H, m), 3.57-3.78 (2H, m), 3.77-3.95 (1H, m), 4.02-4.34 (2H, m), 4.64 (1H, d, $J = 2.7$ Hz), 7.10 (1H, dd, $J = 8.3, 1.5$ Hz), 7.39 (1H, d, $J = 8.3$ Hz), 7.42 (1H, d, $J = 1.5$ Hz).

5 [0417]

I) [(6RS,7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methanol monohydrochloride

To a solution of tert-butyl (6RS,7RS)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (100 mg) in ethanol (0.5 mL) was added 2 N hydrogen chloride-ethanol solution (2.0 mL), and the mixture was stirred at room temperature for 24 hr. The crystals obtained by concentration under reduced pressure were recrystallized from ethyl acetate-ethanol to give the title compound (56.3 mg).

15 ^1H NMR (300 MHz, DMSO- d_6) δ 2.63 (1H, brs), 2.95-3.06 (1H, m), 3.08-3.17 (1H, m), 3.18-3.27 (1H, m), 3.28-3.40 (3H, m), 3.85-3.97 (1H, m), 3.99-4.11 (1H, m), 4.81 (1H, brs), 5.01 (1H, d, $J = 4.5$ Hz), 7.35 (1H, dd, $J = 8.5, 1.9$ Hz), 7.61 (1H, d, $J = 6.4$ Hz), 7.63 (1H, s), 9.21 (2H, brs).

20 [0418]

Example 2

(6RS,7RS)-7-(3,4-dichlorophenyl)-6-(methoxymethyl)-1,4-oxazepane monohydrochloride

[0419]

25 A) tert-butyl (6RS,7RS)-7-(3,4-dichlorophenyl)-6-(methoxymethyl)-1,4-oxazepane-4-carboxylate

To a solution of sodium hydride (10.5 mg) in THF (1 mL) was added a solution of tert-butyl (6RS,7RS)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (65.7 mg) in THF (1 mL), and the mixture was stirred at room temperature for 30 min. To the reaction mixture was added methyl iodide (49.7 mg), and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted solution was washed with distilled water

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and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (58.4 mg).

5 ^1H NMR (300 MHz, CDCl_3) δ 1.50 (9H, d, $J = 6.8$ Hz), 2.37-2.67 (1H, m), 2.96-3.45 (7H, m), 3.46-3.76 (1H, m), 3.76-4.16 (3H, m), 4.57 (1H, brs), 7.10 (1H, t, $J = 7.6$ Hz), 7.28-7.52 (2H, m).

[0420]

10 B) (6RS,7RS)-7-(3,4-dichlorophenyl)-6-(methoxymethyl)-1,4-oxazepane monohydrochloride

To a solution of tert-butyl (6RS,7RS)-7-(3,4-dichlorophenyl)-6-(methoxymethyl)-1,4-oxazepane-4-carboxylate (58 mg) in ethyl acetate (2 mL) was added 4 N hydrogen chloride-ethyl acetate solution (3.0 mL), and the mixture was stirred at room temperature for 2 hr. The crystals obtained by concentration under reduced pressure were recrystallized from ethanol to give the title compound (26.7 mg).

15 ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 2.77-2.91 (1H, m), 2.91-3.04 (2H, m), 3.10 (3H, s), 3.14-3.24 (1H, m), 3.27 (1H, d, $J = 6.4$ Hz), 3.85-3.98 (1H, m), 3.99-4.12 (1H, m), 5.02 (1H, d, $J = 4.5$ Hz), 7.35 (1H, dd, $J = 8.5, 2.1$ Hz), 7.56-7.68 (2H, m), 9.26 (2H, brs).

[0421]

25 Example 3

1-{[(6RS,7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}urea monohydrochloride

[0422]

A) tert-butyl (6RS,7RS)-7-(3,4-dichlorophenyl)-6-
30 {[(methanesulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate

To tert-butyl (6RS,7RS)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (896 mg) were added triethylamine (0.50 mL) and methanesulfonyl chloride (0.26 mL) under ice-cooling, and the mixture was stirred for 1
35 hr. The reaction mixture was concentrated under reduced

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pressure, and the residue was diluted with ethyl acetate. The diluted solution was washed with 1 N hydrochloric acid, distilled water and brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure
5 to give the title compound (1.07 g).

¹H NMR (300 MHz, CDCl₃) δ 1.46-1.56 (9H, m), 2.62-2.78 (1H, m), 2.78-3.00 (3H, m), 3.23-3.85 (4H, m), 3.85-4.13 (4H, m), 4.66 (1H, brs), 7.12 (1H, d, J = 8.3 Hz), 7.42 (2H, d, J = 8.3 Hz).
[0423]

10 B) tert-butyl (6RS,7RS)-6-(azidomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6RS,7RS)-7-(3,4-dichlorophenyl)-6-([(methylsulfonyl)oxy]methyl)-1,4-oxazepane-4-carboxylate (830 mg) in DMF (10 mL) was added sodium azide
15 (178 mg), and the mixture was stirred at 70°C for 18 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated
20 under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (723 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.51 (9H, d), 2.29-2.59 (1H, m), 3.01-3.18 (2H, m), 3.29-3.52 (2H, m), 3.52-3.70 (1H, m), 3.72-
25 3.97 (2H, m), 4.03-4.12 (1H, m), 4.62 (1H, d, J = 6.4 Hz), 7.10 (1H, t, J = 6.4 Hz), 7.42 (2H, d, J = 8.7 Hz).
[0424]

C) tert-butyl (6RS,7SR)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

30 To a solution of tert-butyl (6RS,7RS)-6-(azidomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (723 mg) in THF (7.5 mL) were added triphenylphosphine (567 mg) and water (1.5 mL), and the mixture was stirred at room temperature for 36 hr. The reaction mixture was concentrated under reduced
35 pressure, and the residue was diluted with ethyl acetate. The

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diluted solution was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/methanol) to give the
5 title compound (656 mg).

MS (ESI+): $[M+H]^+$ 375.1.

[0425]

D) tert-butyl (6RS,7SR)-6-[(carbamoylamino)methyl]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

10 To a solution of tert-butyl (6RS,7SR)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (125 mg) in THF (1.5 mL) was added trimethylsilyl isocyanate (57.7 mg), and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was concentrated under reduced pressure,
15 and the residue was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title
20 compound (160 mg).

^1H NMR (300 MHz, CDCl_3) δ 1.48 (9H, s), 2.39 (1H, dt, $J = 10.4$, 3.3 Hz), 2.66 (1H, ddd, $J = 14.0$, 10.6, 4.2 Hz), 3.12-3.25 (1H, m), 3.30 (1H, dd, $J = 15.0$, 2.5 Hz), 3.40 (1H, dt, $J = 14.2$, 4.4 Hz), 3.66-3.88 (2H, m), 4.12-4.19 (2H, m), 4.19-4.30
25 (2H, m), 4.65 (1H, d, $J = 2.7$ Hz), 5.70 (1H, d, $J = 4.9$ Hz), 7.17 (1H, dd, $J = 8.3$, 1.9 Hz), 7.41 (1H, d, $J = 8.3$ Hz), 7.51 (1H, d, $J = 1.5$ Hz).

[0426]

E) 1-{[(6RS,7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}urea monohydrochloride
30

To a solution of tert-butyl (6RS,7SR)-6-[(carbamoylamino)methyl]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (160 mg) in ethanol (0.5 mL) was added 4 N hydrogen chloride-ethyl acetate solution (3.0 mL), and the
35 mixture was stirred at room temperature for 2 hr. The crystals

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obtained by concentration under reduced pressure were recrystallized from ethanol-water to give the title compound (102 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 2.53 (1H, brs), 2.59-2.72 (1H, m),
5 2.77-2.92 (1H, m), 3.18-3.43 (4H, m), 3.92 (1H, ddd, J = 13.4, 7.7, 3.8 Hz), 4.09 (1H, dt, J = 13.6, 4.3 Hz), 4.98 (1H, d, J = 3.0 Hz), 5.78 (2H, s), 6.18 (1H, t, J = 5.9 Hz), 7.35 (1H, dd, J = 8.5, 1.9 Hz), 7.57-7.69 (2H, m), 9.34 (2H, brs).

[0427]

10 Example 4

[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methanol monohydrochloride

[0428]

A) methyl (2RS,3RS)-2-[(benzylamino)methyl]-3-(3,4-
15 dichlorophenyl)-3-hydroxypropanoate

To a solution of methyl 2-[(3,4-dichlorophenyl)(hydroxy)methyl]prop-2-enoate (13.6 g) and triethylamine (8.74 mL) in methanol (100 mL) was added benzylamine (6.84 mL), and the mixture was stirred at room
20 temperature for 3 days. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (12.7 g).

¹H NMR (300 MHz, CDCl₃) δ 2.66-2.76 (2H, m), 3.11-3.23 (1H, m),
25 3.66-3.79 (5H, m), 5.27 (1H, d, J = 4.9 Hz), 7.10 (1H, dd, J = 8.3, 1.5 Hz), 7.26-7.40 (6H, m), 7.45 (1H, d, J = 1.9 Hz), 2H not detected.

[0429]

B) (1RS,2SR)-2-[(benzylamino)methyl]-1-(3,4-
30 dichlorophenyl)propane-1,3-diol

To a suspension of calcium chloride (5.74 g) in THF (80 mL) and ethanol (50 mL) was added sodium borohydride (2.61 g), and the mixture was stirred at room temperature for 30 min. To the reaction mixture was added a solution of methyl (2RS,3RS)-
35 2-[(benzylamino)methyl]-3-(3,4-dichlorophenyl)-3-

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hydroxypropanoate (12.7 g) in THF (20 mL) and ethanol (20 mL) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. To the reaction mixture was added 1 N aqueous hydrochloric acid solution (15 mL), the mixture was stirred for 30 min, and neutralized with 1 N aqueous sodium hydroxide solution (15 mL), and the mixture was filtered through celite. The obtained oil was diluted with ethyl acetate, and the mixture was washed with distilled water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (11.6 g).

MS (ESI+): $[M+H]^+$ 340.1.

[0430]

C) (1RS,2SR)-3-(benzylamino)-2-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1-(3,4-dichlorophenyl)propan-1-ol

To a solution of (1RS,2SR)-2-[(benzylamino)methyl]-1-(3,4-dichlorophenyl)propane-1,3-diol (11.6 g) in THF (100 mL) were added tert-butylchlorodimethylsilane (5.63 g) and imidazole (2.55 g) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted solution was washed with distilled water, saturated aqueous sodium hydrogen carbonate and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (10.9 g).

MS (ESI+): $[M+H]^+$ 454.1.

[0431]

D) N-benzyl-N-[(2RS,3SR)-2-({[tert-butyl(dimethyl)silyl]oxy}methyl)-3-(3,4-dichlorophenyl)-3-hydroxypropyl]-2-chloroacetamide

To a solution of (1RS,2SR)-3-(benzylamino)-2-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1-(3,4-dichlorophenyl)propan-1-ol (10.9 g) and triethylamine (4.00 mL) in THF (100 mL) was

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added chloroacetyl chloride (1.91 mL) under ice-cooling, and the mixture was stirred at 0°C for 1.5 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted solution
5 was washed with distilled water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (12.5 g).

MS (ESI+): [M-OH+H]⁺ 514.1.

[0432]

10 E) (6RS,7SR)-4-benzyl-6-([tert-butyl(dimethyl)silyl]oxy)methyl)-7-(3,4-dichlorophenyl)-1,4-oxazepan-3-one

To a solution of N-benzyl-N-[(2RS,3SR)-2-([tert-butyl(dimethyl)silyl]oxy)methyl)-3-(3,4-dichlorophenyl)-3-
15 hydroxypropyl]-2-chloroacetamide (12.5 g) in THF (470 mL) was added sodium tert-butoxide (2.71 g) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted solution
20 was washed with distilled water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (11.3 g).

MS (ESI+): [M+H]⁺ 494.0.

[0433]

25 F) (6RS,7SR)-4-benzyl-6-([tert-butyl(dimethyl)silyl]oxy)methyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane

To a solution of lithium aluminum hydride (1.49 g) in diethyl ether (120 mL) was added, under a nitrogen stream,
30 aluminum(III) chloride (1.74 g) under ice-cooling, and the mixture was stirred at room temperature for 40 min. The reaction mixture was cooled to -78°C, a solution of (6RS,7SR)-4-benzyl-6-([tert-butyl(dimethyl)silyl]oxy)methyl)-7-(3,4-dichlorophenyl)-1,4-oxazepan-3-one (10.8 g) in THF (80 mL) was
35 added dropwise, and the mixture was stirred at 0°C for 3 hr.

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To the reaction mixture was added 1 N aqueous sodium hydroxide solution (22 mL) at -78°C, and the mixture was stirred at room temperature for 2 hr, and filtered through celite. The filtrate was concentrated under reduced pressure to give the
5 title compound (9.77 g).

¹H NMR (300 MHz, CDCl₃) δ-0.05 (6H, d), 0.83 (9H, s), 2.07-2.23 (1H, m), 2.57-2.77 (2H, m), 2.88 (2H, d, J = 3.8 Hz), 3.39-3.49 (1H, m), 3.51-3.64 (2H, m), 3.65 (2H, s), 3.93-4.04 (1H, m), 4.42 (1H, d, J = 8.3 Hz), 7.22 (1 H, dd, J = 8.3, 2.3 Hz),
10 7.24-7.42 (6 H, m), 7.49 (1 H, d, J = 2.3 Hz).

[0434]

G) tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate

To a solution of (6RS,7SR)-4-benzyl-6-([tert-butyl(dimethyl)silyl]oxy)methyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane (9.77 g) in acetonitrile (100 mL) was added 1-chloroethyl chloroformate (2.63 mL), and the mixture was stirred at room temperature for 15 min. The reaction mixture was concentrated under reduced pressure, methanol (100 mL) was
15 added, and the mixture was heated at 80°C. 1 N Hydrochloric acid (1.00 mL) was added. The reaction mixture was stirred at 80°C for 18 hr, and ice-cooled, and triethylamine (3.40 mL) and di-tert-butyl dicarbonate (4.90 mL) were added. The reaction mixture was stirred at room temperature for 2 hr, and
25 concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl
30 acetate) to give the title compound (7.10 g).

¹H NMR (300 MHz, CDCl₃) δ 1.51 (9H, s), 2.06-2.19 (1H, m), 3.05-3.30 (2H, m), 3.43 (1H, dd, J = 14.7, 6.4 Hz), 3.49-3.67 (2H, m), 4.04-4.12 (3H, m), 4.21 (1H, dd, J = 10.0, 4.7 Hz), 4.33 (1H, d, J = 9.8 Hz), 7.19 (1H, dd, J = 8.3, 1.9 Hz), 7.40
35 (1H, d, J = 8.3 Hz), 7.48 (1H, d, J = 1.9 Hz).

[0435]

H) [(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methanol monohydrochloride

To a solution of tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (150 mg) in ethanol (2 mL) was added 2 N hydrogen chloride-ethanol solution (3.0 mL), and the mixture was stirred at room temperature for 14 hr. The oil obtained by concentration under reduced pressure was crystallized from ethyl acetate-ethanol, and the crystals were recrystallized from ethyl acetate-ethanol to give the title compound (86.5 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 2.36-2.48 (1H, m), 3.04-3.19 (2H, m), 3.19-3.31 (3H, m), 3.46 (1H, dd, J = 14.0, 3.0 Hz), 3.80 (1H, ddd, J = 13.4, 8.9, 4.2 Hz), 4.05 (1H, dt, J = 13.6, 4.2 Hz), 4.44 (1H, d, J = 10.6 Hz), 4.97 (1H, brs), 7.38 (1H, dd, J = 8.3, 1.9 Hz), 7.61-7.71 (2H, m), 9.33 (2H, brs).

[0436]

Example 5

(6RS,7RS)-7-(3,4-dichlorophenyl)-6-[(methanesulfonyl)methyl]-1,4-oxazepane monohydrochloride

[0437]

A) tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-[[methanesulfonyl]oxy]methyl]-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (735 mg) in THF (10 mL) were added triethylamine (0.41 mL) and methanesulfonyl chloride (0.21 mL) under ice-cooling, and the mixture was stirred for 1 hr. Triethylamine (0.14 mL) and methanesulfonyl chloride (0.076 mL) were added, and the mixture was stirred for 1 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted solution was washed with 1 N hydrochloric acid, distilled water and brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to give the title compound

(863 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.50 (9H, s), 2.40 (1H, brs), 2.81-3.08 (3H, m), 3.35-3.90 (5H, m), 3.94-4.17 (3H, m), 4.20 (1H, d, J = 9.4 Hz), 7.16 (1H, dd, J = 8.3, 1.9 Hz), 7.38-7.50 (2H, m).

[0438]

B) tert-butyl (6RS,7RS)-7-(3,4-dichlorophenyl)-6-[(methylsulfonyl)methyl]-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-
10 [(methylsulfonyl)methyl]-1,4-oxazepane-4-carboxylate (200 mg) in DMF (3 mL) was added sodium thiomethoxide (46.3 mg), and the mixture was stirred at room temperature for 16 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl
15 acetate. The diluted solution was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (110 mg).

20 ¹H NMR (300 MHz, CDCl₃) δ 1.51 (9H, s), 1.81-2.02 (3H, m), 2.06-2.47 (3H, m), 3.36-3.99 (5H, m), 4.00-4.23 (2H, m), 7.17 (1H, d, J = 7.6 Hz), 7.42 (2H, d, J = 8.0 Hz).

[0439]

C) tert-butyl (6RS,7RS)-7-(3,4-dichlorophenyl)-6-
25 [(methylsulfonyl)methyl]-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6RS,7RS)-7-(3,4-dichlorophenyl)-6-
[(methylsulfonyl)methyl]-1,4-oxazepane-4-carboxylate (110 mg) in toluene (1.5 mL) was added methachloroperbenzoic acid (170 mg), and the mixture was
30 stirred at room temperature for 20 hr. The reaction mixture was diluted with ethyl acetate, and the mixture was washed with saturated aqueous sodium hydrogen carbonate and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by
35 silica gel chromatography (hexane/ethyl acetate) to give the

title compound (111 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.52 (9H, d, J = 9.4 Hz), 2.50-2.96 (5H, m), 3.17-3.76 (4H, m), 3.76-4.35 (4H, m), 7.21 (1H, dd, J = 8.3, 1.9 Hz), 7.40-7.53 (2H, m).

5 [0440]

D) (6RS,7RS)-7-(3,4-dichlorophenyl)-6-

[(methylsulfonyl)methyl]-1,4-oxazepane monohydrochloride

To a solution of tert-butyl (6RS,7RS)-7-(3,4-dichlorophenyl)-6-[(methylsulfonyl)methyl]-1,4-oxazepane-4-carboxylate (111 mg) in ethyl acetate (1 mL) was added 4 N hydrogen chloride-ethyl acetate solution (3 mL), and the mixture was stirred at room temperature for 2 hr. The crystals obtained by concentration under reduced pressure were recrystallized from ethanol-water to give the title compound
15 (70.3 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 2.77 (1H, d, J = 13.2 Hz), 2.94 (3H, s), 3.05-3.31 (4H, m), 3.44 (1H, dd, J = 14.0, 9.4 Hz), 3.69 (1H, dd, J = 14.2, 2.8 Hz), 3.84 (1H, ddd, J = 13.7, 9.2, 4.3 Hz), 4.06 (1H, dt, J = 13.6, 4.3 Hz), 4.48 (1H, d, J = 9.8 Hz), 7.43 (1H, dd, J = 8.3, 1.9 Hz), 7.69 (1H, d, J = 8.3 Hz), 7.72 (1H, d, J = 1.9 Hz), 9.45 (2H, brs).

[0441]

Example 6

N-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}acetamide monohydrochloride
25 [0442]

A) tert-butyl (6RS,7SR)-6-(azidomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-[(methylsulfonyl)oxy]methyl]-1,4-oxazepane-4-carboxylate (660 mg) in DMF (7 mL) was added sodium azide (142 mg), and the mixture was stirred at 70°C for 20 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted
35 solution was washed with distilled water and brine, and dried

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over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (570 mg).

5 ¹H NMR (300 MHz, CDCl₃) δ 1.51 (9H, brs), 2.14 (1H, brs), 3.20 (2H, d, J = 7.5 Hz), 3.39-3.88 (5H, m), 4.02-4.22 (2H, m), 7.14 (1H, dd, J = 8.3, 1.9 Hz), 7.37-7.49 (2H, m).

[0443]

B) tert-butyl (6RS,7RS)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6RS,7SR)-6-(azidomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (570 mg) in THF (5 mL) were added triphenylphosphine (447 mg) and water (1 mL), and the mixture was stirred at room temperature for 20
15 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by
20 silica gel chromatography (ethyl acetate/methanol) to give the title compound (477 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.53 (9H, s), 1.85-2.04 (1H, m), 2.43-2.67 (2H, m), 3.23-3.38 (1H, m), 3.53 (1H, dd, J = 14.7, 4.5 Hz), 3.61 (1H, d, J = 10.6 Hz), 3.76-4.14 (4H, m), 7.16
25 (1H, d, J = 7.9 Hz), 7.36-7.47 (2H, m), 2H not detected.

[0444]

C) tert-butyl (6RS,7RS)-6-[(acetylamino)methyl]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6RS,7RS)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (144 mg) in
30 THF (1.5 mL) were added triethylamine (0.08 mL) and acetyl chloride (45 mg), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl
35 acetate. The diluted solution was washed with distilled water

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and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (177 mg).

5 ¹H NMR (300 MHz, CDCl₃) δ 1.51 (9H, s), 1.85-2.02 (3H, m), 2.26 (1H, brs), 3.03 (1H, dt, J = 14.0, 7.4 Hz), 3.09-3.32 (2H, m), 3.36 (1H, dd, J = 14.9, 5.5 Hz), 3.54 (1H, td, J = 12.1, 2.3 Hz), 3.92-4.20 (4H, m), 7.13-7.26 (2H, m), 7.41 (1H, d, J = 8.3 Hz), 7.53 (1H, d, J = 1.5 Hz).

10 [0445]

D) N-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}acetamide monohydrochloride

To a solution of tert-butyl (6RS,7RS)-6-[(acetylamino)methyl]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (176 mg) in ethyl acetate (0.5 mL) was added 4 N hydrogen chloride-ethyl acetate solution (3 mL), and the mixture was stirred at room temperature for 2 hr. The crystals obtained by concentration under reduced pressure were recrystallized from ethanol-water to give the title compound
20 (102 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.77 (3H, s), 2.53-2.60 (1H, m), 2.86 (2H, t, J = 5.9 Hz), 3.07-3.31 (4H, m), 3.71-3.88 (1H, m), 3.98 (1H, dt, J = 13.9, 4.4 Hz), 4.37 (1H, d, J = 10.2 Hz), 7.44 (1H, dd, J = 8.3, 1.9 Hz), 7.67 (1H, d, J = 8.3 Hz),
25 7.76 (1H, d, J = 1.9 Hz), 8.06 (1H, t, J = 5.9 Hz), 9.24 (2H, brs).

[0446]

Example 7

1-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}urea monohydrochloride
30

Using tert-butyl (6RS,7RS)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and by a method similar to that of Example 3, steps D) and E), the title compound (45.8 mg) was obtained.

35 ¹H NMR (300 MHz, DMSO-d₆) δ 2.75 (1H, d), 2.93 (3H, s), 3.02-

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3.14 (1H, m), 3.18-3.35 (3H, m), 3.44 (1H, dd, J = 13.5, 9.9 Hz), 3.69 (1H, dd, J = 13.8, 2.3 Hz), 3.84 (1H, ddd, J = 13.7, 9.0, 4.4 Hz), 4.05 (1H, dt, J = 13.8, 4.4 Hz), 4.46 (1H, d, J = 10.0 Hz), 7.40-7.51 (2H, m), 7.63-7.72 (1H, m), 8.90-9.74 (2H, m).

[0447]

Example 8

N-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}methanesulfonamide monohydrochloride

[0448]

A) tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-[[(methylsulfonyl) amino]methyl]-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6RS,7RS)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (144 mg) in THF (1.5 mL) were added triethylamine (0.08 mL) and methanesulfonyl chloride (66 mg), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (186 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.51 (9H, s), 2.21-2.34 (1H, m), 2.79-2.94 (4H, m), 2.98-3.18 (2H, m), 3.43 (1H, dd, J = 15.1, 6.4 Hz), 3.58 (1H, td, J = 12.3, 2.6 Hz), 3.99-4.17 (3H, m), 4.32 (1H, d, J = 9.8 Hz), 6.55 (1H, dd, J = 8.5, 4.3 Hz), 7.20-7.30 (1H, m), 7.37-7.46 (1H, m), 7.53 (1H, d, J = 1.5 Hz).

[0449]

B) N-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}methanesulfonamide monohydrochloride

To a solution of tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-[[(methylsulfonyl) amino]methyl]-1,4-

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oxazepane-4-carboxylate (186 mg) in ethyl acetate (0.5 mL) was added 4 N hydrogen chloride-ethyl acetate solution (3 mL), and the mixture was stirred at room temperature for 2 hr. The crystals obtained by concentration under reduced pressure were
5 recrystallized from ethanol-water to give the title compound (119 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 2.53-2.66 (1H, m), 2.75 (2H, t, J = 6.1 Hz), 2.82 (3H, s), 3.08-3.20 (1H, m), 3.22-3.31 (2H, m), 3.39-3.51 (1H, m), 3.72-3.88 (1H, m), 3.97-4.10 (1H, m), 4.39
10 (1H, d, J = 10.2 Hz), 7.28 (1H, t, J = 6.4 Hz), 7.43 (1H, dd, J = 8.3, 1.9 Hz), 7.68 (1H, d, J = 8.0 Hz), 7.73 (1H, d, J = 1.9 Hz), 9.36 (2H, brs).

[0450]

Example 9

15 N-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}sulfamide monohydrochloride
[0451]

A) tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-[(sulfamoylamino)methyl]-1,4-oxazepane-4-carboxylate

20 To a solution of tert-butyl (6RS,7RS)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (144 mg) in acetonitrile (2 mL) was added N-(tert-butoxycarbonyl)-N-[4-(dimethylazaniumylidene)-1,4-dihydropyridin-1-ylsulfonyl]azanide (190 mg) prepared by the method described
25 in Organic Letters, 2001, 3 (14), 2241-2243, and the mixture was stirred at room temperature for 20 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted solution was washed with 1 N hydrochloric acid and brine, and dried
30 over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (205 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.49 (9H, s), 1.51 (9H, s), 2.10-2.37
35 (1H, m), 2.79-2.97 (1H, m), 2.97-3.22 (2H, m), 3.43 (1H, dd, J

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= 15.1, 6.4 Hz), 3.52-3.67 (1H, m), 4.08 (3H, td, J = 11.1, 3.0 Hz), 4.28 (1H, d, J = 9.8 Hz), 7.16 (1H, brs), 7.21-7.27 (1H, m), 7.41 (1H, d, J = 7.9 Hz), 7.52 (1H, s), 1H not detected.

5 [0452]

B) N-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}sulfamide monohydrochloride

To a solution of tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-[(sulfamoylamino)methyl]-1,4-oxazepane-4-carboxylate (202 mg) in ethanol (1 mL) was added 4 N hydrogen chloride-ethyl acetate solution (3 mL), and the mixture was stirred at room temperature for 18 hr. The crystals obtained by concentration under reduced pressure were recrystallized from ethanol-water to give the title compound (103 mg).

15 ¹H NMR (300 MHz, DMSO-d₆) δ 2.65 (2H, t), 3.08-3.32 (4H, m), 3.40-3.54 (1H, m), 3.80 (1H, ddd, J = 13.5, 8.9, 4.1 Hz), 4.02 (1H, dt, J = 13.8, 4.3 Hz), 4.40 (1H, d, J = 10.0 Hz), 6.56 (2H, s), 6.79 (1H, t, J = 6.4 Hz), 7.41 (1H, dd, J = 8.4, 2.0 Hz), 7.68 (1H, d, J = 8.3 Hz), 7.71 (1H, d, J = 1.9 Hz), 8.59-20 9.90 (2H, m).

[0453]

Example 10

[(6RS,7SR)-7-(3-chloro-4-fluorophenyl)-1,4-oxazepan-6-yl]methanol monohydrochloride

25 [0454]

A) methyl 2-[(3-chloro-4-fluorophenyl)(hydroxy)methyl]prop-2-enoate

To a solution of 3-chloro-4-fluorobenzaldehyde (10.0 g) and methyl acrylate (8.5 mL) in acetonitrile (63 mL) was added 30 1,4-diazabicyclo[2.2.2]octane (1.41 g), and the mixture was stirred at room temperature for 5 days. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (11.5 g).

35 ¹H NMR (300 MHz, CDCl₃) δ 3.11 (1H, d, J = 6.0 Hz), 3.75 (3H,

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s), 5.51 (1H, d, J = 5.7 Hz), 5.85 (1H, t, J = 0.9 Hz), 6.37 (1H, s), 7.06-7.17 (1H, m), 7.20-7.28 (1H, m), 7.44 (1H, dd, J = 7.2, 2.3 Hz).

[0455]

5 B) methyl (2RS,3RS)-2-[(benzylamino)methyl]-3-(3-chloro-4-fluorophenyl)-3-hydroxypropanoate

To a solution of methyl 2-[(3-chloro-4-fluorophenyl)(hydroxy)methyl]prop-2-enoate (11.5 g) and triethylamine (6.85 mL) in methanol (100 mL) was added
10 benzylamine (5.38 mL), and the mixture was stirred at room temperature for 16 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (12.0 g).

15 ¹H NMR (300 MHz, CDCl₃) δ 2.65-2.80 (2H, m), 3.16 (1H, dd, J = 11.7, 5.7 Hz), 3.67 (3H, s), 3.73 (2H, dd, J = 17.8, 12.8 Hz), 5.25 (1H, d, J = 5.3 Hz), 7.04 (1H, t, J = 8.7 Hz), 7.13 (1H, ddd, J = 8.3, 4.2, 2.3 Hz), 7.26-7.45 (6H, m), 2H not detected.

20 [0456]

C) (1RS,2SR)-2-[(benzylamino)methyl]-1-(3-chloro-4-fluorophenyl)propane-1,3-diol

To a suspension of calcium chloride (5.66 g) in THF (80 mL) and ethanol (50 mL) was added sodium borohydride (2.57 g),
25 and the mixture was stirred at room temperature for 30 min. To the reaction mixture was added a solution of methyl (2RS,3RS)-2-[(benzylamino)methyl]-3-(3-chloro-4-fluorophenyl)-3-hydroxypropanoate (12.0 g) in THF (20 mL) and ethanol (20 mL) under ice-cooling, and the mixture was stirred at room
30 temperature for 4 hr. To the reaction mixture was added aqueous 1 N hydrochloric acid (15 mL) solution, the mixture was stirred for 1 hr, and neutralized with 1 N aqueous sodium hydroxide solution (15 mL), and the mixture was filtered through celite. The obtained oil was diluted with ethyl
35 acetate, and the mixture was washed with distilled water and

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brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound as a crude product.

MS (ESI+): $[M+H]^+$ 324.1.

5 [0457]

D) (1RS,2SR)-3-(benzylamino)-2-([tert-butyl(dimethyl)silyl]oxy)methyl)-1-(3-chloro-4-fluorophenyl)propan-1-ol

To a solution of (1RS,2SR)-2-[(benzylamino)methyl]-1-(3-chloro-4-fluorophenyl)propane-1,3-diol (the above-mentioned crude product) in THF (170 mL) were added tert-butylchlorodimethylsilane (5.38 g), triethylamine (7.1 mL) and 4-(dimethylamino)pyridine (415 mg) under ice-cooling, and the mixture was stirred at room temperature for 18 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted solution was washed with distilled water, saturated aqueous sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (14.1 g).

MS (ESI+): $[M+H]^+$ 438.4.

[0458]

E) (6RS,7SR)-4-benzyl-6-([tert-butyl(dimethyl)silyl]oxy)methyl)-7-(3-chloro-4-fluorophenyl)-1,4-oxazepan-3-one

To a solution of (1RS,2SR)-3-(benzylamino)-2-([tert-butyl(dimethyl)silyl]oxy)methyl)-1-(3-chloro-4-fluorophenyl)propan-1-ol (14.1 g) and triethylamine (4.95 mL) in THF (100 mL) was added chloroacetyl chloride (2.59 mL) under ice-cooling, and the mixture was stirred at 0°C for 18 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained mixture was diluted with THF

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(300 mL), 1 N aqueous sodium hydroxide solution (63 mL) was added dropwise under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted solution was washed with distilled water, saturated aqueous sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (6.72 g).

MS (ESI+): $[M+H]^+$ 478.1.

[0459]

F) (6RS,7SR)-4-benzyl-6-({[tert-butyl(dimethyl)silyl]oxy}methyl)-7-(3-chloro-4-fluorophenyl)-1,4-oxazepane

To a solution of aluminum(III) chloride (1.12 g) in diethyl ether (85 mL)-THF (40 mL) was added, under a nitrogen stream, lithium aluminum hydride (960 mg) under ice-cooling, and the mixture was stirred at room temperature for 30 min. The reaction mixture was cooled to 0°C, a solution of (6RS,7SR)-4-benzyl-6-({[tert-butyl(dimethyl)silyl]oxy}methyl)-7-(3-chloro-4-fluorophenyl)-1,4-oxazepan-3-one (6.72 g) in THF (60 mL) was added dropwise, and the mixture was stirred at 0°C for 2 hr. To the reaction mixture was added 1 N aqueous sodium hydroxide solution (14 mL) at -78°C, the mixture was stirred at room temperature for 2 hr, and filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (4.16 g).

^1H NMR (300 MHz, CDCl_3) δ -0.06 (6H, d, $J = 2.6$ Hz), 0.83 (9H, s), 2.08-2.24 (1H, m), 2.58-2.76 (2H, m), 2.89 (2H, d, $J = 3.8$ Hz), 3.39-3.47 (1H, m), 3.50-3.64 (2H, m), 3.66 (2H, s), 3.94-4.04 (1H, m), 4.40 (1H, d, $J = 8.3$ Hz), 7.03-7.13 (1H, m), 7.20-7.28 (2H, m), 7.28-7.39 (4H, m), 7.44 (1H, dd, $J = 7.2, 1.9$ Hz).

[0460]

G) tert-butyl (6RS,7SR)-7-(3-chloro-4-fluorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate

To a solution of (6RS,7SR)-4-benzyl-6-({[tert-butyl(dimethyl)silyl]oxy}methyl)-7-(3-chloro-4-fluorophenyl)-1,4-oxazepane (4.15 g) in acetonitrile (40 mL) was added 1-chloroethyl chloroformate (1.16 mL), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and methanol (40 mL) and 1 N hydrochloric acid (0.50 mL) were added. The reaction mixture was stirred under reflux for 1 hr, and triethylamine (1.50 mL) and di-tert-butyl dicarbonate (2.16 mL) were added at room temperature. The reaction mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (2.90 g).

^1H NMR (300 MHz, CDCl_3) δ 1.51 (9H, s), 2.05-2.19 (1H, m), 3.04-3.30 (2H, m), 3.43 (1H, dd, $J = 14.7, 6.8$ Hz), 3.49-3.67 (2H, m), 4.01-4.16 (3H, m), 4.19 (1H, dd, $J = 10.0, 4.7$ Hz), 4.33 (1H, d, $J = 9.8$ Hz), 7.09 (1H, t, $J = 8.7$ Hz), 7.16-7.25 (1H, m), 7.43 (1H, dd, $J = 7.2, 1.9$ Hz).

[0461]

H) [(6RS,7SR)-7-(3-chloro-4-fluorophenyl)-1,4-oxazepan-6-yl]methanol monohydrochloride

To a solution of tert-butyl (6RS,7SR)-7-(3-chloro-4-fluorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (81 mg) in ethanol (1 mL) was added 14.7 N hydrogen chloride-ethanol solution (2.0 mL), and the mixture was stirred at room temperature for 1 hr. The crystals obtained by concentration under reduced pressure were recrystallized from ethyl acetate-ethanol to give the title compound (48 mg).

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¹H NMR (300 MHz, DMSO-d₆) δ 2.34-2.47 (1H, m), 3.03-3.32 (5H, m), 3.46 (1H, dd, J = 13.8, 2.8 Hz), 3.70-3.87 (1H, m), 4.04 (1H, dt, J = 13.8, 4.5 Hz), 4.43 (1H, d, J = 10.4 Hz), 4.96 (1H, brs), 7.35-7.50 (2H, m), 7.63 (1H, dd, J = 7.3, 1.9 Hz),
5 9.22 (2H, brs).

[0462]

Example 11

1-{[(6RS,7SR)-7-(3-chloro-4-fluorophenyl)-1,4-oxazepan-6-yl]methyl}urea monohydrochloride

10 Using tert-butyl (6RS,7SR)-7-(3-chloro-4-fluorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate, and by a method similar to that of Example 3, the title compound (69.0 mg) was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 2.81 (2H, brs), 3.04-3.29 (3H, m),
15 3.29-3.42 (1H, m), 3.70-3.84 (1H, m), 3.90-4.04 (1H, m), 4.34 (1H, d, J = 10.0 Hz), 6.32 (1H, brs), 7.38-7.51 (2H, m), 7.68-7.75 (1H, m), 9.04 (1H, brs), 9.41 (1H, brs), 3H not detected.

[0463]

Example 12

20 (6RS,7SR)-7-(3-chloro-4-fluorophenyl)-6-[(methylsulfonyl)methyl]-1,4-oxazepane monohydrochloride

Using tert-butyl (6RS,7SR)-7-(3-chloro-4-fluorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate, and by a method similar to that of Example 5, the title compound (45.8 mg) was
25 obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 2.75 (1H, d), 2.93 (3H, s), 3.02-3.14 (1H, m), 3.18-3.35 (3H, m), 3.44 (1H, dd, J = 13.5, 9.9 Hz), 3.69 (1H, dd, J = 13.8, 2.3 Hz), 3.84 (1H, ddd, J = 13.7, 9.0, 4.4 Hz), 4.05 (1H, dt, J = 13.8, 4.4 Hz), 4.46 (1H, d, J
30 = 10.0 Hz), 7.40-7.51 (2H, m), 7.63-7.72 (1H, m), 8.90-9.74 (2H, m).

[0464]

Example 13

35 [(6RS,7SR)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-yl]methanol monohydrochloride

[0465]

A) methyl 2-[(4-chloro-3-fluorophenyl)(hydroxy)methyl]prop-2-enoate

To a solution of 4-chloro-3-fluorobenzaldehyde (50.0 g) and methyl acrylate (42.6 mL) in acetonitrile (158 mL) was added 1,4-diazabicyclo[2.2.2]octane (10.6 g), and the mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (69.1 g).
¹H NMR (300 MHz, CDCl₃) δ 3.19 (1H, d, J = 6.1 Hz), 3.75 (3H, s), 5.51 (1H, d, J = 6.1 Hz), 5.84 (1H, s), 6.36 (1H, s), 7.11 (1H, d, J = 8.3 Hz), 7.20 (1H, dd, J = 9.8, 1.9 Hz), 7.32-7.42 (1H, m).

[0466]

B) methyl (2RS,3RS)-2-[(benzylamino)methyl]-3-(4-chloro-3-fluorophenyl)-3-hydroxypropanoate

To a solution of methyl 2-[(4-chloro-3-fluorophenyl)(hydroxy)methyl]prop-2-enoate (69.1 g) and triethylamine (47.3 mL) in methanol (706 mL) was added benzylamine (37.1 mL), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (58.2 g).

MS (ESI⁺): [M+H]⁺ 352.1.

[0467]

C) (1RS,2SR)-2-[(benzylamino)methyl]-1-(4-chloro-3-fluorophenyl)propane-1,3-diol

To a suspension of calcium chloride (27.6 g) in THF (234 mL) and ethanol (176 mL) was added, under a nitrogen stream, sodium borohydride (12.5 g), and the mixture was stirred at room temperature for 1 hr. To the reaction mixture was added a solution of methyl (2RS,3RS)-2-[(benzylamino)methyl]-3-(4-chloro-3-fluorophenyl)-3-hydroxypropanoate (58.2 g) in THF

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(200 mL) and ethanol (150 mL) under ice-cooling, and the mixture was stirred at room temperature for 5 hr. To the reaction mixture was added 6 N aqueous hydrochloric acid solution (28 mL), the mixture was neutralized with 8 N aqueous sodium hydroxide solution, and the mixture was filtered through celite. The obtained oil was diluted with ethyl acetate, and the diluted solution was washed with distilled water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the title compound (44.5 g).

MS (ESI+): $[M+H]^+$ 324.1.

[0468]

D) (1RS,2SR)-3-(benzylamino)-2-([tert-butyl(dimethyl)silyl]oxy)methyl)-1-(4-chloro-3-fluorophenyl)propan-1-ol

To a solution of (1RS,2SR)-2-[(benzylamino)methyl]-1-(4-chloro-3-fluorophenyl)propane-1,3-diol (44.5 g) and triethylamine (21.1 mL) in THF (416 mL) was added a solution of tert-butylchlorodimethylsilane (22.8 g) in THF (42 mL) under ice-cooling, and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (NH, hexane/ethyl acetate) to give the title compound (29.3 g).

MS (ESI+): $[M+H]^+$ 438.4.

[0469]

E) N-benzyl-N-[(2RS,3SR)-2-([tert-butyl(dimethyl)silyl]oxy)methyl)-3-(4-chloro-3-fluorophenyl)-3-hydroxypropyl]-2-chloroacetamide

To a solution of (1RS,2SR)-3-(benzylamino)-2-([tert-butyl(dimethyl)silyl]oxy)methyl)-1-(4-chloro-3-fluorophenyl)propan-1-ol (29.3 g) and triethylamine (11.2 mL)

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in THF (335 mL) was added chloroacetyl chloride (5.37 mL) under ice-cooling, and the mixture was stirred at 0°C for 2 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted
5 solution was washed with distilled water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the title compound (35.0 g).

MS (ESI+): [M+H]⁺ 514.1.

[0470]

10 F) (6RS,7SR)-4-benzyl-6-([tert-butyl(dimethyl)silyl]oxy)methyl)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-3-one

To a solution of N-benzyl-N-[(2RS,3SR)-2-([tert-butyl(dimethyl)silyl]oxy)methyl)-3-(4-chloro-3-fluorophenyl)-
15 3-hydroxypropyl]-2-chloroacetamide (34.5 g) in THF (1340 mL) was added 1 N aqueous sodium hydroxide solution (80.0 mL) under ice-cooling, and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl
20 acetate. The diluted solution was washed with distilled water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the title compound (31.5 g).

MS (ESI+): [M+H]⁺ 478.1.

25 [0471]

G) (6RS,7SR)-4-benzyl-6-([tert-butyl(dimethyl)silyl]oxy)methyl)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepane

To a solution of aluminum(III) chloride (5.28 g) in THF
30 (396 mL) was added, under a nitrogen stream, lithium aluminum hydride (4.51 g) under ice-cooling, and the mixture was stirred at 0°C for 1 hr. To the reaction mixture was added dropwise a solution of (6RS,7SR)-4-benzyl-6-([tert-butyl(dimethyl)silyl]oxy)methyl)-7-(4-chloro-3-fluorophenyl)-
35 1,4-oxazepan-3-one (31.5 g) in THF (264 mL), and the mixture

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was stirred at 0°C for 2 hr. To the reaction mixture was added aqueous potassium sodium (+)-tartrate tetrahydrate (93.0 g) solution at 0°C, and the mixture was stirred at room temperature overnight, and filtered through celite. The
5 obtained oil was diluted with ethyl acetate, and the mixture was washed with distilled water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the title compound (26.4 g).

¹H NMR (300 MHz, CDCl₃) δ -0.02 - 0.02 (6H, m), 0.89 (9H, s),
10 2.14-2.28 (1H, m), 2.64-2.82 (2H, m), 2.94 (2H, d, J = 4.2 Hz), 3.46-3.74 (5H, m), 4.00-4.10 (1H, m), 4.48 (1H, d, J = 7.9 Hz), 7.12-7.46 (8H, m).

[0472]

H) tert-butyl (6RS,7SR)-7-(4-chloro-3-fluorophenyl)-6-
15 (hydroxymethyl)-1,4-oxazepane-4-carboxylate

To a solution of (6RS,7SR)-4-benzyl-6-([tert-butyl(dimethyl)silyl]oxy)methyl)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepane (26.4 g) in acetonitrile (300 mL) was added 1-chloroethyl chloroformate (7.35 mL), and the mixture was
20 stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, and methanol (300 mL) was added. The mixture was heated to 80°C, and 1 N hydrochloric acid (3.00 mL) was added. The reaction mixture was stirred at 80°C for 2 hr, and ice-cooled, and triethylamine
25 (9.50 mL) and di-tert-butyl dicarbonate (13.7 mL) were added. The reaction mixture was stirred at room temperature overnight, and concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, dried over
30 anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (15.9 g).

¹H NMR (300 MHz, CDCl₃) δ 1.51 (9H, s), 2.06-2.18 (1H, m),
35 3.04-3.34 (2H, m), 3.35-3.71 (3H, m), 4.01-4.29 (4H, m), 4.34

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(1H, d, J = 9.5 Hz), 7.08 (1H, d, J = 8.0 Hz), 7.18 (1H, dd, J = 9.8, 1.9 Hz), 7.30-7.43 (1H, m).

[0473]

I) [(6RS,7SR)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-yl]methanol monohydrochloride

To tert-butyl (6RS,7SR)-7-(4-chloro-3-fluorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (229 mg) was added 2 N hydrogen chloride-ethanol solution (1.02 mL), and the mixture was stirred at room temperature for 1 hr. Further, 14.7 N hydrogen chloride-ethanol solution (2 mL) was added, and the mixture was stirred for 10 min. The oil obtained by concentration under reduced pressure was crystallized from diisopropyl ether-ethanol to give the title compound (146 mg). ¹H NMR (300 MHz, CDCl₃) δ 3.07-3.36 (6H, m), 3.41-3.53 (1H, m), 3.74-3.87 (1H, m), 3.97-4.12 (1H, m), 4.45 (1H, d, J = 10.2 Hz), 4.98 (1H, brs), 7.27 (1H, dd, J = 8.3, 1.9 Hz), 7.47 (1H, dd, J = 10.6, 1.9 Hz), 7.57-7.68 (1H, m), 9.28-9.75 (2H, m).

[0474]

Example 14

[(5RS,6SR)-6-(3,4-dichlorophenyl)-1,4-oxazepan-5-yl]methanol monohydrochloride

[0475]

A) ethyl N-(tert-butoxycarbonyl)-N-[2-(2-ethoxy-2-oxoethoxy)ethyl]glycinate

To a solution of ethyl N-(tert-butoxycarbonyl)-N-(2-hydroxyethyl)glycinate (1.2 g) in THF (17 mL) was added ethyl bromoacetate (0.8 mL) under ice-cooling, and the mixture was stirred for 5 min. To this solution was added sodium hydride (288 mg), and the mixture was stirred under ice-cooling for 5 min, and at room temperature for 60 min. The reaction mixture was ice-cooled again, ice water was added, and the mixture was extracted with ethyl acetate. The extract was washed successively with water and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column

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chromatography (ethyl acetate/hexane) to give the title compound (788 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.23-1.31 (6H, m), 1.42-1.47 (9H, m), 3.47-3.56 (2H, m), 3.65-3.71 (2H, m), 4.03-4.08 (4H, m), 4.13-
5 4.22 (4H, m).

[0476]

B) 4-tert-butyl 5-ethyl 6-hydroxy-2,3-dihydro-1,4-oxazepane-4,5(7H)-dicarboxylate

To a solution of ethyl N-(tert-butoxycarbonyl)-N-[2-(2-
10 ethoxy-2-oxoethoxy)ethyl]glycinate (200 mg) in toluene (5 mL) was added 1.0 M potassium tert-butoxide/tetrahydrofuran solution (2.2 mL), and the mixture was stirred at 90°C for 2 hr. The reaction mixture was cooled to room temperature, 1 N hydrochloric acid (2.0 mL) was added, and the mixture was
15 extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (33 mg).

20 ¹H NMR (300 MHz, DMSO-d₆) δ 1.19-1.28 (3H, m), 1.35-1.42 (9H, m), 3.40-3.65 (2H, m), 3.76-4.30 (6H, m), 11.2 (1H, s).

[0477]

C) 4-tert-butyl 5-ethyl 6-(3,4-dichlorophenyl)-2,3-dihydro-1,4-oxazepane-4,5(7H)-dicarboxylate

25 To a mixture of 60% sodium hydride (233 mg) and anhydrous diethyl ether (12 mL) was added a solution of 4-tert-butyl 5-ethyl 6-hydroxy-2,3-dihydro-1,4-oxazepane-4,5(7H)-dicarboxylate (837 mg) in diethyl ether (8 mL) under ice-cooling and the mixture was stirred for 90 min. A solution of
30 trifluoromethanesulfonic anhydride (0.59 mL) in diethyl ether (8 mL) was added dropwise. After stirring at room temperature for 40 min, aqueous saturated ammonium chloride was added for partitioning. The aqueous layer was extracted twice with ethyl acetate, the extract was dried over anhydrous sodium sulfate,
35 and the solvent was evaporated under reduced pressure. The

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residue was used without further purification for the next reaction.

[0478]

To a mixture of the above-mentioned resultant product and
5 tetrakis(triphenylphosphine)palladium(0) (168 mg) in toluene
(20 mL)-ethanol (4 mL) was added 2.5 M aqueous sodium hydrogen
carbonate solution (1.8 mL), and the reaction system was
purged with argon. To the reaction mixture was added 3,4-
dichlorophenylboronic acid (667 mg), and the mixture was
10 heated at 80°C for 2 hr. The reaction mixture was cooled to
room temperature, and diluted with ethyl acetate. The diluted
solution was washed with water and brine, and dried over
anhydrous sodium sulfate. The solvent was evaporated under
reduced pressure. The residue was purified by silica gel
15 column chromatography (ethyl acetate/hexane) to give the title
compound (0.99 g).

¹H NMR (300 MHz, CDCl₃) δ 0.93-0.98 (3H, m), 1.42 (9H, s),
3.83-3.86 (4H, m), 3.93-4.00 (2H, m), 4.41 (2H, s), 7.02 (1H,
dd, J = 8.4, 2.1 Hz), 7.28 (1H, d, J = 2.1 Hz), 7.40 (1H, d, J
20 = 8.4 Hz).

[0479]

D) 4-tert-butyl 5-ethyl (5RS,6SR)-6-(3,4-dichlorophenyl)-1,4-
oxazepane-4,5-dicarboxylate

To a solution (4.5 mL) of 4-tert-butyl 5-ethyl 6-(3,4-
25 dichlorophenyl)-2,3-dihydro-1,4-oxazepane-4,5(7H)-
dicarboxylate (450 mg) in THF were added sodium borohydride
(86 mg) and water (3 drops), and the mixture was stirred at
room temperature for 3 days. To the reaction solution were
added water and 0.1 N hydrochloric acid, and the mixture was
30 extracted with ethyl acetate. The ethyl acetate layer was
washed with water and brine, and dried over anhydrous sodium
sulfate. The solvent was evaporated under reduced pressure.
The residue was purified by silica gel column chromatography
(ethyl acetate/hexane) to give the title compound (135 mg).

35 ¹H NMR (300 MHz, CDCl₃) δ 1.11 (1.68H, t, J = 7.2 Hz), 1.15

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(1.32H, t, J = 7.2 Hz), 1.47 (3.96H, s), 1.50 (5.04H, s),
3.40-3.48 (2H, m), 3.60-3.88 (5H, m), 4.03-4.11 (2H, m), 4.59
(0.44H, d, J = 9.0 Hz), 4.87 (0.56H, d, J = 9.0 Hz), 7.09-7.15
(1H, m), 7.35-7.40 (2H, m).

5 [0480]

E) tert-butyl (5RS,6SR)-6-(3,4-dichlorophenyl)-5-
(hydroxymethyl)-1,4-oxazepane-4-carboxylate

To a solution of sodium borohydride (49 mg) in THF (1.25
mL)-EtOH (0.9 mL) was added calcium chloride (72 mg), and the
10 mixture was stirred at room temperature for 20 min. To this
reaction mixture was added a solution of 4-tert-butyl 5-ethyl
(5RS,6SR)-6-(3,4-dichlorophenyl)-1,4-oxazepane-4,5-
dicarboxylate (135 mg) in THF (1.25 mL), and the mixture was
stirred at room temperature for 16 hr. The reaction mixture
15 was poured into 10% aqueous citric acid solution, and the
mixture was extracted with ethyl acetate. The extract was
washed with water and brine, and dried over anhydrous sodium
sulfate. The solvent was evaporated under reduced pressure.
The residue was purified by silica gel column chromatography
20 (ethyl acetate/hexane) to give the title compound (118 mg).
¹H NMR (300 MHz, CDCl₃) δ 1.51 (9H, s), 3.00-3.28 (2H, m),
3.44-3.90 (8H, m), 4.00-4.26 (1H, m), 7.14-7.18 (1H, m), 7.37
(1H, d, J = 8.1 Hz), 7.42 (1H, brs).

[0481]

25 F) [(5RS,6SR)-6-(3,4-dichlorophenyl)-1,4-oxazepan-5-
yl]methanol monohydrochloride

Using tert-butyl (5RS,6SR)-6-(3,4-dichlorophenyl)-5-
(hydroxymethyl)-1,4-oxazepane-4-carboxylate (88 mg), and by a
method similar to that of Example 1, step I), the title
30 compound (67 mg) was obtained.

MS (ESI⁺): [M+H]⁺ 276.2.

[0482]

Example 15

(5RS,6SR)-6-(3,4-dichlorophenyl)-5-[(methylsulfonyl)methyl]-
35 1,4-oxazepane monohydrochloride

[0483]

A) tert-butyl (5RS,6SR)-6-(3,4-dichlorophenyl)-5-
[(methylsulfanyl)methyl]-1,4-oxazepane-4-carboxylate

Using tert-butyl (5RS,6SR)-6-(3,4-dichlorophenyl)-5-
5 (hydroxymethyl)-1,4-oxazepane-4-carboxylate (114 mg), and by a
method similar to that of Example 5, steps A) and B), the
title compound (106 mg) was obtained.

¹H NMR (300 MHz, CDCl₃) δ 1.52 (4.5H, s), 1.54 (4.5H, s), 1.98
(3H, d, J = 3.3 Hz), 2.60 (2H, brs), 3.00-3.40 (2H, m), 3.52-
10 3.84 (5H, m), 4.45 (1H, brs), 7.02-7.12 (1H, m), 7.30-7.42
(2H, m).

[0484]

B) tert-butyl (5RS,6SR)-6-(3,4-dichlorophenyl)-5-
[(methylsulfonyl)methyl]-1,4-oxazepane-4-carboxylate

15 Using tert-butyl (5RS,6SR)-6-(3,4-dichlorophenyl)-5-
[(methylsulfanyl)methyl]-1,4-oxazepane-4-carboxylate (100 mg),
and by a method similar to that of Example 5, step C), the
title compound (102 mg) was obtained.

¹H NMR (300 MHz, CDCl₃) δ 1.37 (9H, s), 1.72 (1H, brs), 2.46
20 (3H, s), 3.20 (3H, s), 4.23 (4H, s), 5.08-5.34 (1H, m), 5.40-
5.61 (1H, m), 6.62-6.86 (3H, m).

[0485]

C) (5RS,6SR)-6-(3,4-dichlorophenyl)-5-
[(methylsulfonyl)methyl]-1,4-oxazepane monohydrochloride

25 Using tert-butyl (5RS,6SR)-6-(3,4-dichlorophenyl)-5-
[(methylsulfonyl)methyl]-1,4-oxazepane-4-carboxylate (100 mg),
and by a method similar to that of Example 1, step I), the
title compound (72 mg) was obtained.

MS (ESI⁺): [M+H]⁺ 338.0.

30 [0486]

Example 16

(6RS)-6-(3,4-dichlorophenyl)-1,4-oxazepan-6-ol
monohydrochloride

[0487]

35 A) tert-butyl (6RS)-6-(3,4-dichlorophenyl)-6-hydroxy-1,4-

oxazepane-4-carboxylate

To a solution of tert-butyl 6-oxo-1,4-oxazepane-4-carboxylate (418 mg) prepared by the method described in WO2004/074291 in THF (12 mL) was added 0.5 M 3,4-dichlorophenylmagnesium bromide-THF (4.7 mL) under ice-cooling. The reaction mixture was stirred at room temperature for 1.5 hr, and poured into water, and the mixture was extracted with ethyl acetate. The extract was washed successively with dil. hydrochloric acid, saturated aqueous sodium hydrogen carbonate, water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (455 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.52 (9H, s), 3.10-3.27 (2H, m), 3.54-3.72 (2H, m), 3.88-4.15 (4H, m), 5.09 (1H, s), 7.40 (1H, d, J = 8.7 Hz), 7.49-7.52 (1H, m), 7.77 (1H, s).

[0488]

B) (6RS)-6-(3,4-dichlorophenyl)-1,4-oxazepan-6-ol monohydrochloride

Using tert-butyl (6RS)-6-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepane-4-carboxylate (108 mg), and by a method similar to that of Example 1, step I), the title compound (84 mg) was obtained.

MS (ESI⁺): [M+H]⁺ 262.0.

[0489]

Example 17

(6RS)-6-(3,4-dichlorophenyl)-6-methoxy-1,4-oxazepane monohydrochloride

[0490]

A) tert-butyl (6RS)-6-(3,4-dichlorophenyl)-6-methoxy-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6RS)-6-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepane-4-carboxylate (130 mg) in DMF (3.0 mL) were added 60% sodium hydride (44 mg) and methyl iodide (0.068

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mL) at room temperature, and the mixture was stirred for 30 min. To the reaction mixture was added ice water, and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (186 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.28-1.34 (9H, m), 3.13 (3H, s), 3.59-3.95 (8H, m), 7.32-7.35 (1H, m), 7.43 (1H, d, J = 8.4 Hz), 7.56-7.60 (1H, m).

[0491]

B) (6RS)-6-(3,4-dichlorophenyl)-6-methoxy-1,4-oxazepane monohydrochloride

Using tert-butyl (6RS)-6-(3,4-dichlorophenyl)-6-methoxy-1,4-oxazepane-4-carboxylate (114 mg), and by a method similar to that of Example 1, step I), the title compound (84 mg) was obtained.

MS (ESI⁺): [M+H]⁺ 276.1.

[0492]

Example 18

(6RS)-6-(3,4-dichlorophenyl)-6-ethoxy-1,4-oxazepane monohydrochloride

[0493]

A) tert-butyl (6RS)-6-(3,4-dichlorophenyl)-6-ethoxy-1,4-oxazepane-4-carboxylate

Using tert-butyl (6RS)-6-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepane-4-carboxylate (158 mg) and ethyl iodide (0.052 mL), and by a method similar to that of Example 17, step A), the title compound (160 mg) was obtained.

¹H NMR (300 MHz, CDCl₃) δ 1.17 (3H, t, J = 6.9 Hz), 1.36 (9H, brs), 3.12 (1H, brs), 3.46 (2H, brs), 3.60-3.66 (3H, m), 3.78-3.93 (4H, m), 7.35 (1H, dd, J = 8.4, 2.1 Hz), 7.42 (1H, d, J = 8.4 Hz), 7.57 (1H, brs).

[0494]

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B) (6RS)-6-(3,4-dichlorophenyl)-6-ethoxy-1,4-oxazepane
monohydrochloride

Using tert-butyl (6RS)-6-(3,4-dichlorophenyl)-6-ethoxy-
1,4-oxazepane-4-carboxylate (140 mg), and by a method similar
5 to that of Example 1, step I), the title compound (104 mg) was
obtained.

MS (ESI+): [M+H]⁺ 290.0.

[0495]

Example 19

10 (7RS)-7-(3,4-dichlorophenyl)-7-(methoxymethyl)-1,4-oxazepane
monohydrochloride

[0496]

A) 1-(3,4-dichlorophenyl)-2-methoxyethanone

A solution (about 100 mL) of 3,4-dichlorophenylmagnesium
15 bromide in diethyl ether was prepared from a mixture of
magnesium (flakes) (2.07 g) in diethyl ether (100 mL) and 1-
bromo-3,4-dichlorobenzene (17.5 g). A solution of
methoxyacetonitrile (5.0 g) in diethyl ether (10 mL) was added
dropwise to a solution of 3,4-dichlorophenylmagnesium bromide
20 in diethyl ether under ice-cooling, and the resulting mixture
was stirred under ice-cooling for 20 min. The reaction mixture
was quenched with water, the mixture was acidified with 1 N
hydrochloric acid, and the mixture was stirred under ice-
cooling for 15 min. The reaction mixture was extracted with
25 ethyl acetate, the organic layer was washed with water and
brine, and dried over anhydrous magnesium sulfate, and the
solvent was evaporated to give a pale-yellow oil. The oil was
purified by silica gel column chromatography (eluent;
hexane:ethyl acetate (19:1 - 1:1)) to give the title compound
30 (10.5 g).

¹H NMR (300 MHz, CDCl₃) δ 3.49 (3H, s), 4.63 (2H, s), 7.55 (1H,
d, J = 8.4 Hz), 7.77 (1H, dd, J = 8.4, 1.8 Hz), 8.03 (1H, d, J
= 1.8 Hz).

[0497]

35 B) (3RS)-3-(3,4-dichlorophenyl)-3-hydroxy-4-

methoxybutanenitrile

To a solution of 1.6 M n-butyllithium/hexane solution (20 mL) in THF (50 mL) was added dropwise a solution of acetonitrile (1.23 g) in THF (5 mL) at -78°C, and the mixture was stirred for 15 min, and at -40°C for 15 min. A solution of 1-(3,4-dichlorophenyl)-2-methoxyethanone (5.00 g) in THF (30 mL) was added dropwise at -78°C, and the mixture was gradually warmed with stirring to room temperature, and stirred for 20 min. The reaction mixture was quenched with water, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate (0% - 100%)) to give the title compound (5.63 g).

¹H NMR (300 MHz, CDCl₃) δ 2.82 (1H, d, J = 16.5 Hz), 2.92 (1H, d, J = 16.5 Hz), 3.24 (1H, s), 3.45 (3H, s), 3.54 (1H, d, J = 9.3 Hz), 3.68 (1H, d, J = 9.3 Hz), 7.32 (1H, dd, J = 8.7, 2.1 Hz), 7.46 (1H, d, J = 8.7 Hz), 7.62 (1H, d, J = 2.1 Hz).

[0498]

C) (2RS)-4-amino-2-(3,4-dichlorophenyl)-1-methoxybutan-2-ol

To a solution of (3RS)-3-(3,4-dichlorophenyl)-3-hydroxy-4-methoxybutanenitrile (5.56 g) in THF (100 mL) was added lithium aluminum hydride (812 mg) by small portions at room temperature. The mixture was stirred at room temperature for 10 min, and the reaction mixture was quenched with water. The precipitate was filtered off, and washed with THF. The filtrate was concentrated, 0.1 N aqueous potassium hydroxide solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (NH, eluent; hexane:ethyl acetate (0% - 100%)) to give the title compound (3.02 g).

¹H NMR (300 MHz, CDCl₃) δ 1.87 (1H, ddd, J = 14.6, 5.3, 3.3

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Hz), 2.00-2.20 (3H, m), 2.63 (1H, ddd, $J = 12.6, 10.5, 3.3$ Hz), 3.00 (1H, ddd, $J = 12.6, 4.0, 5.3$ Hz), 3.20-3.50 (3H, m), 3.35 (3H, s), 7.32 (1H, dd, $J = 8.4, 2.1$ Hz), 7.39 (1H, d, $J = 8.4$ Hz), 7.66 (1H, d, $J = 2.1$ Hz).

5 [0499]

D) 2-chloro-N-[(3RS)-3-(3,4-dichlorophenyl)-3-hydroxy-4-methoxybutyl]acetamide

To a solution of (2RS)-4-amino-2-(3,4-dichlorophenyl)-1-methoxybutan-2-ol (3.00 g) and triethylamine (1.60 mL) in THF
10 (50 mL) was added dropwise chloroacetyl chloride (0.91 mL) under ice-cooling, and the mixture was stirred for 20 min. The reaction mixture was quenched with water, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate, and
15 the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate (0% - 100%)) to give the title compound (2.13 g).

^1H NMR (300 MHz, CDCl_3) δ 1.60-2.00 (1H, br), 1.95-2.20 (2H, m), 3.05-3.20 (1H, m), 3.20-3.55 (1H, m), 3.37 (3H, s), 3.50
20 (2H, s), 3.93 (2H, s), 7.05-7.20 (1H, m), 7.24 (1H, dd, $J = 8.4, 2.1$ Hz), 7.43 (1H, d, $J = 8.4$ Hz), 7.55 (1H, d, $J = 2.1$ Hz).

[0500]

E) (7RS)-7-(3,4-dichlorophenyl)-7-(methoxymethyl)-1,4-
25 oxazepan-3-one

To a solution of 2-chloro-N-[(3RS)-3-(3,4-dichlorophenyl)-3-hydroxy-4-methoxybutyl]acetamide (2.10 g) in THF (150 mL) was added sodium tert-butoxide (592 mg), and the mixture was heated under reflux for 10 min. The reaction
30 mixture was quenched with water, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate (1:1) - ethyl
35 acetate:methanol (4:1)) to give the title compound (2.13 g).

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¹H NMR (300 MHz, CDCl₃) δ 2.34 (1H, dd, J = 15.3, 9.9 Hz), 2.72 (1H, dd, J = 15.3, 7.8 Hz), 3.10-3.25 (1H, m), 3.25 (3H, s), 3.35 (1H, d, J = 9.9 Hz), 3.53 (1H, d, J = 9.9 Hz), 3.55-3.70 (1H, m), 4.03 (1H, d, J = 17.1 Hz), 4.30 (1H, d, J = 17.1 Hz), 5 6.20-6.35 (1H, m), 7.22 (1H, dd, J = 8.6, 2.1 Hz), 7.40-7.50 (2H, m).

[0501]

F) (7RS)-7-(3,4-dichlorophenyl)-7-(methoxymethyl)-1,4-oxazepane monohydrochloride

10 To a solution of (7RS)-7-(3,4-dichlorophenyl)-7-(methoxymethyl)-1,4-oxazepan-3-one (535 mg) in THF (10 mL) was added 1 M borane-THF solution (5 mL), and the mixture was stirred at 70°C for 30 min. The reaction mixture was quenched with water, 2N hydrochloric acid (5 mL) was added, and the 15 mixture was stirred at 70°C for 10 min. The solvent was evaporated under reduced pressure, the residue was alkalified with potassium hydroxide, and the mixture was extracted three times with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and the 20 solvent was evaporated. The residue was purified by silica gel column chromatography (NH, eluent; hexane:ethyl acetate (1:1)-(0:10)) to give the title compound as a free amine form (397 mg).

[0502]

25 The free amine form (390 mg) of the title compound was dissolved in ethanol, 2 N hydrogen chloride-ethanol (1 mL) was added, and the solvent was evaporated. The residue was crystallized from ethanol-ethyl acetate to give the title compound (372 mg).

30 ¹H NMR (300 MHz, DMSO-d₆) δ 2.30-2.45 (1H, m), 2.75 (1H, dd, J = 16.4, 7.8 Hz), 3.00-3.55 (8H, m), 3.19 (3H, s), 3.65 (1H, dd, J = 14.3, 7.8 Hz), 3.95-4.10 (1H, m), 7.38 (1H, dd, J = 8.5, 2.1 Hz), 7.61 (1H, d, J = 8.5 Hz), 7.64 (1H, d, J = 2.1 Hz).

35 [0503]

Example 20

[(7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]methanol
monohydrochloride
[0504]

5 A) 1-(3,4-dichlorophenyl)-2-(4-methoxyphenoxy)ethanone

To a solution of magnesium (2.23 g) and iodine (5 mg) in diethyl ether (20 mL) was added dropwise a solution of 1-bromo-3,4-dichlorobenzene (20.7 g) in diethyl ether (20 mL), and the mixture was stirred at 35°C for 1 hr. The reaction
10 mixture was cooled to -10°C, and diethyl ether (100 mL) was added. A solution of (4-methoxyphenoxy)acetonitrile (10 g) in diethyl ether (20 mL) was added dropwise at -10°C, and the mixture was stirred for 1 hr while warming to room temperature. To the reaction mixture was added 1 N aqueous HCl
15 solution (200 mL), and the mixture was stirred at room temperature for 1 hr, and extracted with ethyl acetate. The obtained extract was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The obtained residue was purified by
20 silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (15.6 g).

¹H NMR (300 MHz, CDCl₃) δ 3.72-3.86 (3H, s), 5.12 (2H, s), 6.76-6.98 (4H, m), 7.57 (1H, d, J = 8.3 Hz), 7.84 (1H, dd, J = 8.5, 2.1 Hz), 8.09 (1H, d, J = 1.9 Hz).

25 [0505]

B) (3RS)-3-(3,4-dichlorophenyl)-3-hydroxy-4-(4-methoxyphenoxy)butanenitrile

To a mixed solution of acetonitrile (3.54 mL) and THF (30 mL) was added dropwise a solution of n-butyllithium in hexane
30 (1.6 M, 42.1 mL), and the mixture was stirred at -78°C for 30 min. To the reaction mixture was added dropwise a solution of 1-(3,4-dichlorophenyl)-2-(4-methoxyphenoxy)ethanone (14 g) in THF (45 mL), and the mixture was stirred at -78°C for 10 min, and then stirred for 1 hr while warming to room temperature.
35 The reaction mixture was diluted with water, and the mixture

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was extracted with ethyl acetate. The obtained extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (11.73 g).

¹H NMR (300 MHz, CDCl₃) δ 2.86-3.14 (2H, m), 3.29 (1H, s), 3.77 (3H, s), 4.06-4.24 (2H, m), 6.84 (4H, s), 7.33-7.42 (1H, m), 7.50 (1H, d, J = 8.7 Hz), 7.70 (1H, d, J = 2.3 Hz).

10 [0506]

C) (2RS)-4-amino-2-(3,4-dichlorophenyl)-1-(4-methoxyphenoxy)butan-2-ol

To a solution of lithium aluminum hydride (2.53 g) in diethyl ether (50 mL) was added aluminum chloride (2.96 g), and the mixture was stirred at 0°C for 30 min. To the reaction mixture was added dropwise a solution of (3RS)-3-(3,4-dichlorophenyl)-3-hydroxy-4-(4-methoxyphenoxy)butanenitrile (11.7 g) in THF (50 mL), and the mixture was stirred at 0°C for 15 min, and then stirred while warming to room temperature for 2 hr. To the reaction mixture was added ice, and the precipitate was filtered off through celite. The filtrate was diluted with water, and the mixture was extracted with ethyl acetate. The obtained extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the title compound (10.8 g).

¹H NMR (300 MHz, CDCl₃) δ 1.94-2.10 (1H, m), 2.25 (1H, ddd, J = 14.4, 10.2, 3.8 Hz), 2.63-2.83 (1H, m), 2.99-3.14 (1H, m), 3.17-3.47 (3H, m), 3.68-3.78 (3H, m), 3.85 (1H, d, J = 9.1 Hz), 3.94-4.05 (1H, m), 6.67-6.89 (4H, m), 7.41 (2H, s), 7.75 (1H, s).

30 [0507]

D) N-benzyl-2-chloro-N-[(3RS)-3-(3,4-dichlorophenyl)-3-hydroxy-4-(4-methoxyphenoxy)butyl]acetamide

To a solution of (2RS)-4-amino-2-(3,4-dichlorophenyl)-1-(4-methoxyphenoxy)butan-2-ol (6.7 g) in methanol (20 mL) were

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added magnesium sulfate (3.35 g), triethylamine (1.3 mL) and benzaldehyde (2.1 mL), and the mixture was stirred at room temperature for 1.5 hr. To the reaction mixture was added sodium borohydride (3.55 g), and the mixture was stirred at 0°C for 10 min, and then stirred while warming to room temperature for 1.5 hr. The reaction mixture was filtered through celite, and the filtrate was concentrated. The concentrated residue was diluted with water, and the mixture was extracted with ethyl acetate. The obtained extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 4-(benzylamino)-2-(3,4-dichlorophenyl)-1-(4-methoxyphenoxy)butan-2-ol (8.47 g). To a solution of 4-(benzylamino)-2-(3,4-dichlorophenyl)-1-(4-methoxyphenoxy)butan-2-ol (8.47 g) in THF (45 mL) were added triethylamine (2.85 mL) and chloroacetyl chloride (1.64 mL), and the mixture was stirred at 0°C for 10 min, and then stirred while warming to room temperature for 2 hr. The reaction mixture was diluted with water, and the mixture was extracted with ethyl acetate. The obtained extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (7.41 g).

¹H NMR (300 MHz, CDCl₃) δ 2.13-2.43 (2H, m), 2.99 (1H, ddd, J = 15.4, 11.0, 4.9 Hz), 3.26-3.60 (2H, m), 3.68-4.22 (7H, m), 4.40-4.66 (2H, m), 6.67-6.97 (4H, m), 7.07-7.72 (8H, m).

[0508]

E) (7RS)-4-benzyl-7-(3,4-dichlorophenyl)-7-[(4-methoxyphenoxy)methyl]-1,4-oxazepan-3-one

To a solution of N-benzyl-2-chloro-N-[(3RS)-3-(3,4-dichlorophenyl)-3-hydroxy-4-(4-methoxyphenoxy)butyl]acetamide (7.41 g) in THF (741 mL) was added sodium tert-butoxide (1.37 g), and the mixture was stirred at 0°C for 2 hr, and then stirred while warming to room temperature for 14 hr. To the reaction mixture was added water, and the mixture was

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concentrated. The concentrated residue was diluted with water, and the mixture was extracted with ethyl acetate. The obtained extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (6.02 g).

¹H NMR (300 MHz, CDCl₃) δ 2.36 (1H, dd, J = 15.3, 10.0 Hz), 2.80 (1H, dd, J = 15.6, 8.1 Hz), 3.22 (1H, dd, J = 13.8, 7.7 Hz), 3.56-3.88 (5H, m), 4.00 (1H, d, J = 9.4 Hz), 4.20 (1H, d, J = 17.0 Hz), 4.41-4.62 (2H, m), 4.63-4.76 (1H, m), 6.60-6.85 (4H, m), 7.15-7.40 (6H, m), 7.45 (1H, d, J = 8.7 Hz), 7.53 (1H, d, J = 1.9 Hz).

[0509]

15 F) (7RS)-4-benzyl-7-(3,4-dichlorophenyl)-7-[(4-methoxyphenoxy)methyl]-1,4-oxazepane

To a solution of lithium aluminum hydride (934 mg) in diethyl ether (30 mL) was added aluminum chloride (1.09 g), and the mixture was stirred at 0°C for 10 min. To the reaction mixture was added dropwise a solution of (7RS)-4-benzyl-7-(3,4-dichlorophenyl)-7-[(4-methoxyphenoxy)methyl]-1,4-oxazepan-3-one (6.02 g) in THF (30 mL), and the mixture was stirred at 0°C for 15 min, and stirred while warming to room temperature for 2 hr. To the reaction mixture was added ice, and the precipitate was filtered off through celite. The filtrate was diluted with water, and the mixture was extracted with ethyl acetate. The obtained extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the title compound (5.46 g).

¹H NMR (300 MHz, CDCl₃) δ 2.18-2.45 (1H, m), 2.52-2.88 (5H, m), 3.46-3.63 (2H, m), 3.63-3.84 (5H, m), 3.85-4.00 (2H, m), 6.57-6.83 (4H, m), 7.16-7.44 (7H, m), 7.60 (1H, d, J = 2.3 Hz).

[0510]

35 G) tert-butyl (7RS)-7-(3,4-dichlorophenyl)-7-[(4-

methoxyphenoxy)methyl]-1,4-oxazepane-4-carboxylate

To a solution of (7RS)-4-benzyl-7-(3,4-dichlorophenyl)-7-[(4-methoxyphenoxy)methyl]-1,4-oxazepane (5.46 g) in acetonitrile (30 mL) were added triethylamine (2.2 mL) and 1-chloroethyl chloroformate (1.76 mL), and the mixture was stirred at 90°C for 1.5 hr. 1-Chloroethyl chloroformate (1.0 mL) was added, and the mixture was stirred at 90°C for 1 hr. The solvent was evaporated under reduced pressure. To the residue was added methanol (50 mL), and the mixture was stirred at 80°C for 1 hr. The solvent was evaporated under reduced pressure. To a solution of the residue in THF (50 mL) were added triethylamine (1.75 mL) and di-tert-butyl dicarbonate (2.92 mL), and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was diluted with water, and the mixture was extracted with ethyl acetate. The obtained extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (4.75 g).

¹H NMR (300 MHz, CDCl₃) δ 1.44 (9H, s), 2.12-2.36 (1H, m), 2.71 (1H, dd, J = 15.3, 7.3 Hz), 3.25-3.63 (3H, m), 3.67-4.00 (8H, m), 6.64-6.89 (4H, m), 7.18-7.33 (1H, m), 7.43 (1H, d, J = 8.3 Hz), 7.57 (1H, d, J = 2.3 Hz).

[0511]

H) tert-butyl (7RS)-7-(3,4-dichlorophenyl)-7-(hydroxymethyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (7RS)-7-(3,4-dichlorophenyl)-7-[(4-methoxyphenoxy)methyl]-1,4-oxazepane-4-carboxylate (4.75 g) in acetonitrile (70 mL) and water (14 mL) was added ceric ammonium nitrate (16.18 g) at 0°C, and the mixture was stirred at 0°C for 30 min. The reaction mixture was diluted with water, and the mixture was extracted with ethyl acetate. The obtained extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under

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reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (3.36 g).

¹H NMR (300 MHz, CDCl₃) δ 1.42 (9H, s), 1.87-2.08 (1H, m), 2.17 (1H, d, J = 9.1 Hz), 2.45 (1H, dd, J = 14.9, 7.4 Hz), 3.20-3.97 (8H, m), 7.19 (1H, dd, J = 8.5, 2.1 Hz), 7.39-7.52 (2H, m).

[0512]

I) [(7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]methanol monohydrochloride

Using tert-butyl (7RS)-7-(3,4-dichlorophenyl)-7-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (200 mg), and by a method similar to that of Example 1, step I), the title compound (172 mg) was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 2.36 (1H, dd, J = 16.3, 9.8 Hz), 2.76 (1H, dd, J = 16.3, 8.0 Hz), 3.13 (3H, brs), 3.24-3.52 (3H, m), 3.62 (1H, dd, J = 13.8, 7.8 Hz), 3.93-4.08 (1H, m), 4.97-5.21 (1H, m), 7.35 (1H, dd, J = 8.3, 1.9 Hz), 7.57 (1H, d, J = 1.9 Hz), 7.63 (1H, d, J = 8.7 Hz), 9.18 (2H, brs).

[0513]

Example 21

N-{[(7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]methyl}methanesulfonamide monohydrochloride

[0514]

A) tert-butyl (7RS)-7-(3,4-dichlorophenyl)-7-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (7RS)-7-(3,4-dichlorophenyl)-7-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (2 g), phthalimide (0.86 g) and triphenylphosphine (4.17 g) in THF (40 mL) was added dropwise a solution (2.2 M, 7.2 mL) of diethyl azodicarboxylate in toluene at 0°C, and the mixture was stirred at 0°C for 30 min, and then for 6 hr while warming to room temperature. To the reaction mixture were added phthalimide (0.43 g) and a solution (2.2 M, 3.6 mL) of diethyl azodicarboxylate in toluene, and the mixture was stirred at

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room temperature for 14 hr. The reaction mixture was diluted with water, and the mixture was extracted with ethyl acetate. The obtained extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane) and silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (1.49 g).

¹H NMR (300 MHz, CDCl₃) δ 1.42 (9H, s), 2.26 (1H, brs), 2.45-2.62 (1H, m), 3.31-3.77 (5H, m), 3.83-3.97 (3H, m), 7.22 (1H, dd, J = 8.5, 2.1 Hz), 7.34-7.42 (1H, m), 7.50 (1H, d, J = 1.9 Hz), 7.66-7.74 (2H, m), 7.74-7.83 (2H, m).

[0515]

B) tert-butyl (7RS)-7-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (7RS)-7-(3,4-dichlorophenyl)-7-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1,4-oxazepane-4-carboxylate (1.39 g) in ethanol (14 mL) was added hydrazine (2.8 mL), and the mixture was stirred at room temperature for 14 hr. The precipitate was removed by filtration, and the solvent of the filtrate was evaporated under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. The obtained extract was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the title compound (0.9 g).

¹H NMR (300 MHz, CDCl₃) δ 1.20-1.32 (2H, m), 1.43 (9H, s), 2.07-2.20 (1H, m), 2.25-2.40 (1H, m), 2.64 (1H, d, J = 13.2 Hz), 2.91 (1H, d, J = 13.6 Hz), 3.28-3.44 (2H, m), 3.47-3.91 (4H, m), 7.16 (1H, dd, J = 8.5, 2.1 Hz), 7.41-7.47 (2H, m).

[0516]

C) tert-butyl (7RS)-7-(3,4-dichlorophenyl)-7-

{[(methylsulfonyl)amino]methyl}-1,4-oxazepane-4-carboxylate

Using tert-butyl (7RS)-7-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (160 mg), and in

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the same manner as in Example 8, step A), the title compound (167 mg) was obtained.

¹H NMR (300 MHz, CDCl₃) δ 1.37-1.49 (9H, m), 2.13-2.31 (1H, m), 2.43 (1H, brs), 2.75 (3H, s), 3.13-3.25 (1H, m), 3.29-3.92 (7H, m), 4.44 (1H, t, J = 6.4 Hz), 7.18 (1H, dd, J = 8.5, 2.1 Hz), 7.43-7.50 (2H, m).

[0517]

D) N-{[(7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]methyl}methanesulfonamide monohydrochloride

10 Using tert-butyl (7RS)-7-(3,4-dichlorophenyl)-7-[(methanesulfonyl)amino]methyl)-1,4-oxazepane-4-carboxylate (167 mg), and in the same manner as in Example 8, step B), the title compound (99 mg) was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 2.30-2.48 (1H, m), 2.67-2.88 (4H, m), 2.99-3.48 (6H, m), 3.58-3.76 (1H, m), 3.88-4.09 (1H, m), 7.05 (1H, t, J = 6.6 Hz), 7.33-7.46 (1H, m), 7.57-7.73 (2H, m), 9.22 (2H, brs).

[0518]

Example 22

20 N-{[(7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]methyl}sulfamide monohydrochloride

[0519]

A) tert-butyl (7RS)-7-({[(tert-butoxycarbonyl)sulfamoyl]amino}methyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

Using tert-butyl (7RS)-7-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (160 mg), and in the same manner as in Example 9, step A), the title compound (101 mg) was obtained.

30 ¹H NMR (300 MHz, CDCl₃) δ 1.45 (18H, d, J = 14.4 Hz), 2.19 (1H, d, J = 13.6 Hz), 2.48 (1H, brs), 3.16 (2H, brs), 3.32-3.99 (6H, m), 5.25 (1H, brs), 7.12-7.21 (1H, m), 7.39-7.54 (2H, m), 1H not detected.

[0520]

35 B) N-{[(7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-7-

yl)methyl}sulfamide monohydrochloride

Using tert-butyl (7RS)-7-([[(tert-butoxycarbonyl)sulfamoyl]amino)methyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (101 mg), and in the same manner
5 as in Example 9, step B), the title compound (64 mg) was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 2.39 (1H, dd, J = 16.2, 9.8 Hz), 2.70-2.85 (1H, m), 2.86-3.00 (1H, m), 3.06-3.19 (4H, m), 3.24-3.30 (1H, m), 3.54-3.66 (1H, m), 3.97 (1H, d, J = 15.1 Hz),
10 6.43-6.63 (3H, m), 7.35 (1H, dd, J = 8.5, 2.1 Hz), 7.58 (1H, d, J = 2.3 Hz), 7.65 (1H, d, J = 8.7 Hz), 9.18 (2H, brs).

[0521]

Example 23

[(2RS)-2-(3,4-dichlorophenyl)-1,4-oxazepan-2-yl]methanol
15 monohydrochloride

[0522]

A) 1,2-dichloro-4-{1-[(4-methoxyphenoxy)methyl]ethenyl}benzene

To a solution of methyltriphenylphosphonium bromide (60.3 g) in THF (800 mL) was added potassium tert-butoxide (20.7 g),
20 and the mixture was stirred at room temperature for 1 hr. To the reaction mixture was added dropwise a solution of 1-(3,4-dichlorophenyl)-2-(4-methoxyphenoxy)ethanone (48 g) in THF (400 mL), and the mixture was stirred at room temperature for 3 hr. The reaction mixture was diluted with water, and the
25 mixture was extracted with ethyl acetate. The obtained extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title
30 compound (15.1 g).

¹H NMR (300 MHz, CDCl₃) δ 3.73-3.88 (3H, m), 4.79 (2H, s), 5.49 (1H, s), 5.60 (1H, s), 6.81-6.93 (4H, m), 7.27-7.38 (2H, m), 7.57 (1H, d, J = 1.9 Hz).

[0523]

35 B) (2RS)-2-(3,4-dichlorophenyl)-2-[(4-

methoxyphenoxy)methyl]oxirane

To a solution of 1,2-dichloro-4-{1-[(4-methoxyphenoxy)methyl]ethenyl}benzene (15.1 g) in toluene (161 mL) was added methachloroperbenzoic acid (21.6 g), and the mixture was stirred at 60°C for 14 hr. The reaction mixture was cooled to 0°C, and diluted with saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The obtained extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (5.08 g).

¹H NMR (300 MHz, CDCl₃) δ 2.85 (1H, d, J = 5.3 Hz), 3.22 (1H, d, J = 5.3 Hz), 3.77 (3H, s), 4.20-4.26 (1H, m), 4.32-4.39 (1H, m), 6.79-6.88 (4H, m), 7.29-7.35 (1H, m), 7.40-7.45 (1H, m), 7.57 (1H, d, J = 2.3 Hz).

[0524]

C) tert-butyl [(2RS)-2-(3,4-dichlorophenyl)-2-hydroxy-3-(4-methoxyphenoxy)propyl](3-hydroxypropyl)carbamate

To a solution of (2RS)-2-(3,4-dichlorophenyl)-2-[(4-methoxyphenoxy)methyl]oxirane (5.0 g) in acetonitrile (15 mL) were added potassium carbonate (4.2 g) and 3-amino-1-propanol (1.41 mL), and the mixture was stirred at 100°C for 5 hr. The reaction mixture was cooled to room temperature, di-tert-butyl dicarbonate (5.28 mL) was added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with water, and the mixture was extracted with ethyl acetate. The obtained extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (5.55 g).

¹H NMR (300 MHz, CDCl₃) δ 1.39-1.86 (12H, m), 3.09-3.90 (10H, m), 3.92-4.08 (1H, m), 5.70 (1H, brs), 6.82 (4H, s), 7.27-7.58 (2H, m), 7.61-7.87 (1H, m).

[0525]

D) tert-butyl (2RS)-2-(3,4-dichlorophenyl)-2-[(4-methoxyphenoxy)methyl]-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl [(2RS)-2-(3,4-dichlorophenyl)-2-hydroxy-3-(4-methoxyphenoxy)propyl] (3-hydroxypropyl)carbamate (5.55 g) in toluene (120 mL) was added cyanomethylenetriethylphosphorane (4.7 mL), and the mixture was stirred at 100°C for 10 hr. The reaction mixture was diluted with water, and the mixture was extracted with ethyl acetate. The obtained extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (3.18 g).

¹H NMR (300 MHz, CDCl₃) δ 1.29-1.55 (9H, m), 1.68-1.84 (1H, m), 1.93-2.09 (1H, m), 2.91-3.10 (1H, m), 3.41-4.08 (9H, m), 4.29-4.65 (1H, m), 6.65-6.81 (4H, m), 7.28-7.36 (1H, m), 7.38-7.48 (1H, m), 7.52-7.70 (1H, m).

[0526]

E) tert-butyl (2RS)-2-(3,4-dichlorophenyl)-2-(hydroxymethyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (2RS)-2-(3,4-dichlorophenyl)-2-[(4-methoxyphenoxy)methyl]-1,4-oxazepane-4-carboxylate (3.18 g) in acetonitrile (80 mL) and water (20 mL) was added ceric ammonium nitrate (10.8 g) at 0°C, and the mixture was stirred at 0°C for 1 hr. The reaction mixture was diluted with water, and the mixture was extracted with ethyl acetate. The obtained extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (NH, ethyl acetate/hexane) to give the title compound (1.9 g).

¹H NMR (300 MHz, CDCl₃) δ 1.46-1.78 (10H, m), 1.93-2.12 (1H, m), 2.65-2.89 (1H, m), 3.05 (1H, d, J = 15.4 Hz), 3.23-3.40 (1H, m), 3.51-3.77 (2H, m), 3.89-4.36 (3H, m), 4.66 (1H, d, J

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= 15.1 Hz), 7.20-7.36 (1H, m), 7.42 (1H, d, J = 8.3 Hz), 7.55 (1H, d, J = 1.9 Hz).

[0527]

F) [(2RS)-2-(3,4-dichlorophenyl)-1,4-oxazepan-2-yl]methanol
5 monohydrochloride

Using tert-butyl (2RS)-2-(3,4-dichlorophenyl)-2-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (240 mg), and by a method similar to that in Example 1, step I), the title compound (165 mg) was obtained.

10 ¹H NMR (300 MHz, DMSO-d₆) δ 1.05 (1H, t, J = 7.0 Hz), 1.78 (1H, dd, J = 14.4, 2.6 Hz), 1.91-2.09 (1H, m), 2.91 (1H, d, J = 11.7 Hz), 3.29 (1H, d, J = 11.0 Hz), 3.37-3.69 (4H, m), 3.97 (1H, d, J = 13.2 Hz), 4.15 (1H, dd, J = 14.4, 6.0 Hz), 7.36 (1H, dd, J = 8.5, 2.1 Hz), 7.58 (1H, d, J = 1.9 Hz), 7.68 (1H,
15 d, J = 8.7 Hz), 8.34 (1H, brs), 9.87 (1H, d).

[0528]

Example 24

N-{[(2RS)-2-(3,4-dichlorophenyl)-1,4-oxazepan-2-yl]methyl}methanesulfonamide monohydrochloride

20 [0529]

A) tert-butyl (2RS)-2-(3,4-dichlorophenyl)-2-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1,4-oxazepane-4-carboxylate

Using tert-butyl (2RS)-2-(3,4-dichlorophenyl)-2-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (1.0 g), and in
25 the same manner as in Example 21, step A), the title compound (1.01 g) was obtained.

¹H NMR (300 MHz, CDCl₃) δ 1.44 (9H, d, J = 11.3 Hz), 1.70-1.93 (2H, m), 3.02-3.43 (1H, m), 3.57-4.24 (7H, m), 7.28-7.43 (2H, m), 7.54 (1H, brs), 7.62-7.83 (4H, m).

30 [0530]

B) tert-butyl (2RS)-2-(aminomethyl)-2-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

Using tert-butyl (2RS)-2-(3,4-dichlorophenyl)-2-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-1,4-oxazepane-4-
35 carboxylate (1.0 g), and in the same manner as in Example 21,

step B), the title compound (0.54 g) was obtained.

¹H NMR (300 MHz, CDCl₃) δ 1.46 (9H, d, J = 5.3 Hz), 1.75 (1H, brs), 1.90-2.03 (1H, m), 2.71-3.17 (3H, m), 3.23-3.47 (1H, m), 3.53-3.72 (1H, m), 3.87-4.06 (2H, m), 4.16-4.51 (1H, m), 7.13-7.26 (1H, m), 7.39-7.59 (2H, m), 2H not detected.

[0531]

C) tert-butyl (2RS)-2-(3,4-dichlorophenyl)-2-

{[(methylsulfonyl)amino]methyl}-1,4-oxazepane-4-carboxylate

Using tert-butyl (2RS)-2-(aminomethyl)-2-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (135 mg), and in the same manner as in Example 8, step A), the title compound (117 mg) was obtained.

¹H NMR (300 MHz, CDCl₃) δ 1.48 (9H, s), 1.72 (1H, brs), 2.01 (1H, brs), 2.68 (3H, s), 2.73-2.88 (1H, m), 3.10-3.66 (4H, m), 3.89-4.20 (2H, m), 4.54 (1H, d, J = 15.4 Hz), 5.74 (1H, brs), 7.14-7.23 (1H, m), 7.41-7.56 (2H, m).

[0532]

D) N-{[(2RS)-2-(3,4-dichlorophenyl)-1,4-oxazepan-2-yl]methyl}methanesulfonamide monohydrochloride

Using tert-butyl (2RS)-2-(3,4-dichlorophenyl)-2-{[(methylsulfonyl)amino]methyl}-1,4-oxazepane-4-carboxylate (117 mg), and in the same manner as in Example 8, step B), the title compound (73 mg) was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 1.67-1.84 (4H, m), 1.92-2.09 (1H, m), 2.97 (1H, brs), 3.08-3.29 (2H, m), 3.47-3.61 (2H, m), 3.72 (1H, dd, J = 13.6, 7.2 Hz), 3.87-4.02 (2H, m), 7.34 (1H, dd, J = 8.5, 2.1 Hz), 7.58 (1H, d, J = 1.9 Hz), 7.66 (1H, d, J = 8.3 Hz), 7.90 (1H, t, J = 6.2 Hz), 9.01 (1H, brs), 9.48 (1H, brs).

[0533]

30 Example 25

[(6RS,7SR)-6-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]methanol monohydrochloride

[0534]

A) (4SR)-4-[(1RS)-1-(3,4-dichlorophenyl)-2-nitroethyl]-2,2-dimethyl-1,3-dioxolane

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To a solution of (E)-2,2-dimethyl-4-(2-nitrovinyl)-1,3-dioxolane (22.29 g) synthesized according to the method described in Tetrahedron Letters, 36 (25), 4447-4450 (1995) in THF (200 mL) was added 1 M THF solution (193 mL) of bromo(3,4-dichlorophenyl)magnesium in an inert atmosphere at -78°C. The reaction mixture was stirred at room temperature for 2 hr, and added to aqueous ammonium chloride, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (12.16 g).

¹H NMR (300 MHz, CDCl₃) δ 1.30 (3H, s), 1.32 (3H, s), 3.38-3.46 (1H, m), 3.66 (1H, ddd, J = 8.7, 6.4, 3.8 Hz), 3.99 (1H, dd, J = 8.3, 6.4 Hz), 4.37 (1H, td, J = 6.9, 3.6 Hz), 4.70-4.85 (2H, m), 7.13 (1H, dd, J = 8.3, 2.3 Hz), 7.37-7.47 (2H, m).

[0535]

B) (2RS)-2-(3,4-dichlorophenyl)-2-[(4SR)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanamine

A solution of (4SR)-4-[(1RS)-1-(3,4-dichlorophenyl)-2-nitroethyl]-2,2-dimethyl-1,3-dioxolane (12.16 g) and Raney-nickel (10 g) in ethanol (100 mL) was stirred under a hydrogen atmosphere at room temperature for 5 hr. The reaction mixture was filtered through celite, and the solvent of the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/ethyl acetate) to give the title compound (3.40 g).

MS (ESI+): [M+H]⁺ 290.3.

[0536]

C) (2RS)-N-benzyl-2-(3,4-dichlorophenyl)-2-[(4SR)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanamine

A solution of (2RS)-2-(3,4-dichlorophenyl)-2-[(4SR)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanamine (3.40 g) and benzaldehyde (1.22 mL) in toluene (30 mL) was subjected to azeotropic distillation with dehydration, and the reaction

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mixture was concentrated. To the residue was added methanol (20 mL), and sodium borohydride (222 mg) was added at 0°C. The reaction mixture was stirred at room temperature for 30 min, and 1 N hydrochloric acid was added. The reaction mixture was basified with aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (3.72 g).

¹H NMR (300 MHz, CDCl₃) δ 1.27 (3H, s), 1.30 (3H, s), 1.45 (1H, brs), 2.84-2.93 (3H, m), 3.52 (1H, t, J = 7.9 Hz), 3.67-3.81 (2H, m), 4.00 (1H, dd, J = 8.1, 6.2 Hz), 4.26-4.35 (1H, m), 7.08 (1H, dd, J = 8.1, 2.1 Hz), 7.19-7.41 (7H, m).

15 [0537]

D) N-benzyl-2-chloro-N-[(2RS)-2-(3,4-dichlorophenyl)-2-[(4SR)-2,2-dimethyl-1,3-dioxolan-4-yl]ethyl]acetamide

To a solution of (2RS)-N-benzyl-2-(3,4-dichlorophenyl)-2-[(4SR)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanamine (3.72 g) and triethylamine (1.63 mL) in THF (30 mL) was added chloroacetyl chloride (0.783 mL) at 0°C, and the reaction mixture was stirred at room temperature for 2 hr. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (3.99 g).

¹H NMR (300 MHz, CDCl₃) δ 1.29 (3H, s), 1.33 (3H, s), 3.23-3.58 (3H, m), 3.70-4.01 (3H, m), 4.10-4.87 (4H, m), 7.01-7.22 (3H, m), 7.27-7.46 (5H, m).

[0538]

E) N-benzyl-N-[(2R,3S)-4-[[tert-butyl(dimethyl)silyl]oxy]-2-(3,4-dichlorophenyl)-3-hydroxybutyl]-2-chloroacetamide

35 A solution of N-benzyl-2-chloro-N-[(2RS)-2-(3,4-

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dichlorophenyl)-2-[(4SR)-2,2-dimethyl-1,3-dioxolan-4-yl]ethyl}acetamide (3.99 g) and 2N hydrochloric acid (10 mL) in THF (10 mL) was stirred at 50°C for 4 hr. The reaction mixture was basified with 1 N aqueous sodium hydroxide solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in DMF (20 mL), triethylamine (1.45 mL), tert-butyl(dimethyl)silyl chloride (1.45 g) and 4-dimethylaminopyridine (10 mg) were added, and the mixture was stirred at room temperature for 5 hr. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (4.13 g).

¹H NMR (300 MHz, CDCl₃) δ -0.02 (3H, s), -0.01 (3H, s), 0.87 (9H, s), 3.05-3.26 (3H, m), 3.41 (1H, dd, J = 10.2, 6.8 Hz), 3.60 (1H, d, J = 3.4 Hz), 3.80-3.89 (1H, m), 4.03-4.27 (3H, m), 4.38 (1H, d, J = 17.3 Hz), 4.70 (1H, d, J = 17.0 Hz), 7.06-7.25 (3H, m), 7.27-7.45 (5H, m).

[0539]

F) (6RS,7SR)-4-benzyl-7-([tert-butyl(dimethyl)silyl]oxy)methyl)-6-(3,4-dichlorophenyl)-1,4-oxazepan-3-one

To a solution of N-benzyl-N-[(2R,3S)-4-([tert-butyl(dimethyl)silyl]oxy)-2-(3,4-dichlorophenyl)-3-hydroxybutyl]-2-chloroacetamide (4.13 g) in THF (100 mL) was added sodium tert-butoxide (897 mg) at 0°C, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel

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column chromatography (ethyl acetate/hexane) to give the title compound (3.52 g).

MS (ESI+): $[M+H]^+$ 494.2.

[0540]

5 G) [(6RS,7SR)-4-benzyl-6-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]methanol

To a solution of (6RS,7SR)-4-benzyl-7-([tert-butyl(dimethyl)silyl]oxy)methyl)-6-(3,4-dichlorophenyl)-1,4-oxazepan-3-one (3.11 g) in THF (20 mL) was added 1 M THF solution (13.8 mL) of borane-THF complex at 0°C, and the mixture was stirred at 60°C for 2 hr. To the reaction mixture was added methanol, and the solvent was evaporated under reduced pressure. To the residue was added 6 N hydrochloric acid (8 mL), and the reaction mixture was stirred at 60°C overnight. The reaction mixture was basified with 8 N aqueous sodium hydroxide solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (2.22 g).

^1H NMR (300 MHz, CDCl_3) δ 1.86 (1H, brs), 2.63-2.80 (2H, m), 2.82-2.91 (1H, m), 2.95-3.14 (2H, m), 3.18 (2H, d, $J = 8.7$ Hz), 3.64-3.76 (3H, m), 4.04-4.10 (1H, m), 4.20 (1H, dt, $J = 8.7, 4.3$ Hz), 7.13 (1H, dd, $J = 8.3, 2.3$ Hz), 7.27-7.38 (6H, m), 7.44 (1H, d, $J = 1.9$ Hz).

[0541]

H) (6RS,7SR)-4-benzyl-7-([tert-butyl(dimethyl)silyl]oxy)methyl)-6-(3,4-dichlorophenyl)-1,4-oxazepane

A solution of [(6RS,7SR)-4-benzyl-6-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]methanol (1.63 g), triethylamine (0.741 mL), tert-butyldimethylsilyl chloride (738 mg) and 4-dimethylaminopyridine (catalytic amount) in DMF (10 mL) was stirred at room temperature for 2 hr. The reaction mixture was

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added to water, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (1.93 g).

¹H NMR (300 MHz, CDCl₃) δ -0.08 (3H, s), -0.04 (3H, s), 0.86 (9H, s), 2.59-2.88 (3H, m), 2.99-3.16 (3H, m), 3.34 (1H, dd, J = 10.2, 6.8 Hz), 3.60-3.71 (3H, m), 3.98 (1H, dt, J = 12.1, 3.6 Hz), 4.08-4.17 (1H, m), 7.18-7.38 (7H, m), 7.48 (1H, d, J = 1.9 Hz).

[0542]

I) [(6RS,7SR)-6-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]methanol monohydrochloride

To a solution of (6RS,7SR)-4-benzyl-7-([tert-butyl(dimethyl)silyl]oxy)methyl)-6-(3,4-dichlorophenyl)-1,4-oxazepane (250 mg) in acetonitrile (1.5 mL) was added 1-chloroethyl chloroformate (0.0786 mL), and the mixture was stirred at room temperature for 1.5 hr. The solvent was evaporated under reduced pressure. To the residue was added methanol (1.5 mL), and the reaction mixture was stirred at 60°C for 3 hr. The solvent was evaporated under reduced pressure. The residue was solidified with diisopropyl ether, and the obtained crude crystals were recrystallized from ethanol/ether/water to give the title compound (76.8 mg).

MS (ESI+): [M+H]⁺ 276.2.

[0543]

Example 26

(6RS,7SR)-6-(3,4-dichlorophenyl)-7-[(methylsulfonyl)methyl]-1,4-oxazepane monohydrochloride

[0544]

A) tert-butyl (6RS,7SR)-6-(3,4-dichlorophenyl)-7-(hydroxymethyl)-1,4-oxazepane-4-carboxylate

A solution of [(6RS,7SR)-6-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]methanol monohydrochloride (1.04 g), di-tert-

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butyl dicarbonate (799 mg) and triethylamine (1.02 mL) in THF (10 mL) was stirred at room temperature for 3 hr. The solvent was evaporated under reduced pressure. The residue was added to water, and the mixture was extracted with ethyl acetate.

5 The extract was washed with brine, and dried over anhydrous magnesium sulfate. 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).

10 ¹H NMR (300 MHz, CDCl₃) δ 1.46 (9H, d, J = 11.3 Hz), 1.73-1.85 (1H, m), 2.94-3.45 (5H, m), 3.57-3.85 (2H, m), 3.94-4.27 (3H, m), 7.06-7.20 (1H, m), 7.29-7.48 (2H, m).

[0545]

B) (6RS,7SR)-6-(3,4-dichlorophenyl)-7-

15 [(methylsulfonyl)methyl]-1,4-oxazepane monohydrochloride

Using tert-butyl (6RS,7SR)-6-(3,4-dichlorophenyl)-7-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (101.8 mg), and by a method similar to that in Example 5, the title compound (30.4 mg) was obtained.

20 MS (ESI+): [M+H]⁺ 338.2.

[0546]

Example 27

N-{[(6RS,7SR)-6-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]methyl}acetamide monohydrochloride

25 Using tert-butyl (6RS,7SR)-6-(3,4-dichlorophenyl)-7-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (920 mg) and by a method similar to that in Example 21, steps A) and B) and Example 6, steps C) and D), the title compound (55.7 mg) was obtained.

30 MS (ESI+): [M+H]⁺ 317.3.

[0547]

Example 28

1-{[(6RS,7SR)-6-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]methyl}urea monohydrochloride

35 Using tert-butyl (6RS,7SR)-6-(3,4-dichlorophenyl)-7-

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(hydroxymethyl)-1,4-oxazepane-4-carboxylate (920 mg), and by a method similar to that in Example 21, steps A) and B) and Example 3, steps D) and E), the title compound (74.3 mg) was obtained.

5 MS (ESI+): [M+H]⁺ 318.2.

[0548]

Example 29

N-{[(6RS,7SR)-6-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]methyl}methanesulfonamide monohydrochloride

10 Using tert-butyl (6RS,7SR)-6-(3,4-dichlorophenyl)-7-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (920 mg), and by a method similar to that in Example 21, the title compound (39.0 mg) was obtained.

MS (ESI+): [M+H]⁺ 353.2.

15 [0549]

Example 30

N-{[(6RS,7SR)-6-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]methyl}sulfamide monohydrochloride

20 Using tert-butyl (6RS,7SR)-6-(3,4-dichlorophenyl)-7-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (920 mg), and by a method similar to that in Example 21, steps A) and B) and Example 9, the title compound (66.6 mg) was obtained.

MS (ESI+): [M+H]⁺ 354.2.

[0550]

25 Example 31

1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one monohydrochloride

[0551]

30 A) tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate

tert-Butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (67.28 g) was separated by HPLC (CHIRALPAK AD, 50 mmID×500 mmL, manufactured
35 by DAICEL CHEMICAL INDUSTRIES, LTD., mobile phase:

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hexane/ethanol = 900/100) to give tert-butyl (6R,7S)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (29.9 g, >99.6% ee., recovery rate 98%) having a longer retention time and the title compound (31.3 g, >99.9% ee., recovery rate 100%) having a shorter retention time.

¹H NMR (300 MHz, CDCl₃) δ 1.51 (9H, s), 2.06-2.17 (1H, m), 3.05-3.28 (2H, m), 3.43 (1H, dd, J = 14.9, 6.6 Hz), 3.49-3.65 (2H, m), 4.02-4.12 (3H, m), 4.21 (1H, dd, J = 9.8, 4.5 Hz), 4.33 (1H, d, J = 9.8 Hz), 7.19 (1H, dd, J = 8.3, 1.9 Hz), 7.40 (1H, d, J = 8.3 Hz), 7.48 (1H, d, J = 1.9 Hz).

[0552]

B) tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-[[(methanesulfonyl)oxy]methyl]-1,4-oxazepane-4-carboxylate

Methanesulfonyl chloride (1.366 mL, 17.65 mmol) was added dropwise to a solution of tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (5.11 g, 13.58 mmol) and triethylamine (2.84 mL, 20.37 mmol) in THF (50 mL) under ice-cooling, and the mixture was stirred under ice-cooling for 2 hr. The reaction mixture was diluted with aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, and dried over anhydrous sodium sulfate, and the solvent was evaporated to give the title compound (5.95 g).

¹H NMR (300 MHz, CDCl₃) δ 1.50 (9H, s), 2.33-2.46 (1H, m), 2.89 (1H, brs), 3.02 (2H, brs), 3.41-3.55 (1H, m), 3.57-3.90 (4H, m), 3.97-4.16 (3H, m), 4.20 (1H, d, J = 9.4 Hz), 7.16 (1H, dd, J = 8.3, 1.9 Hz), 7.41-7.47 (2H, m).

[0553]

C) tert-butyl (6R,7R)-6-[(3-cyano-2-oxopyridin-1(2H)-yl)methyl]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

60% Sodium hydride (0.086 g) was added to a mixed solution of 3-cyano-2-hydroxypyridine (0.206 g) in 1,2-dimethoxyethane (4 mL)-DMF (2 mL) under ice-cooling, and the mixture was stirred for 5 min. To the reaction solution was

added lithium bromide (0.248 g), and the mixture was stirred at room temperature for 0.5 hr. To the reaction solution was added a solution of tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-{[(methylsulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate (0.65 g) in 1,2-dimethoxyethane (4 mL), and the mixture was stirred at 60°C overnight. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (0.59 g, 86%).
¹H NMR (300 MHz, CDCl₃) δ 1.52 (9H, s), 2.91 (1H, brs), 3.06-3.28 (2H, m), 3.56-3.76 (2H, m), 3.79-4.12 (5H, m), 6.25 (1H, t, J = 6.2 Hz), 7.32 (1H, d, J = 7.9 Hz), 7.37-7.53 (2H, m), 7.76 (1H, d, J = 6.0 Hz), 8.27 (1H, d, J = 4.9 Hz).

[0554]

D) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-{[2-oxo-3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl]methyl}-1,4-oxazepane-4-carboxylate

Sodium hydrogen carbonate (829 mg, 9.87 mmol) and hydroxylamine hydrochloride (686 mg, 9.87 mmol) were added to a solution of tert-butyl (6R,7R)-6-[(3-cyano-2-oxopyridin-1(2H)-yl)methyl]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (590 mg, 1.23 mmol) in DMSO (4 mL), and the mixture was stirred at 80°C for 5 hr. The reaction mixture was diluted with water, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was diluted with THF (10 mL), diazabicycloundecene (0.184 mL, 1.23 mmol) and carbonyl-1,1'-bisimidazole (299 mg, 1.85 mmol) were added, and the mixture was stirred at 70°C for 2 hr. The reaction mixture was concentrated under reduced pressure, and the residue was acidified with 1 N hydrochloric acid, and the mixture was extracted with ethyl acetate. The extract was washed with

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brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography, and recrystallized from ethanol-hexane to give the title compound (480 mg, 0.893 mmol, 72.6%).

¹H NMR (300 MHz, CDCl₃) δ 1.53 (9H, s), 2.89 (1H, brs), 3.05-3.30 (2H, m), 3.62 (1H, t, J = 11.7 Hz), 3.77 (1H, t, J = 11.5 Hz), 3.95-4.16 (4H, m), 4.34 (1H, d, J = 12.1 Hz), 6.47 (1H, t, J = 6.6 Hz), 7.19-7.28 (1H, m), 7.29-7.35 (1H, m), 7.53 (1H, brs), 8.26 (1H, d, J = 6.4 Hz), 8.57 (1H, d, J = 5.3 Hz), 10.39 (1H, brs).

[0555]

E) 1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one monohydrochloride

A 14 N hydrogen chloride-ethanol solution (2 mL, 28.00 mmol) was added to a solution of tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-{[2-oxo-3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl]methyl}-1,4-oxazepane-4-carboxylate (795 mg, 1.48 mmol) in ethanol (8 mL). The reaction mixture was stirred at room temperature for 3 hr, and at 80°C for 15 min. The reaction mixture was concentrated under reduced pressure, and the residue was collected by filtration, and washed with ethanol-hexane to give the title compound (655 mg, 1.383 mmol, 93%).

¹H NMR (300 MHz, DMSO-d₆) δ 3.10-3.39 (5H, m), 3.76-3.90 (2H, m), 3.98-4.09 (2H, m), 4.55 (1H, d, J = 9.8 Hz), 6.39 (1H, t, J = 7.0 Hz), 7.42 (1H, dd, J = 8.3, 1.9 Hz), 7.59 (1H, d, J = 8.3 Hz), 7.66 (1H, d, J = 1.9 Hz), 7.85 (1H, dd, J = 6.8, 1.9 Hz), 7.90 (1H, dd, J = 7.2, 2.3 Hz), 9.45 (1H, brs), 12.00 (1H, brs), 1H not detected.

MS (ESI+): [M+H]⁺ 437.0.

[0556]

Example 32

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-

yl)methyl}acetamide 0.5 fumarate

[0557]

A) tert-butyl (6S,7R)-6-(azidomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

5 To a solution of tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-{[(methylsulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate (1.43 g) in DMF (15 mL) was added sodium azide (322 mg), and the mixture was stirred at 70°C overnight. The solvent was evaporated under reduced pressure, distilled water
10 was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the title compound (1.23 g).

15 MS (ESI+): [M+H-Boc]⁺ 301.0, 302.9.

[0558]

B) tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6S,7R)-6-(azidomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (1.23 g) in
20 THF (12.5 mL) and distilled water (2.5 mL) was added triphenylphosphine (967 mg), and the mixture was stirred at room temperature overnight. To the reaction mixture was added distilled water, and the mixture was extracted twice with
25 ethyl acetate. The combined organic layers were washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/methanol) to give the title compound (1.12 g).

30 MS (ESI+): [M+H]⁺ 375.4, 377.3.

[0559]

C) tert-butyl (6R,7R)-6-[(acetylamino)methyl]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (150 mg) in
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THF (2 mL) were added triethylamine (0.084 mL) and acetyl chloride (47 mg), and the mixture was stirred at under ice-cooling for 2 hr. The solvent was evaporated under reduced pressure, distilled water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (162 mg).

MS (ESI+): [M+H-Boc]⁺ 317.0.

[0560]

D) N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}acetamide 0.5 fumarate

To a solution of tert-butyl (6R,7R)-6-[(acetylamino)methyl]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (160 mg) in ethanol (0.5 mL) was added 4.0 M hydrogen chloride-ethyl acetate solution (3 mL), and the mixture was stirred at room temperature for 1.5 hr. The solvent was evaporated under reduced pressure. To the residue was added 1 N aqueous sodium hydroxide solution, and the mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in ethanol, and a solution of fumaric acid (39.3 mg) in ethanol was added. The solvent was evaporated under reduced pressure. The obtained crystals were recrystallized from ethanol-ethyl acetate to give the title compound (73.5 mg) as colorless crystals.

¹H NMR (300 MHz, DMSO-d₆) δ 1.73 (3H, s), 2.17 (1H, td, J = 8.9, 4.4 Hz), 2.78-3.05 (6H, m), 3.58 (1H, ddd, J = 12.7, 8.7, 4.2 Hz), 3.91 (1H, dt, J = 12.6, 3.2 Hz), 4.27 (1H, d, J = 9.5 Hz), 6.49 (1H, s), 7.29-7.46 (1H, m), 7.54-7.72 (2H, m), 7.88 (1H, t, J = 5.3 Hz), 2H not detected.

MS (ESI+): [M+H]⁺ 317.3, 319.3.

[0561]

Example 33

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
2-methoxyacetamide monohydrochloride

5 [0562]

A) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-
{[(methoxyacetyl)amino]methyl}-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (165 mg) in
10 THF (2.5 mL) were added triethylamine (89 mg) and
methoxyacetyl chloride (71.6 mg), and the mixture was stirred
at room temperature for 1 hr. The solvent was evaporated under
reduced pressure, distilled water was added to the residue,
and the mixture was extracted twice with ethyl acetate. The
15 combined organic layers were washed with brine, and dried over
anhydrous magnesium sulfate. The solvent was evaporated under
reduced pressure. The residue was purified by silica gel
chromatography (hexane/ethyl acetate) to give the title
compound (161 mg).

20 MS (ESI+): [M+1]⁺ 447.1, 449.0.

[0563]

B) N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
yl]methyl}-2-methoxyacetamide monohydrochloride

To a solution of tert-butyl (6R,7R)-7-(3,4-
25 dichlorophenyl)-6-{[(methoxyacetyl)amino]methyl}-1,4-
oxazepane-4-carboxylate (161 mg) in ethanol (1 mL) was added
14.0 M hydrogen chloride-ethanol solution (2 mL), and the
mixture was stirred at room temperature for 1 hr. The solvent
was evaporated under reduced pressure. The obtained crystals
30 were recrystallized from ethanol to give the title compound
(125 mg) as colorless crystals.

¹H NMR (300 MHz, DMSO-d₆) δ 2.54-2.69 (1H, m), 2.79-2.90 (1H,
m), 3.01 (1H, dq, J = 8.5, 7.0 Hz), 3.07-3.32 (7H, m), 3.71-
3.86 (3H, m), 3.91-4.03 (1H, m), 4.39 (1H, d, J = 10.2 Hz),
35 7.45 (1H, dd, J = 8.3, 2.1 Hz), 7.67 (1H, d, J = 8.3 Hz), 7.76

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(1H, d, J = 1.9 Hz), 8.07 (1H, t, J = 6.1 Hz), 9.02 (1H, brs), 9.42 (1H, brs).

MS (ESI+): [M+H]⁺ 347.0, 349.0.

[0564]

5 Example 34

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}methanesulfonamide monohydrochloride

[0565]

A) tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-

10 {[(methanesulfonyl)amino]methyl}-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (150 mg) in THF (2 mL) were added triethylamine (60.7 mg) and methanesulfonyl chloride (68.7 mg) under ice-cooling, and the mixture was stirred for 1 hr. The solvent was evaporated under reduced pressure, distilled water was added to the residue, and the mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (161 mg).

MS (ESI+): [M+H-Boc]⁺ 353.0, 355.0.

[0566]

25 B) N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}methanesulfonamide monohydrochloride

To a solution of tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-{[(methanesulfonyl)amino]methyl}-1,4-oxazepane-4-carboxylate (162 mg) in ethanol (0.5 mL) was added 4.0 M hydrogen chloride-ethyl acetate solution (3 mL), and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure. The obtained crystals were recrystallized from ethanol-water to give the title compound (109 mg) as colorless crystals.

35 ¹H NMR (300 MHz, DMSO-d₆) δ 2.52-2.61 (1H, m), 2.69-2.79 (2H,

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m), 2.83 (3H, s), 3.15 (1H, dt, J = 13.1, 4.0 Hz), 3.20-3.32 (2H, m), 3.44 (1H, dd, J = 13.8, 2.3 Hz), 3.79 (1H, ddd, J = 13.6, 8.9, 4.2 Hz), 4.02 (1H, dt, J = 13.8, 4.4 Hz), 4.38 (1H, d, J = 10.2 Hz), 7.26 (1H, t, J = 6.4 Hz), 7.42 (1H, dd, J = 8.3, 2.1 Hz), 7.69 (1H, d, J = 8.1 Hz), 7.72 (1H, d, J = 1.9 Hz), 9.19 (2H, brs).

MS (ESI+): [M+H]⁺ 352.9, 355.0.

[0567]

Example 35

10 N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}sulfamide monohydrochloride

[0568]

A) tert-butyl (6S,7R)-6-({[(tert-butoxycarbonyl)sulfamoyl]amino}methyl)-7-(3,4-dichlorophenyl)-
15 1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (100 mg) in acetonitrile (2 mL) was added N-(tert-butoxycarbonyl)-N-[4-(dimethylazaniumylidene)-1,4-dihydropyridin-1-ylsulfonyl]azanide (181 mg) prepared by the method described in Organic Letters, 2001, 3 (14), 2241-2243, and the mixture was stirred at room temperature for 12 hr. The reaction mixture was concentrated under reduced pressure, distilled water was added to the residue, and the mixture was extracted
25 twice with ethyl acetate. The combined organic layers were washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (172 mg).

30 ¹H NMR (300 MHz, CDCl₃) δ 1.50 (18H, d, J = 5.3 Hz), 2.16-2.36 (1H, m), 2.79-2.94 (1H, m), 2.97-3.19 (2H, m), 3.43 (1H, dd, J = 15.1, 6.4 Hz), 3.58 (1H, td, J = 12.3, 2.3 Hz), 4.01-4.15 (3H, m), 4.28 (1H, d, J = 9.4 Hz), 6.88 (1H, brs), 7.15 (1H, dd, J = 8.1, 4.3 Hz), 7.20-7.29 (1H, m), 7.41 (1H, d, J = 8.3
35 Hz), 7.52 (1H, d, J = 1.5 Hz).

[0569]

B) N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}sulfamide monohydrochloride

To a solution of tert-butyl (6S,7R)-6-({[(tert-butoxycarbonyl)sulfamoyl]amino}methyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (172 mg) in ethanol (0.5 mL) was added 4.0 M hydrogen chloride-ethyl acetate solution (3 mL), and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure. The obtained crystals were recrystallized from ethanol-water to give the title compound (89 mg) as colorless crystals.

¹H NMR (300 MHz, DMSO-d₆) δ 2.52-2.61 (1H, m), 2.61-2.70 (2H, m), 3.10-3.31 (3H, m), 3.39-3.54 (1H, m), 3.80 (1H, ddd, J = 12.5, 8.3, 3.8 Hz), 4.02 (1H, dt, J = 14.0, 3.8 Hz), 4.40 (1H, d, J = 10.2 Hz), 6.56 (2H, s), 6.78 (1H, t, J = 6.4 Hz), 7.41 (1H, dd, J = 8.3, 1.9 Hz), 7.67 (1H, d, J = 8.3 Hz), 7.71 (1H, d, J = 1.9 Hz), 9.19 (2H, brs).

MS (ESI+): [M+H]⁺ 354.1, 356.0.

[0570]

20 Example 36

N-[(6R,7S)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]acetamide monofumarate

[0571]

A) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-formyl-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (10 g) in acetonitrile (133 mL) was added Dess-Martin periodinane (13.53 g) under ice-cooling, and the mixture was stirred under ice-cooling for 3 hr. To the reaction mixture were added saturated aqueous sodium hydrogen carbonate and aqueous saturated sodium thiosulfate solution at room temperature, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was extracted with ethyl acetate. The extract was washed with distilled water and

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brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (8.3 g).

5 ¹H NMR (300 MHz, CDCl₃) δ 1.43-1.56 (9H, m), 2.87-3.37 (2H, m), 3.48-3.77 (2H, m), 3.80-4.20 (2H, m), 4.34 (1H, d, J = 15.1 Hz), 4.69-5.13 (1H, m), 7.18 (1H, d, J = 8.3 Hz), 7.33-7.40 (1H, m), 7.40-7.56 (1H, m), 9.46-9.85 (1H, m).

MS (ESI⁺): [M+H-Boc]⁺ 274.0.

10 [0572]

B) (6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-6-carboxylic acid

To a mixed solution of tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-formyl-1,4-oxazepane-4-carboxylate (7.3 g) in 2-methyl-2-butene (45 mL), tert-butanol (100 mL) and THF (100 mL) was added dropwise a solution of sodium chlorite (10.58 g) and potassium dihydrogenphosphate (16.38 g) in water (160 mL) under ice-cooling, and the mixture was stirred under ice-cooling for 2 hr. The reaction mixture was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (7.0 g).

25 ¹H NMR (300 MHz, CDCl₃) δ 1.34-1.56 (9H, m), 2.73-3.08 (1H, m), 3.14-3.91 (3H, m), 3.94-4.25 (3H, m), 4.73 (1H, d, J = 10.2 Hz), 7.16 (1H, dd, J = 8.3, 1.9 Hz), 7.37 (1H, d, J = 8.3 Hz), 7.45 (1H, d, J = 1.9 Hz), 1H not detected.

[0573]

30 C) tert-butyl (6R,7S)-7-(3,4-dichlorophenyl)-6-([2-(trimethylsilyl)ethoxy]carbonyl)amino)-1,4-oxazepane-4-carboxylate

To a solution of (6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-6-carboxylic acid (1.0 g) in toluene (10 mL) were added diphenylphosphoryl azide (0.828 mL)

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and triethylamine (0.536 mL) at room temperature, and the mixture was stirred at 90°C for 30 min. To the reaction mixture was added 2-(trimethylsilyl)ethanol (0.727 mL) at 90°C, and the mixture was stirred at 90°C for 2 hr. The reaction mixture was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (0.67 g).

¹H NMR (300 MHz, CDCl₃) δ 0.00 (9H, s), 1.53 (9H, s), 1.61-1.65 (2H, m), 3.04-3.24 (1H, m), 3.41-3.77 (2H, m), 3.86-4.20 (7H, m), 5.05-6.02 (1H, m), 7.14-7.25 (1H, m), 7.37 (2H, s).

[0574]

D) tert-butyl (6R,7S)-6-amino-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7S)-7-(3,4-dichlorophenyl)-6-([2-(trimethylsilyl)ethoxy]carbonyl)amino)-1,4-oxazepane-4-carboxylate (0.67 g) in THF (5 mL) was added tetra-n-butylammonium fluoride (5.2 mL) at room temperature, and the mixture was stirred at 50°C for 5 hr. The reaction mixture was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the title compound (0.4 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.51 (11H, s), 3.08 (1H, brs), 3.32-3.84 (5H, m), 3.94 (1H, d, J = 9.1 Hz), 4.05-4.13 (1H, m), 7.22 (1H, dd, J = 8.3, 1.9 Hz), 7.39-7.46 (1H, m), 7.50 (1H, d, J = 1.9 Hz).

MS (ESI⁺): [M+H]⁺ 361.1.

[0575]

E) tert-butyl (6R,7S)-6-(acetylamino)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7S)-6-amino-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (1.3 g) in THF (13

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mL) were added triethylamine (0.752 mL) and acetyl chloride (0.385 mL) at 0°C, and the mixture was gradually warmed from 0°C to room temperature, and stirred overnight. The reaction mixture was diluted with ethyl acetate. The diluted solution
5 was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (0.965 g).

10 ¹H NMR (300 MHz, CDCl₃) δ 1.54 (9H, s), 1.87 (3H, s), 3.02-3.23 (1H, m), 3.45-3.73 (2H, m), 3.83-4.17 (4H, m), 4.45 (1H, brs), 6.83 (1H, brs), 7.20 (1H, dd, J = 8.3, 1.9 Hz), 7.32-7.58 (2H, m).

MS (ESI⁺): [M+H-t-Bu]⁺ 346.9.

15 [0576]

F) N-[(6R,7S)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]acetamide monofumarate

To tert-butyl (6R,7S)-6-(acetylamino)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (200 mg) was added
20 4.0 M hydrogen chloride-ethyl acetate solution (4 mL), and the mixture was stirred at room temperature for 1 hr. The residue obtained by concentration under reduced pressure was desalted by a solid phase extraction resin (column: PL StratoSphere solid phase extraction resin (PL-HCO₃ MP StratoSpheresTM), 500
25 mg, StratoSphere, mobile phase: methanol). To a solution of the residue obtained by concentration under reduced pressure in ethanol was added a solution of fumaric acid (33.7 mg) in ethanol. The mixture was concentrated under reduced pressure to give the title compound (130 mg).

30 ¹H NMR (300 MHz, DMSO-d₆) δ 1.74 (3H, s), 2.87-3.14 (4H, m), 3.59-3.80 (1H, m), 3.97-4.17 (2H, m), 4.47 (1H, d, J = 8.7 Hz), 6.56 (2H, s), 7.23-7.39 (1H, m), 7.47-7.67 (2H, m), 8.31 (1H, d, J = 8.7 Hz).

MS (ESI⁺): [M+H]⁺ 303.2.

35 [0577]

Example 37

N-[(6R,7S)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]sulfamide monohydrochloride

[0578]

- 5 A) tert-butyl (6R,7S)-6-[[tert-butoxycarbonyl)sulfamoyl]amino]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7S)-6-amino-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (300 mg) in
10 acetonitrile (5 mL) was added N-(tert-butoxycarbonyl)-N-[4-(dimethylazaniumylidene)-1,4-dihydropyridin-1-ylsulfonyl]azanide (375 mg) prepared by the method described in Organic Letters, 3 (14), 2241-2243 (2001), and the mixture was stirred at room temperature overnight. The reaction
15 mixture was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title
20 compound (200 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.36-1.65 (18H, m), 2.92-3.28 (1H, m), 3.41-4.29 (7H, m), 6.79 (1H, brs), 7.19 (1H, dd, J = 8.1, 2.1 Hz), 7.36-7.43 (1H, m), 7.47 (1H, d, J = 1.9 Hz), 1H not detected.

25 MS (ESI⁺): [M-H]⁺ 538.1.

[0579]

B) N-[(6R,7S)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]sulfamide monohydrochloride

To tert-butyl (6R,7S)-6-[[tert-butoxycarbonyl)sulfamoyl]amino]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (200 mg) was added 4.0 M hydrogen chloride-ethyl acetate solution (4 mL), and the mixture was stirred at room temperature for 2 hr. The residue obtained by concentration under reduced pressure was washed with ethyl
35 acetate-hexane to give the title compound (105 mg).

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¹H NMR (300 MHz, DMSO-d₆) δ 3.24 (2H, dd, J = 6.2, 4.0 Hz), 3.41 (1H, dd, J = 14.4, 7.6 Hz), 3.51-3.62 (1H, m), 3.79-3.97 (2H, m), 4.02-4.20 (1H, m), 4.48 (1H, d, J = 8.7 Hz), 6.71 (2H, s), 7.20 (1H, d, J = 9.1 Hz), 7.40 (1H, dd, J = 8.3, 2.3 Hz), 7.61 (1H, d, J = 8.3 Hz), 7.67 (1H, d, J = 1.9 Hz), 9.41-9.83 (2H, m).

MS (ESI+): [M+H]⁺ 340.0.

[0580]

Example 38

10 N-{[(6S,7R)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-yl]methyl}-2-methoxyacetamide monohydrochloride

[0581]

A) tert-butyl (6S,7R)-7-(4-chloro-3-fluorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate

15 A racemate (14.7 g) of tert-butyl (6RS,7SR)-7-(3-chloro-4-fluorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate was separated by HPLC (CHIRALPAK AD, 50 mmID×500 mmL, manufactured by DAICEL CHEMICAL INDUSTRIES, LTD., mobile phase: hexane/ethanol = 900/100) to give the title compound 20 (7.1 g) having a shorter retention time.

¹H NMR (300 MHz, CDCl₃) δ 1.51 (9H, s), 2.03-2.20 (1H, m), 3.02-3.74 (5H, m), 4.02-4.16 (3H, m), 4.21 (1H, dd, J = 9.8, 4.5 Hz), 4.34 (1H, d, J = 9.8 Hz), 7.08 (1H, d, J = 8.3 Hz), 7.18 (1H, dd, J = 10.0, 1.7 Hz), 7.29-7.41 (1H, m).

25 [0582]

B) tert-butyl (6S,7R)-7-(4-chloro-3-fluorophenyl)-6-[(methanesulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6S,7R)-7-(4-chloro-3-fluorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate 30 (4.50 g) in THF (41.7 mL) were added triethylamine (3.49 mL) and methanesulfonyl chloride (1.94 mL) under ice-cooling, and the mixture was stirred for 3 hr. To the reaction mixture was added distilled water, and the mixture was extracted with ethyl acetate. The extract was washed with distilled water and 35 brine, and dried over anhydrous sodium sulfate, and the

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solvent was evaporated under reduced pressure to give the title compound (6.01 g).

¹H NMR (300 MHz, CDCl₃) δ 1.50 (9H, s), 2.33-2.46 (1H, m), 2.85-3.08 (3H, m), 3.42-3.57 (1H, m), 3.57-3.92 (5H, m), 3.96-4.18 (2H, m), 4.22 (1H, d, J = 9.4 Hz), 7.05 (1H, d, J = 8.3 Hz), 7.15 (1H, dd, J = 9.4, 1.9 Hz), 7.34-7.43 (1H, m).

[0583]

C) tert-butyl (6S,7R)-6-(azidomethyl)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepane-4-carboxylate

10 To a solution of tert-butyl (6S,7R)-7-(4-chloro-3-fluorophenyl)-6-{[(methylsulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate (4.00 g) in DMF (46 mL) was added sodium azide (891 mg), and the mixture was stirred at 70°C overnight. To the reaction mixture was added distilled water, and the mixture was extracted with ethyl acetate. The extract was washed with distilled water and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel filtration to give the title compound (6.76 g).

20 MS (ESI⁺): [M+H-Boc]⁺ 285.1.

[0584]

D) tert-butyl (6R,7R)-6-(aminomethyl)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6S,7R)-6-(azidomethyl)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepane-4-carboxylate (3.51 g) in THF (38 mL) and distilled water (7.7 mL) was added triphenylphosphine (2.87 g), and the mixture was stirred at room temperature overnight. To the reaction mixture was added distilled water, and the mixture was extracted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/methanol) to give the title compound (2.42 g).

35 MS (ESI⁺): [M+H]⁺ 359.1.

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[0585]

E) tert-butyl (6R,7R)-7-(4-chloro-3-fluorophenyl)-6-
{[(methoxyacetyl)amino]methyl}-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7R)-6-(aminomethyl)-7-(4-
5 chloro-3-fluorophenyl)-1,4-oxazepane-4-carboxylate (1.30 g) in
THF (18 mL) were added triethylamine (0.757 mL) and
methoxyacetyl chloride (472 mg), and the mixture was stirred
at room temperature for 4 hr. To the reaction mixture was
added distilled water, and the mixture was extracted with
10 ethyl acetate. The diluted solution was washed with distilled
water and brine, and dried over anhydrous sodium sulfate. The
solvent was evaporated under reduced pressure. The residue was
purified by silica gel chromatography (hexane/ethyl acetate)
to give the title compound (1.11 g).

15 MS (ESI+): [M+H]⁺ 431.2.

[0586]

F) N-{[(6S,7R)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-
yl]methyl}-2-methoxyacetamide monohydrochloride

To a solution of tert-butyl (6R,7R)-7-(4-chloro-3-
20 fluorophenyl)-6-{[(methoxyacetyl)amino]methyl}-1,4-oxazepane-
4-carboxylate (1.11 g) in ethanol (13 mL) was added 14.0 M
hydrogen chloride-ethanol solution (12.0 mL), and the mixture
was stirred at room temperature for 1 hr. The crystals
obtained by concentration under reduced pressure were
25 recrystallized from ethanol-hexane to give the title compound
(715 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 2.55-2.69 (1H, m), 2.80-2.90 (1H,
m), 2.95-3.31 (8H, m), 3.72-3.85 (3H, m), 3.92-4.01 (1H, m),
4.39 (1H, d, J = 10.2 Hz), 7.33 (1H, dd, J = 8.3, 1.5 Hz),
30 7.55 (1H, dd, J = 10.6, 1.5 Hz), 7.58-7.66 (1H, m), 8.00-8.14
(1H, m), 8.92-9.58 (2H, m).

MS (ESI+): [M+H]⁺ 331.1.

[0587]

Example 39

35 N-{[(6S,7R)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-

yl)methyl}-2-[(²H₃)methyloxy]acetamide monohydrochloride

[0588]

A) tert-butyl (6R,7R)-7-(4-chloro-3-fluorophenyl)-6-
[({[(²H₃)methyloxy]acetyl)amino)methyl]-1,4-oxazepane-4-
5 carboxylate

To a solution of tert-butyl (6R,7R)-6-(aminomethyl)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepane-4-carboxylate (300 mg), 2-(²H₃)methoxyacetic acid (93 mg), 1H-benzotriazol-1-ol (136 mg) and triethylamine (0.291 mL) in THF (4.2 mL) was added N-
10 [3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (192 mg), and the mixture was stirred overnight. To the reaction mixture was added distilled water, and the mixture was extracted with ethyl acetate. The extract was washed with distilled water and brine, and dried over anhydrous sodium
15 sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (275 mg).

MS (ESI+): [M+H-Boc]⁺ 334.3.

20 [0589]

B) N-{[(6S,7R)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-yl)methyl}-2-[(²H₃)methyloxy]acetamide monohydrochloride

To tert-butyl (6R,7R)-7-(4-chloro-3-fluorophenyl)-6-
[({[(²H₃)methyloxy]acetyl)amino)methyl]-1,4-oxazepane-4-
25 carboxylate (275 mg) was added 4.0 M hydrogen chloride-ethyl acetate solution (4.75 mL), and the mixture was stirred at room temperature for 1 hr. The crystals obtained by concentration under reduced pressure were pulverized with ethanol-diisopropyl ether to give the title compound (206 mg).

30 ¹H NMR (300 MHz, DMSO-d₆) δ 2.54-2.71 (1H, m), 2.78-2.91 (1H, m), 2.93-3.38 (7H, m), 3.77-3.86 (1H, m), 3.90-4.05 (1H, m), 4.40 (1H, d, J = 10.2 Hz), 7.33 (1H, dd, J = 8.3, 1.5 Hz), 7.48-7.66 (2H, m), 8.00-8.14 (1H, m), 8.94-9.75 (2H, m).

[0590]

35 Example 40

N-{[(6S,7R)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-yl]methyl}-2-ethoxyacetamide monohydrochloride
[0591]

A) tert-butyl (6R,7R)-7-(4-chloro-3-fluorophenyl)-6-
5 {[(ethoxyacetyl)amino]methyl}-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7R)-6-(aminomethyl)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepane-4-carboxylate (150 mg), ethoxyacetic acid (35 mg), 1H-benzotriazol-1-ol (67.8 mg) and triethylamine (0.146 mL) in THF (2.1 mL) was added N-[3-
10 (dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (96 mg), and the mixture was stirred overnight. To the reaction mixture was added distilled water, and the mixture was extracted with ethyl acetate. The extract was washed with distilled water and brine, and dried over anhydrous sodium
15 sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (125 mg).

MS (ESI+): [M+H]⁺ 445.1.

20 [0592]

B) N-{[(6S,7R)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-yl]methyl}-2-ethoxyacetamide monohydrochloride

To tert-butyl (6R,7R)-7-(4-chloro-3-fluorophenyl)-6-
{[(ethoxyacetyl)amino]methyl}-1,4-oxazepane-4-carboxylate (125
25 mg) was added 4.0 M hydrogen chloride-ethyl acetate solution (2.11 mL), and the mixture was stirred at room temperature for 1 hr. The residue obtained by concentration under reduced pressure was recrystallized from ethanol-diisopropyl ether to give the title compound (92.0 mg).

30 ¹H NMR (300 MHz, DMSO-d₆) δ 1.14 (3H, t, J = 7.0 Hz), 2.57-2.72 (1H, m), 2.78-2.90 (1H, m), 2.97-3.29 (5H, m), 3.44 (2H, q, J = 6.9 Hz), 3.73-3.86 (3H, m), 3.91-4.03 (1H, m), 4.40 (1H, d, J = 10.2 Hz), 7.33 (1H, dd, J = 8.1, 1.7 Hz), 7.55 (1H, dd, J = 10.6, 1.9 Hz), 7.58-7.67 (1H, m), 7.97 (1H, t), 8.99-9.70 (2H,
35 m).

[0593]

Example 41

N-{[(6S,7R)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-yl]methyl}-2-(1-methylethoxy)acetamide monohydrochloride

5 [0594]

A) tert-butyl (6R,7R)-7-(4-chloro-3-fluorophenyl)-6-({[(1-methylethoxy)acetyl]amino}methyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7R)-6-(aminomethyl)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepane-4-carboxylate (300 mg),
10 (1-methylethoxy)acetic acid (119 mg), 1H-benzotriazol-1-ol (136 mg) and triethylamine (0.291 mL) in THF (4.2 mL) was added N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (192 mg), and the mixture was stirred at room temperature overnight. To the reaction mixture was added
15 distilled water, and the mixture was extracted with ethyl acetate. The extract was washed with distilled water and brine, and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate)
20 to give the title compound (384 mg).

MS (ESI+): [M+H-Boc]⁺ 359.3.

[0595]

B) N-{[(6S,7R)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-yl]methyl}-2-(1-methylethoxy)acetamide monohydrochloride

25 To tert-butyl (6R,7R)-7-(4-chloro-3-fluorophenyl)-6-({[(1-methylethoxy)acetyl]amino}methyl)-1,4-oxazepane-4-carboxylate (384 mg) was added 4.0 M hydrogen chloride-ethyl acetate solution (6.28 mL), and the mixture was stirred at room temperature for 1 hr. The residue obtained by
30 concentration under reduced pressure was crystallized from ethanol-hexane solvent to give the title compound (153.4 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 1.11 (6H, d, J = 6.0 Hz), 2.56-2.71 (1H, m), 2.78-2.91 (1H, m), 2.99-3.33 (7H, m), 3.48-3.62 (1H, m), 3.76-3.87 (1H, m), 3.90-4.05 (1H, m), 4.40 (1H, d, J = 9.8
35 Hz), 7.32 (1H, d, J = 8.3 Hz), 7.48-7.69 (2H, m), 7.83 (1H, t,

J = 6.0 Hz), 8.92-9.62 (2H, m).

MS (ESI+): [M+H]⁺ 359.2.

[0596]

Example 42

5 1-{[(6S,7R)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-yl]methyl}pyridin-2(1H)-one monohydrochloride

[0597]

A) tert-butyl (6R,7R)-7-(4-chloro-3-fluorophenyl)-6-[(2-oxopyridin-1(2H)-yl)methyl]-1,4-oxazepane-4-carboxylate

10 60% Sodium hydride (45.3 mg, 1.13 mmol) was added to a mixed solution of 2-hydroxypyridine (86 mg, 0.91 mmol) in 1,2-dimethoxyethane (2 mL) and DMF (1 mL) at room temperature. After stirring at room temperature for 5 min, lithium bromide (131 mg, 1.51 mmol) was added at room temperature. After
15 stirring for 10 min, to the reaction mixture was added a solution of tert-butyl (6S,7R)-7-(4-chloro-3-fluorophenyl)-6-[[methylsulfonyl]oxy]methyl]-1,4-oxazepane-4-carboxylate (331 mg, 0.76 mmol) in 1,2-dimethoxyethane (2 mL). The reaction mixture was stirred at 80°C overnight. To the reaction mixture
20 was added water, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (267 mg,
25 0.611 mmol, 81%).

¹H NMR (300 MHz, CDCl₃) δ 1.33-1.58 (9H, m), 2.55-2.96 (1H, m), 3.11-3.35 (1H, m), 3.45-3.80 (3H, m), 3.82-4.01 (2H, m), 4.02-4.26 (2H, m), 6.12 (1H, brs), 6.44 (1H, d, J = 9.1 Hz), 6.88-7.31 (4H, m), 7.37 (1H, t, J = 7.6 Hz), 7.78 (1H, brs).

30 MS (ESI+): [M+H]⁺ 437.2.

[0598]

B) 1-{[(6S,7R)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-yl]methyl}pyridin-2(1H)-one monohydrochloride

14 N Hydrogen chloride-ethanol solution (1 mL, 14.00
35 mmol) was added to a solution (3 mL) of tert-butyl (6R,7R)-7-

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(4-chloro-3-fluorophenyl)-6-[(2-oxopyridin-1(2H)-yl)methyl]-1,4-oxazepane-4-carboxylate (267 mg, 0.61 mmol) in ethanol, and the mixture was stirred at room temperature for 3 hr. The residue was concentrated, diethyl ether was added, and the mixture was stirred for a while. The insoluble material was collected by filtration to give the title compound (227 mg, 0.608 mmol, 100%).

¹H NMR (300 MHz, DMSO-d₆) δ 3.04-3.32 (5H, m), 3.64 (1H, dd, J = 13.2, 5.3 Hz), 3.77-3.88 (1H, m), 3.91-4.06 (2H, m), 4.54 (1H, d, J = 9.4 Hz), 6.17 (1H, td, J = 6.7, 1.3 Hz), 6.27-6.33 (1H, m), 7.29-7.40 (2H, m), 7.46 (1H, dd, J = 6.6, 1.7 Hz), 7.50-7.61 (2H, m), 9.24 (1H, brs), 9.80 (1H, brs).
MS (ESI+): [M+H]⁺ 337.1.

[0599]

15 Example 43

1-{[(6S,7R)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-yl)methyl}-3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one monohydrochloride

[0600]

20 A) tert-butyl (6R,7R)-7-(4-chloro-3-fluorophenyl)-6-[(3-cyano-2-oxopyridin-1(2H)-yl)methyl]-1,4-oxazepane-4-carboxylate

60% Sodium hydride (0.274 g, 6.85 mmol) was added to a mixed solution of 3-cyano-2-hydroxypyridine (0.658 g, 5.48 mmol) in 1,2-dimethoxyethane (10 mL)-DMF (5 mL) under ice-cooling, and the mixture was stirred for 20 min. To the reaction solution was added lithium bromide (0.793 g, 9.13 mmol), and the mixture was stirred at room temperature for 1.5 hr. To the reaction solution was added a solution of tert-butyl (6S,7R)-7-(4-chloro-3-fluorophenyl)-6-
30 {[(methanesulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate (2 g, 4.57 mmol) in 1,2-dimethoxyethane (10 mL), and the mixture was stirred at 60°C overnight. The reaction mixture was concentrated under reduced pressure, water was added to the residue, and the mixture was extracted with ethyl acetate. The
35 extract was washed with brine, and dried over anhydrous sodium

sulfate. The solvent was evaporated under reduced pressure.

The residue was purified by silica gel column chromatography to give the title compound (1.757 g, 3.80 mmol, 83%).

¹H NMR (300 MHz, CDCl₃) δ 1.52 (9H, s), 2.90 (1H, brs), 3.06-3.28 (2H, m), 3.55-3.75 (2H, m), 3.81-4.12 (5H, m), 6.26 (1H, t, J = 6.2 Hz), 7.18 (2H, d, J = 7.9 Hz), 7.41 (1H, t, J = 7.9 Hz), 7.76 (1H, d, J = 6.4 Hz), 8.31 (1H, d, J = 5.3 Hz).

[0601]

B) tert-butyl (6R,7R)-7-(4-chloro-3-fluorophenyl)-6-{[2-oxo-3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl]methyl}-1,4-oxazepane-4-carboxylate

Sodium hydrogen carbonate (2.53 g, 30.14 mmol) and hydroxylamine monohydrochloride (2.094 g, 30.14 mmol) were added to a solution of tert-butyl (6R,7R)-7-(4-chloro-3-fluorophenyl)-6-[(3-cyano-2-oxopyridin-1(2H)-yl)methyl]-1,4-oxazepane-4-carboxylate (1.74 g, 3.77 mmol) in DMSO (4 mL), and the mixture was stirred at 80°C overnight. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in THF (15 mL), diazabicycloundecene (0.564 mL, 3.77 mmol) and 1,1'-carbonyldiimidazole (0.917 g, 5.66 mmol) were added, and the mixture was heated under reflux for 2 hr. The reaction mixture was concentrated under reduced pressure, 1 N hydrochloric acid was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (1.826 g, 3.51 mmol, 93%).

¹H NMR (300 MHz, CDCl₃) δ 1.54 (9H, s), 2.79-2.96 (1H, m), 3.13 (1H, t, J = 11.5 Hz), 3.26 (1H, dd, J = 14.7, 4.5 Hz), 3.61 (1H, t, J = 11.3 Hz), 3.76 (1H, t, J = 11.9 Hz), 4.01 (1H, d, J = 10.2 Hz), 4.05-4.18 (3H, m), 4.49 (1H, d, J = 12.5 Hz),

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6.49 (1H, t, J = 7.0 Hz), 7.07 (1H, dd, J = 8.3, 1.5 Hz), 7.15 (1H, t, J = 7.7 Hz), 7.35 (1H, d, J = 9.8 Hz), 8.28 (1H, dd, J = 7.4, 1.7 Hz), 8.69 (1H, d, J = 6.0 Hz), 10.46 (1H, brs).

[0602]

- 5 C) 1-{[(6S,7R)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-yl]methyl}-3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one monohydrochloride

14 N Hydrogen chloride-ethanol solution (0.5 mL, 7.00 mmol) was added to a solution of tert-butyl (6R,7R)-7-(4-chloro-3-fluorophenyl)-6-{[2-oxo-3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl]methyl}-1,4-oxazepane-4-carboxylate (180 mg, 0.35 mmol) in ethanol (2 mL), and the mixture was stirred at room temperature for 3 hr. The reaction mixture was diluted with ethanol (4 mL), and the mixture was
15 heated under reflux for 10 min. The precipitated crystals were collected by filtration to give the title compound (149 mg, 0.325 mmol, 94%).

¹H NMR (300 MHz, DMSO-d₆) δ 3.08-3.35 (5H, m), 3.76-3.89 (2H, m), 3.98-4.10 (2H, m), 4.55 (1H, d, J = 9.8 Hz), 6.41 (1H, t, J = 7.0 Hz), 7.30 (1H, dd, J = 8.1, 1.7 Hz), 7.49 (1H, dd, J = 10.6, 1.9 Hz), 7.56 (1H, t, J = 8.1 Hz), 7.85 (1H, dd, J = 6.6, 2.1 Hz), 7.91 (1H, dd, J = 7.2, 2.3 Hz), 9.19 (1H, brs), 9.71 (1H, brs), 12.22 (1H, brs).

MS (ESI+): [M+H]⁺ 421.0.

25 [0603]

Example 44

1-{[(6S,7R)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-yl]methyl}-2-oxo-1,2-dihydropyridine-3-carboxylic acid monohydrochloride

30 [0604]

A) tert-butyl (6R,7R)-7-(4-chloro-3-fluorophenyl)-6-{[3-(methoxycarbonyl)-2-oxopyridin-1(2H)-yl]methyl}-1,4-oxazepane-4-carboxylate

Methyl 2-hydroxypyridine-3-carboxylate (1.48 g) and
35 potassium carbonate (2.23 g) were added to a solution of tert-

butyl (6S,7R)-7-(4-chloro-3-fluorophenyl)-6-

{[(methanesulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate
(3.53 g) in 1,2-dimethoxyethane (70 mL). The reaction mixture

was stirred at 80°C overnight. The reaction mixture was

5 concentrated under reduced pressure, water was added to the
residue, and the mixture was extracted with ethyl acetate. The
extract was washed with brine, and dried over anhydrous sodium
sulfate. The solvent was evaporated under reduced pressure.
The residue was purified by silica gel column chromatography
10 to give the title compound (2.88 g).

¹H NMR (300 MHz, CDCl₃) δ 1.51 (9H, brs), 2.99 (1H, brs), 3.17
(2H, d, J = 13.6 Hz), 3.43-3.79 (3H, m), 3.87 (3H, s), 3.89-
4.12 (4H, m), 6.23 (1H, brs), 7.06-7.24 (2H, m), 7.29-7.44
(1H, m), 7.97-8.16 (1H, m), 8.20 (1H, brs).

15 MS (ESI+): [M+H]⁺ 495.1.

[0605]

B) 1-{[(6S,7R)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-
yl]methyl}-2-oxo-1,2-dihydropyridine-3-carboxylic acid
monohydrochloride

20 2 N Aqueous sodium hydroxide solution (8.73 mL) was added
to a solution of tert-butyl (6R,7R)-7-(4-chloro-3-
fluorophenyl)-6-{[3-(methoxycarbonyl)-2-oxopyridin-1(2H)-
yl]methyl}-1,4-oxazepane-4-carboxylate (2.88 g) in ethanol (25
mL), and the mixture was stirred at 40°C for 2 hr. The
25 reaction mixture was concentrated under reduced pressure,
diethyl ether was added to the residue, and the mixture was
extracted with water. The aqueous layer was neutralized with 1
N hydrochloric acid, and the mixture was extracted with ethyl
acetate. The extract was washed with brine, and dried over
30 anhydrous sodium sulfate. The solvent was evaporated under
reduced pressure. To a solution of the residue in ethyl
acetate (5 mL) was added 4 N hydrogen chloride-ethyl acetate
solution (22 mL), and the mixture was stirred at room
temperature for 2 hr. The reaction mixture was concentrated
35 under reduced pressure, acetonitrile was added to the residue,

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and the precipitate was collected by filtration. The obtained solid was dissolved in 10% aqueous acetonitrile (17 mL), and an insoluble material was filtered off. To the mother liquor was added acetonitrile (50 mL), and the mixture was stirred overnight. The obtained crystals were collected by filtration to give the title compound (2.01 g).

¹H NMR (300 MHz, DMSO-d₆) δ 3.10-3.31 (5H, m), 3.77-3.87 (1H, m), 3.92 (1H, dd, J = 13.6, 5.7 Hz), 4.03 (1H, dt, J = 13.8, 4.4 Hz), 4.15 (1H, dd, J = 13.6, 7.6 Hz), 4.58 (1H, d, J = 9.4 Hz), 6.66 (1H, t, J = 7.0 Hz), 7.26 (1H, dd, J = 8.1, 1.7 Hz), 7.46 (1H, dd, J = 10.4, 1.7 Hz), 7.51-7.58 (1H, m), 8.06 (1H, dd, J = 6.8, 1.9 Hz), 8.27 (1H, dd, J = 7.2, 1.9 Hz), 9.12 (1H, brs), 9.70 (1H, brs), 14.24 (1H, brs).

MS (ESI+): [M+H]⁺ 381.1.

15 [0606]

Example 45

(1S)-1-[(6R,7R)-6-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]ethane-1,2-diol monohydrochloride

[0607]

20 A) (2RS,3RS)-4-{[tert-butyl(dimethyl)silyl]oxy}-2-(3,4-dichlorophenyl)-3-hydroxybutanenitrile

To a solution of 3,4-dichlorobenzyl cyanide (28.3 g) in THF (300 mL) was added dropwise 1.6 M n-butyllithium/hexane solution (100 mL) under argon purging at -78°C, and the mixture was stirred for 10 min. Then, 2-(tert-butyltrimethylsilyloxy)acetaldehyde (29.2 g) was added dropwise at -78°C, and the mixture was stirred for 10 min. The mixture was quenched with water at -78°C, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate (10% - 50%)) to give a yellow oil (53.5 g), which was crystallized from ice-cooled hexane to give the title compound (23.3 g) as colorless crystals.

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¹H NMR (300 MHz, CDCl₃) δ 0.10 (6H, d, J = 3.0 Hz), 0.92 (9H, s), 2.54 (1H, d, J = 6.4 Hz), 3.50-3.63 (1H, m), 3.64-3.74 (1H, m), 3.85-3.96 (1H, m), 4.05 (1H, d, J = 5.3 Hz), 7.15-7.31 (1H, m), 7.48 (2H, m).

5 The mother liquor in the above-mentioned crystallization was concentrated to give an about 6:1 mixture of (2RS,3SR)-4-
{[tert-butyl(dimethyl)silyl]oxy}-2-(3,4-dichlorophenyl)-3-
hydroxybutanenitrile and (2RS,3RS)-4-
{[tert-butyl(dimethyl)silyl]oxy}-2-(3,4-dichlorophenyl)-3-
10 hydroxybutanenitrile as a yellow oil (27.5 g).

[0608]

B) (2RS)-(3,4-dichlorophenyl)[(4RS)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanenitrile

To a solution of (2RS,3RS)-4-
15 {[tert-butyl(dimethyl)silyl]oxy}-2-(3,4-dichlorophenyl)-3-
hydroxybutanenitrile (152 g) in toluene (1000 mL) were added
2,2-dimethoxypropane (131.8 g) and p-toluenesulfonic acid
(8.02 g), and the mixture was stirred under nitrogen purging
at 80°C for 2 hr. Under ice-cooling, the mixture was
20 neutralized with saturated aqueous sodium hydrogen carbonate,
and the mixture was extracted with ethyl acetate. The organic
layer was washed with brine, and dried over anhydrous
magnesium sulfate, and the solvent was evaporated. The residue
was crystallized from diisopropyl ether to give the title
25 compound (99 g) as colorless crystals.

¹H NMR (300 MHz, CDCl₃) δ 1.35 (3H, s), 1.48 (3H, s), 3.79-3.90
(2H, m), 4.06 (1H, dd, J = 9.1, 6.1 Hz), 4.37 (1H, q, J = 5.7
Hz), 7.24 (1H, dd, J = 8.3, 2.3 Hz), 7.47-7.51 (2H, m).

[0609]

30 C) (2RS)-2-(3,4-dichlorophenyl)-2-[(4RS)-2,2-dimethyl-1,3-
dioxolan-4-yl]ethanamine

To a solution of (2RS)-(3,4-dichlorophenyl)[(4RS)-2,2-
dimethyl-1,3-dioxolan-4-yl]ethanenitrile (10.0 g) in toluene
(100 mL) was added dropwise 1.5 M diisobutylaluminum
35 hydride/toluene solution (51.3 mL) under nitrogen purging at -

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78°C, and the mixture was stirred for 3 hr. The reaction was quenched with water at -78°C, aqueous potassium carbonate solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and the solvent was evaporated to give the title compound (10.2 g) as a colorless oil. This was used for the next step without purification.

¹H NMR (300 MHz, CDCl₃) δ 1.2-1.7 (2H, br), 1.36 (3H, s), 1.44 (3H, s), 2.70 (1H, td, J = 8.7, 4.9 Hz), 2.97 (1H, dd, J = 12.8, 8.3 Hz), 3.26 (1H, dd, J = 12.8, 4.9 Hz), 3.46-3.52 (1H, m), 3.76 (1H, dd, J = 8.3, 6.0 Hz), 4.19-4.28 (1H, m), 7.06 (1H, dd, J = 8.1, 2.1 Hz), 7.32 (1H, d, J = 2.3 Hz), 7.41 (1H, d, J = 8.3 Hz).

[0610]

15 D) (2RS)-N-benzyl-2-(3,4-dichlorophenyl)-2-[(4RS)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanamine

To a solution of (2RS)-2-(3,4-dichlorophenyl)-2-[(4RS)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanamine (10.1 g) in toluene (200 mL) was added benzaldehyde (4.43 g) at room temperature. The mixture was heated under reflux for 1 hr while dehydrating by a Dean-Stark trap, cooled to room temperature, and concentrated under reduced pressure. To the residue was added methanol (60 mL), sodium tetrahydroborate (658 mg) was added under ice-cooling, and the mixture was stirred for 1 hr. The reaction was quenched with water, methanol was evaporated under reduced pressure, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate (5% - 100%)) to give the title compound (7.96 g) as a yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 1.31-1.37 (3H, m), 1.38-1.44 (3H, m), 1.59 (2H, brs), 2.82-2.96 (1H, m), 3.08-3.22 (1H, m), 3.49 (1H, dd, J = 8.7, 6.8 Hz), 3.67-3.85 (2H, m), 4.07-4.25 (1H, m), 4.70 (1H, s), 7.03 (1H, dd, J = 8.3, 1.9 Hz), 7.17-7.41

(7H, m).

MS (ESI+): $[M+H]^+$ 380.2.

[0611]

E) (2RS,3RS)-4-(benzylamino)-3-(3,4-dichlorophenyl)butane-1,2-
5 diol

To a solution of (2RS)-N-benzyl-2-(3,4-dichlorophenyl)-2-
[(4RS)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanamine (7.95 g) in
THF (32 mL) was added 1.0 N hydrochloric acid (31.4 mL) at
room temperature, and the mixture was stirred under nitrogen
10 purging at 50°C for 3 hr. Saturated aqueous sodium hydrogen
carbonate solution was added, and the mixture was extracted
twice with ethyl acetate. The organic layer was washed with
brine, and dried over anhydrous sodium sulfate, and the
solvent was evaporated to give the title compound (7.50 g) as
15 a pale-brown oil. This was used without purification for the
next step.

^1H NMR (300 MHz, CDCl_3) δ 1.60-2.63 (2H, m), 2.89 (1H, ddd, J =
11.2, 8.4, 3.0 Hz), 3.01 (1H, dd), 3.11 (1H, d, J = 11.3 Hz),
3.23 (1H, dd, J = 11.7, 3.8 Hz), 3.47 (1H, dd, J = 11.5, 3.2
20 Hz), 3.76-3.91 (2H, m), 3.97 (1H, dt, J = 8.3, 3.4 Hz), 4.70
(1H, s), 7.03 (1H, dd, J = 8.3, 1.9 Hz), 7.18-7.47 (7H, m).

MS (ESI+): $[M+H]^+$ 340.2.

[0612]

F) (2RS,3RS)-4-(benzylamino)-1-([tert-
25 butyl(dimethyl)silyl]oxy)-3-(3,4-dichlorophenyl)butan-2-ol

A solution of tert-butyldimethylchlorosilane (3.65 g) in
THF (10 mL) was added dropwise to a solution of (2RS,3RS)-4-
(benzylamino)-3-(3,4-dichlorophenyl)butane-1,2-diol (7.50 g)
and triethylamine (9.22 mL) in THF (35 mL) at 0°C. Under
30 nitrogen purging, the mixture was stirred at room temperature
for 3 hr, water was added at 0°C, and the mixture was extracted
with ethyl acetate. The organic layer was washed with brine,
and dried over anhydrous sodium sulfate, and the solvent was
evaporated. The residue was purified by silica gel column
35 chromatography (eluent; hexane:ethyl acetate (0% - 100%)) to

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give the title compound (6.42 g) as a pale-yellow oil.

¹H NMR (300 MHz, CDCl₃) δ -0.09-0.05 (6H, m), 0.80-0.93 (9H, m), 1.55-2.67 (1H, m), 2.91-3.05 (2H, m), 3.07-3.19 (1H, m), 3.28 (1H, dd, J = 10.6, 4.5 Hz), 3.39-3.51 (1H, m), 3.79 (2H, s), 3.87 (1H, dt, J = 7.7, 4.1 Hz), 4.71 (1H, s), 7.06 (1H, dd, J = 8.1, 2.1 Hz), 7.19-7.45 (7H, m).

MS (ESI⁺): [M+H]⁺ 454.2.

[0613]

G) N-benzyl-N-[(2RS,3RS)-4-{[tert-butyl(dimethyl)silyl]oxy}-2-(3,4-dichlorophenyl)-3-hydroxybutyl]-2-chloroacetamide

To a solution of (2RS,3RS)-4-(benzylamino)-1-{[tert-butyl(dimethyl)silyl]oxy}-3-(3,4-dichlorophenyl)butan-2-ol (6.40 g) and triethylamine (2.16 mL) in THF (50 mL) was added dropwise chloroacetyl chloride (1.23 mL) at 0°C. The mixture was stirred at 0°C for 20 min, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate (0% - 30%)) to give the title compound (6.83 g) as a pale-yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 0.00 (6H, s), 0.87 (9H, s), 1.55-1.80 (1H, br), 3.00-5.00 (10H, m), 6.95-7.50 (8H, m).

[0614]

H) (6RS,7RS)-4-benzyl-7-([tert-butyl(dimethyl)silyl]oxy)methyl)-6-(3,4-dichlorophenyl)-1,4-oxazepan-3-one

To a solution of N-benzyl-N-[(2RS,3RS)-4-{[tert-butyl(dimethyl)silyl]oxy}-2-(3,4-dichlorophenyl)-3-hydroxybutyl]-2-chloroacetamide (44.7 g) in THF (450 mL) was added sodium methoxide (5.46 g) at 0°C. The mixture was stirred at room temperature for 2 hr, water was added, and methanol was evaporated under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried

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over anhydrous sodium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate (10% - 50%)) to give the title compound (40.6 g) as a pale-yellow oil.

5 ^1H NMR (300 MHz, CDCl_3) δ 0.86-0.91 (6H, m), 2.05-2.11 (9H, m), 2.98 (1H, ddd, $J = 10.0, 7.4, 3.0$ Hz), 3.39-3.48 (1H, m), 3.50-3.78 (3H, m), 4.10 (1H, d, $J = 14.8$ Hz), 4.47 (1H, d, $J = 15.9$ Hz), 4.68-4.79 (1H, m), 5.05 (1H, d, $J = 14.8$ Hz), 6.89 (1H, dd, $J = 8.3, 1.9$ Hz), 7.13 (1H, d, $J = 1.9$ Hz), 7.21-7.27
10 (2H, m), 7.28-7.45 (5H, m).

MS (ESI+): $[\text{M}+\text{H}]^+$ 494.1.

[0615]

I) (6RS,7RS)-4-benzyl-7-({[tert-butyl(dimethyl)silyl]oxy}methyl)-6-(3,4-dichlorophenyl)-1,4-
15 oxazepane

To a solution of (6RS,7RS)-4-benzyl-7-({[tert-butyl(dimethyl)silyl]oxy}methyl)-6-(3,4-dichlorophenyl)-1,4-oxazepan-3-one (40.5 g) in THF (150 mL) was added dropwise 1.2 M borane-THF complex/THF solution (150 mL) at room temperature,
20 and the mixture was stirred under nitrogen purging at 60°C for 2 hr. After cooling to room temperature, water was added carefully, and the mixture was stirred at room temperature for 1 hr, and extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate,
25 and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate (0% - 50%)) to give the title compound (30.7 g) as a pale-yellow oil.

^1H NMR (300 MHz, CDCl_3) δ 0.00-0.03 (6H, m), 0.84-0.90 (9H, m),
30 1.58-1.65 (2H, m), 2.52-2.65 (1H, m), 2.69-2.79 (1H, m), 2.82-3.07 (2H, m), 3.41-3.57 (2H, m), 3.59 (1H, d, $J = 2.7$ Hz), 3.61-3.72 (1H, m), 3.73-3.84 (1H, m), 4.06-4.20 (1H, m), 7.17 (1H, dd, $J = 8.3, 1.9$ Hz), 7.20-7.36 (6H, m), 7.59 (1H, d, $J = 2.3$ Hz).

35 MS (ESI+): $[\text{M}+\text{H}]^+$ 480.2.

[0616]

J) tert-butyl (6R,7R)-6-(3,4-dichlorophenyl)-7-(hydroxymethyl)-1,4-oxazepane-4-carboxylate

To a solution of (6RS,7RS)-4-benzyl-7-([tert-butyl(dimethyl)silyl]oxy)methyl)-6-(3,4-dichlorophenyl)-1,4-oxazepane (10.0 g) in acetonitrile (50 mL) was added 1-chloroethyl chloroformate (4.46 g), and the mixture was stirred under nitrogen purging at 80°C for 2 hr. After cooling to room temperature, water was added, the mixture was stirred at 80°C for 10 min, and the solvent was evaporated. To the residue were added water (50 mL), THF (50 mL) and triethylamine (3.16 g), then di-tert-butyl dicarbonate (6.81 g) was added dropwise, and the mixture was stirred at room temperature overnight. After evaporation of the solvent, the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate (10% - 100%)) to give tert-butyl (6RS,7RS)-6-(3,4-dichlorophenyl)-7-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (7.14 g) as a colorless solid.

¹H NMR (300 MHz, CDCl₃) δ 1.29-1.55 (9H, m), 1.61-1.79 (1H, m), 2.07-2.27 (1H, m), 2.82-2.99 (1H, m), 3.22-3.99 (7H, m), 4.11-4.33 (1H, m), 7.03 (1H, d, J = 8.3 Hz), 7.29 (1H, d, J = 1.9 Hz), 7.38 (1H, d, J = 7.9 Hz).

MS (ESI⁺): [M+H-Boc]⁺ 276.0.

tert-Butyl (6RS,7RS)-6-(3,4-dichlorophenyl)-7-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (25.6 g) was separated by HPLC (column: CHIRALPAK AD LF001, 50 mmID×500 mmL, manufactured by DAICEL CHEMICAL INDUSTRIES, LTD., mobile phase: hexane/2-propanol = 900/100) to give the title compound (11.4 g) having a longer retention time (enantiomer excess 99.9% ee).

In addition, tert-butyl (6S,7S)-6-(3,4-dichlorophenyl)-7-(hydroxymethyl)-1,4-oxazepane-4-carboxylate was obtained as a

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compound (12.3 g) having a shorter retention time (enantiomer excess >99.9% ee).

[0617]

K) tert-butyl (6R,7R)-6-(3,4-dichlorophenyl)-7-formyl-1,4-oxazepane-4-carboxylate

To a solution of oxalyl chloride (1.52 g) in THF (20 mL) was added dimethyl sulfoxide (1.87 g) at -78°C, and the mixture was stirred for 20 min. A solution of tert-butyl (6R,7R)-6-(3,4-dichlorophenyl)-7-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (3.0 g) in THF (10 mL) and triethylamine (7.78 mL) were added at -78°C, and the mixture was warmed to room temperature and stirred for 1 hr. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate (0% - 50%)) to give the title compound (2.89 g) as a colorless solid.

¹H NMR (300 MHz, CDCl₃) δ 1.29-1.54 (9H, m), 3.30 (1H, dt, J = 9.4, 5.5 Hz), 3.67 (4H, brs), 3.89 (1H, brs), 4.04-4.23 (2H, m), 7.10 (1H, dd, J = 8.3, 2.3 Hz), 7.33-7.37 (1H, m), 7.40 (1H, d, J = 8.3 Hz), 9.60 (1H, brs).

[0618]

L) tert-butyl (6R,7S)-6-(3,4-dichlorophenyl)-7-ethenyl-1,4-oxazepane-4-carboxylate

A suspension of methyltriphenylphosphonium bromide (3.59 g) in THF (30 mL) was cooled under nitrogen purging to -78°C, and 1.6 M n-butyllithium/hexane solution (5.79 mL) was added. The mixture was warmed to 0°C, and stirred for 20 min, and a solution of tert-butyl (6R,7R)-6-(3,4-dichlorophenyl)-7-formyl-1,4-oxazepane-4-carboxylate (2.89 g) in THF (50 mL) was added. After stirring at 0°C for 20 min, and at room temperature for 2 hr, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate, and

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the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent; hexane:ethyl acetate (0% - 30%)) to give the title compound (1.10 g) as a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 1.30-1.50 (9H, m), 2.88 (1H, brs),
5 3.25-3.60 (3H, m), 3.65-4.40 (4H, m), 4.95-5.15 (2H, m), 5.51-5.72 (1H, m), 6.96-7.04 (1H, m), 7.24-7.29 (1H, m), 7.37 (1H, d, J = 7.9 Hz).

MS (ESI⁺): [M+H-t-Bu]⁺ 316.0.

[0619]

10 M). tert-butyl (6R,7R)-6-(3,4-dichlorophenyl)-7-[(1S)-1,2-dihydroxyethyl]-1,4-oxazepane-4-carboxylate

To a mixed solution of tert-butyl (6R,7S)-6-(3,4-dichlorophenyl)-7-ethenyl-1,4-oxazepane-4-carboxylate (1.08 g) and 4-methylmorpholine N-oxide (680 mg) in acetonitrile (6
15 mL)/acetone (6 mL)/water (6 mL) was added osmium(VIII) oxide immobilized catalyst I (Wako Pure Chemical Industries, Ltd. cat. 153-02581) (700 mg), and the mixture was stirred under nitrogen purging at room temperature overnight. The catalyst was filtered off through celite, and the filtrate was
20 concentrated. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated (product about 1.07 g). 900 mg therefrom was purified by HPLC (column: Sunrise C18-SAC 20×150 mm, mobile
25 phase: water/acetonitrile (containing 5 mM ammonium acetate)) to give the title compound (diastereomer having a shorter retention time) (610 mg) as a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 1.30-1.54 (9H, m), 2.22 (1H, brs),
2.65 (1H, brs), 2.91-3.06 (1H, m), 3.19-3.83 (7H, m), 3.89
30 (1H, brs), 3.95 (1H, dd, J = 10.6, 3.0 Hz), 4.26 (1H, brs), 6.99-7.08 (1H, m), 7.29 (1H, d, J = 2.3 Hz), 7.40 (1H, d, J = 8.3 Hz).

MS (ESI⁺): [M+H-Boc]⁺ 306.0.

In addition, tert-butyl (6R,7R)-6-(3,4-dichlorophenyl)-7-
35 [(1R)-1,2-dihydroxyethyl]-1,4-oxazepane-4-carboxylate (170 mg)

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having a longer retention time was obtained as a colorless oil.

^1H NMR (300 MHz, CDCl_3) δ 1.31-1.56 (9H, m), 2.09-2.66 (2H, m), 3.17-4.01 (10H, m), 4.21 (1H, brs), 7.08 (1H, dd, $J = 8.3, 1.5$ Hz), 7.33 (1H, d, $J = 1.5$ Hz), 7.39 (1H, d, $J = 8.3$ Hz).

MS (ESI+): $[\text{M}+\text{H}-\text{Boc}]^+$ 306.0.

[0620]

N) (1S)-1-[(6R,7R)-6-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]ethane-1,2-diol monohydrochloride

To a solution of tert-butyl (6R,7R)-6-(3,4-dichlorophenyl)-7-[(1S)-1,2-dihydroxyethyl]-1,4-oxazepane-4-carboxylate (450 mg) in ethanol (8 mL) was added 12 mol/kg hydrogen chloride-ethanol solution (8 mL), and the mixture was stirred at room temperature for 15 min. The solvent was evaporated under reduced pressure, and the residue was crystallized from water-ethanol-diethyl ether to give the title compound (340 mg) as colorless crystals.

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 2.86-3.74 (8H, m), 3.74-4.25 (3H, m), 4.49 (1H, brs), 4.74 (1H, brs), 7.34 (1H, dd, $J = 8.3, 1.9$ Hz), 7.62 (1H, d, $J = 8.3$ Hz), 7.66 (1H, d, $J = 1.9$ Hz), 9.17 (1H, brs), 9.77 (1H, brs).

MS (ESI+): $[\text{M}+\text{H}]^+$ 306.2.

[0621]

Example 46

(1R)-1-[(6R,7R)-6-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]ethane-1,2-diol monohydrochloride

To a solution of tert-butyl (6R,7R)-6-(3,4-dichlorophenyl)-7-[(1R)-1,2-dihydroxyethyl]-1,4-oxazepane-4-carboxylate (170 mg) obtained in Example 45, step M) in ethanol (5 mL) was added 12 mol/kg hydrogen chloride-ethanol solution (5 mL), and the mixture was stirred at room temperature for 15 min. The solvent was evaporated under reduced pressure, and the residue was crystallized from water-ethanol-diethyl ether to give the title compound (115 mg) as colorless crystals.

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^1H NMR (300 MHz, DMSO- d_6) δ 2.83-4.67 (12H, m), 4.90 (1H, brs), 7.34 (1H, d, $J = 7.6$ Hz), 7.64 (2H, brs), 9.09 (1H, brs), 9.74 (1H, brs).

MS (ESI+): $[\text{M}+\text{H}]^+$ 306.2.

5 [0622]

Example 47

[(7S)-7-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]methanol
monohydrochloride

[0623]

10 A) tert-butyl (7S)-7-(3,4-dichlorophenyl)-7-(hydroxymethyl)-
1,4-oxazepane-4-carboxylate

A racemate (50.4 g) of tert-butyl (7RS)-7-(3,4-dichlorophenyl)-7-(hydroxymethyl)-1,4-oxazepane-4-carboxylate was separated by SFC (column: CHIRALPAK AD-H, 30 mmID $\times$ 250 mmL, 15 manufactured by DAICEL CHEMICAL INDUSTRIES, LTD., mobile phase: carbon dioxide/2-propanol = 65/35) to give the title compound (20 g) having a longer retention time.

^1H NMR (400 MHz, MeOD) δ 1.39 (9H, s), 2.17-2.11 (1H, m), 2.48-2.43 (1H, m), 3.54-3.43 (5H, m), 3.73-3.62 (2H, m), 3.87-3.84 20 (1H, d, $J = 12$ Hz), 7.30-7.27 (1H, d, $J = 12$ Hz), 7.48-7.46 (1H, d, $J = 8$ Hz), 7.53 (1H, s), 1H not detected.

MS (ESI+): $[\text{M}+\text{H}]^+$ 376.0.

[0624]

B) [(7S)-7-(3,4-dichlorophenyl)-1,4-oxazepan-7-yl]methanol
25 monohydrochloride

To a solution of tert-butyl (7S)-7-(3,4-dichlorophenyl)-7-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (206.2 mg) in ethanol (2 mL) was added 4 N hydrogen chloride/ethyl acetate solution (2 mL), and the mixture was stirred overnight. The 30 solvent was evaporated under reduced pressure, and the obtained crystals were recrystallized from ethanol and ethyl acetate to give the title compound (134.5 mg).

^1H NMR (300 MHz, DMSO- d_6) δ 2.34 (1H, dd, $J = 16.2, 9.8$ Hz), 2.76 (1H, dd, $J = 16.6, 7.6$ Hz), 3.01-3.21 (3H, m), 3.24-3.37 35 (2H, m), 3.40-3.50 (1H, m), 3.55-3.67 (1H, m), 3.95-4.07 (1H,

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m), 5.08 (1H, t, J = 5.9 Hz), 7.35 (1H, dd, J = 8.7, 2.3 Hz), 7.57 (1H, d, J = 1.9 Hz), 7.61-7.67 (1H, m), 8.83-9.24 (2H, m).

MS (ESI+): [M+H]⁺ 277.1.

5. [0625]

Example 48

[(6R*,7R*)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methanol monohydrochloride (retention time short)

[0626]

10 tert-Butyl (6RS,7RS)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (15.8 g) was separated by HPLC (CHIRALPAK AD, 50 mmID×500 mmL, manufactured by DAICEL CHEMICAL INDUSTRIES, LTD., mobile phase: hexane/2-propanol = 800/200) to give tert-butyl (6R*,7R*)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate
15 (7.9 g, >99.9% ee., recovery rate 100%) having a shorter retention time. Using this compound, and in the same manner as in Example 1, step I, the title compound was obtained.

MS (ESI+): [M+H]⁺ 276.1.

20. [0627]

Example 49

[(6R*,7R*)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methanol monohydrochloride (retention time long)

[0628]

25 tert-Butyl (6RS,7RS)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate was separated by a method similar to that in Example 48, and the title compound was obtained using tert-butyl (6R*,7R*)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate having a longer
30 retention time and in the same manner as in Example 1, step I.

MS (ESI+): [M+H]⁺ 276.1.

[0629]

Example 50

(6RS,7SR)-7-(3,4-dichlorophenyl)-6-[(methylsulfonyl)methyl]-
35 1,4-oxazepane monohydrochloride

[0630]

Using tert-butyl (6RS,7RS)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 5, the title compound was obtained.

5 MS (ESI+): [M+H]⁺ 338.0.

[0631]

Example 51

N-{[(6RS,7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}acetamide monohydrochloride

10 [0632]

Using tert-butyl (6RS,7SR)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 6, steps C and D, the title compound was obtained.

15 MS (ESI+): [M+H]⁺ 317.0.

[0633]

Example 52

1-{[(6RS,7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-3-ethylurea monohydrochloride

20 [0634]

Using tert-butyl (6RS,7SR)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate and ethyl isocyanate, and in the same manner as in Example 3, steps D and E, the title compound was obtained.

25 MS (ESI+): [M+H]⁺ 346.1.

[0635]

Example 53

N-{[(6RS,7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}methanesulfonamide monohydrochloride

30 [0636]

Using tert-butyl (6RS,7SR)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 8, the title compound was obtained.

MS (ESI+): [M+H]⁺ 353.0.

35 [0637]

Example 54

N-{[(6RS,7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}sulfamide monohydrochloride

[0638]

- 5 Using tert-butyl (6RS,7SR)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 9, the title compound was obtained.

MS (ESI+): [M+H]⁺ 354.1.

[0639]

10 Example 55

{[(6R*,7R*)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methoxy}acetic acid monohydrochloride

[0640]

- A) tert-butyl (6R*,7R*)-7-(3,4-dichlorophenyl)-6-{[2-(morpholin-4-yl)-2-oxoethoxy]methyl}-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R*,7R*)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (retention time long) (500 mg) obtained in Example 49 in THF
20 (4.5 mL) was added 4-(chloroacetyl)morpholine (0.346 mL), and the mixture was stirred at room temperature for 3 hr. To the reaction mixture was added distilled water, and the mixture was extracted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried over
25 anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (649 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.46-1.56 (9H, m), 2.54-2.67 (1H, m),
30 3.12-4.08 (18H, m), 4.56-4.64 (1H, m), 7.05-7.15 (1H, m), 7.36-7.48 (2H, m).

[0641]

B) {[(6R*,7R*)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methoxy}acetic acid

- 35 To a solution of tert-butyl (6R*,7R*)-7-(3,4-

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dichlorophenyl)-6-{{[2-(morpholin-4-yl)-2-oxoethoxy]methyl}-
1,4-oxazepane-4-carboxylate (649 mg) in THF (2.5 mL) and
methanol (2.5 mL) was added a solution of lithium hydroxide
monohydrate (108 mg) in distilled water (1.5 mL), and the
5 mixture was stirred at 70°C for 2 hr. Furthermore, a solution
of lithium hydroxide monohydrate (108 mg) in distilled water
(1.5 mL) was added, the mixture was stirred at 70°C overnight,
and neutralized with aqueous ammonium chloride solution, and
the mixture was extracted with ethyl acetate. The extract was
10 washed with distilled water and brine, and dried over
anhydrous sodium sulfate, and the solvent was evaporated under
reduced pressure to give the title compound (381 mg).

MS (ESI+): [M-H]⁺ 432.2.

[0642]

15 C) {[(6R*, 7R*)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
yl]methoxy}acetic acid monohydrochloride

Using {[(6R*, 7R*)-4-(tert-butoxycarbonyl)-7-(3,4-
dichlorophenyl)-1,4-oxazepan-6-yl]methoxy}acetic acid (127
mg), and in the same manner as in Example 38, step F, the
20 title compound (159 g) was obtained.

MS (ESI+): [M+H]⁺ 334.6.

[0643]

Example 56

1-([(6R*, 7R*)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
25 yl]methoxy)acetyl)azetidin-3-ol monohydrochloride

[0644]

tert-Butyl (6R*, 7R*)-7-(3,4-dichlorophenyl)-6-
(hydroxymethyl)-1,4-oxazepane-4-carboxylate (retention time
long) obtained in Example 49 was led to a carboxylic acid
30 derivative by an operation similar to that in Example 55,
steps A and B. Using the carboxylic acid derivative and
azetidin-3-ol, and by amidation according to Example 41, step
A and an operation similar to that in Example 1, step 1, the
title compound was obtained.

35 MS (ESI+): [M+H]⁺ 389.3.

[0645]

Example 57

(6R*, 7R*)-7-(3,4-dichlorophenyl)-6-([2-(1,1-dioxidothiomorpholin-4-yl)-2-oxoethoxy]methyl)-1,4-oxazepane
5 monohydrochloride

tert-Butyl (6R*, 7R*)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (retention time long) obtained in Example 49 was led to a carboxylic acid derivative by an operation similar to that in Example 55,
10 steps A and B. Using the carboxylic acid derivative and thiomorpholine 1,1-dioxide, and by amidation according to Example 41, step A and an operation similar to that in Example 1, step 1, the title compound was obtained.

MS (ESI+): [M+H]⁺ 451.3.

15 [0646]

Example 58

2-([(6R*, 7R*)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methoxy)benzoic acid monohydrochloride

[0647]

20 A) tert-butyl (6R*, 7R*)-7-(3,4-dichlorophenyl)-6-([2-(methoxycarbonyl)phenoxy]methyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R*, 7R*)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (retention time long) (500 mg) obtained in Example 49, methyl
25 salicylate (0.257 mL) and triphenylphosphine (1.05 g) in THF (5 mL) was added dropwise diethyl azodicarboxylate (1.8 mL, 2.2 M toluene solution) under ice-cooling, and the mixture was gradually warmed from 0°C to room temperature and stirred overnight. The reaction mixture was diluted with ethyl
30 acetate. The diluted solution was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (160 mg).

35 ¹H NMR (300 MHz, CDCl₃) δ 1.40-1.52 (9H, m), 3.15-3.52 (2H, m),

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3.54-3.75 (3H, m), 3.77-4.02 (6H, m), 4.18-4.32 (1H, m), 4.73 (1H, d, J = 3.0 Hz), 6.70 (1H, d, J = 8.3 Hz), 6.93 (1H, t, J = 7.4 Hz), 7.15 (1H, d, J = 7.9 Hz), 7.31-7.43 (2H, m), 7.46 (1H, brs), 7.75 (1H, d, J = 6.4 Hz).

5 MS (ESI+): [M+H-Boc]⁺ 410.2.

[0648]

B) 2-{[(6R*,7R*)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methoxy}benzoic acid

To a solution of tert-butyl (6R*,7R*)-7-(3,4-dichlorophenyl)-6-{[2-(methoxycarbonyl)phenoxy]methyl}-1,4-oxazepane-4-carboxylate (160 mg) in methanol (2 mL) was added 8 N aqueous sodium hydroxide solution (1 mL) at room temperature, and the mixture was stirred at room temperature overnight. The reaction mixture was neutralized with 10% aqueous citric acid solution, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give the title compound (110 mg).

MS (ESI-): [M-H]⁺ 494.0.

20 [0649]

C) 2-{[(6R*,7R*)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methoxy}benzoic acid monohydrochloride

To 2-{[(6R*,7R*)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methoxy}benzoic acid (50 mg) was added 4.0 M hydrogen chloride-ethyl acetate solution (4 mL), and the mixture was stirred at room temperature for 1 hr. The residue obtained by concentration under reduced pressure was washed with ethyl acetate-hexane to give the title compound (20 mg).

30 ¹H NMR (300 MHz, DMSO-d₆) δ 3.01 (1H, brs), 3.43 (2H, brs), 3.56-4.16 (6H, m), 5.19 (1H, d, J = 3.8 Hz), 6.91 (1H, d, J = 8.3 Hz), 7.00 (1H, t, J = 7.2 Hz), 7.34-7.49 (2H, m), 7.55-7.61 (1H, m), 7.66 (1H, d, J = 1.9 Hz), 7.72 (1H, dd, J = 7.6, 1.9 Hz), 9.06 (1H, brs), 9.70 (1H, brs).

35 MS (ESI+): [M+H]⁺ 396.1.

[0650]

Example 59

3-{[(6R*,7R*)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methoxy}benzoic acid monohydrochloride

5 [0651]

In the same manner as in Example 58, the title compound was obtained.

MS (ESI+): [M+H]⁺ 396.2.

[0652]

10 Example 60

4-{[(6R*,7R*)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methoxy}benzoic acid monohydrochloride

[0653]

15 In the same manner as in Example 58, the title compound was obtained.

MS (ESI+): [M+H]⁺ 395.9.

[0654]

Example 61

1-[(2-{[(6R*,7R*)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methoxy}phenyl)carbonyl]azetidin-3-ol monohydrochloride

20 [0655]

Using 2-{[(6R*,7R*)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methoxy}benzoic acid (60 mg) obtained in Example 58, step B), and in the same manner as in
25 Example 39, the title compound (20 mg) was obtained.

MS (ESI+): [M+H]⁺ 451.0.

[0656]

Example 62

30 N-[(6RS,7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]acetamide monohydrochloride

[0657]

A) methyl (2RS,3SR)-3-(3,4-dichlorophenyl)oxirane-2-carboxylate

To a solution of 3,4-dichlorobenzaldehyde (51.0 g) and
35 methyl chloroacetate (51 mL) in methanol (500 mL) was added

28% sodium methoxide/methanol (68 mL) solution under ice-cooling, and the mixture was stirred at room temperature overnight. The resultant product was collected by filtration, and washed with distilled water to give the title compound
5 (90.9 g).

^1H NMR (300 MHz, CDCl_3) δ 3.46 (1H, d, $J = 1.5$ Hz), 3.84 (3H, s), 4.07 (1H, d, $J = 1.9$ Hz), 7.14 (1H, dd, $J = 8.3, 1.9$ Hz), 7.38 (1H, d, $J = 1.9$ Hz), 7.45 (1H, d, $J = 8.3$ Hz).

[0658]

10 B) (2RS,3SR)-3-(3,4-dichlorophenyl)oxirane-2-carboxylic acid

To a solution of methyl (2RS,3SR)-3-(3,4-dichlorophenyl)oxirane-2-carboxylate (90.9 g) in methanol (500 mL) was added 4 N sodium hydroxide solution (138 mL), and the mixture was stirred at room temperature for 2 hr. The reaction
15 solution was filtered and washed with methanol. To the mother liquor was added 3 N hydrochloric acid (400 mL), and the mixture was stirred at room temperature for 1 hr. The resultant product was collected by filtration, and washed with distilled water to give the title compound (57.3 g).

20 ^1H NMR (300 MHz, CDCl_3) δ 3.72 (1H, d, $J = 1.9$ Hz), 4.20 (1H, d, $J = 1.9$ Hz), 7.37 (1H, dd, $J = 8.3, 1.9$ Hz), 7.58-7.84 (2H, m), 13.39 (1H, brs).

[0659]

25 C) (2RS,3SR)-N-benzyl-3-(3,4-dichlorophenyl)-N-(2-hydroxyethyl)oxirane-2-carboxamide

To a mixed solution of (2RS,3SR)-3-(3,4-dichlorophenyl)oxirane-2-carboxylic acid (50.0 g) and 2-(benzylamino)ethanol (38.9 g) in THF (700 mL)-methanol (100 mL) was added 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-
30 methylmorpholinium chloride (71.2 g), and the mixture was stirred at room temperature overnight. The reaction solution was concentrated, the residue was diluted with ethyl acetate, and the mixture was washed with saturated aqueous sodium hydrogen carbonate, water and brine, and dried over anhydrous
35 sodium sulfate. The solvent was evaporated under reduced

pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (42.2 g).

¹H NMR (300 MHz, CDCl₃) δ 1.93-2.82 (1H, m), 3.42-4.26 (6H, m),
5 4.45-4.92 (2H, m), 6.76-7.60 (8H, m).

[0660]

D) (6RS,7RS)-4-benzyl-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepan-5-one

To a solution of (2RS,3SR)-N-benzyl-3-(3,4-dichlorophenyl)-N-(2-hydroxyethyl)oxirane-2-carboxamide (42.2
10 g) in acetonitrile (350 mL) was added scandium(III) trifluoromethanesulfonate (5.67 g), and the mixture was stirred at room temperature for 20 min. The reaction mixture was concentrated under reduced pressure, and the residue was
15 purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (31.0 g).

¹H NMR (300 MHz, CDCl₃) δ 3.08-3.56 (2H, m), 3.66-4.10 (2H, m),
4.09-4.51 (3H, m), 4.55-4.96 (2H, m), 7.21 (1H, dd, J = 8.3, 1.9 Hz), 7.27-7.56 (7H, m).

20 [0661]

E) (6RS,7SR)-4-benzyl-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-ol

To a solution of lithium aluminum hydride (11.2 g) in THF (120 mL) was added, in an argon stream, aluminum(III) chloride (10.5 g) at room temperature, and the mixture was stirred at
25 room temperature for 40 min. The reaction mixture was cooled to 0°C, a solution of (6RS,7RS)-4-benzyl-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepan-5-one (28.9 g) in THF (100 mL) was added dropwise, and the mixture was stirred for 3 hr. To the reaction mixture was added 10% aqueous Rochelle
30 salt solution (90 mL) at 0°C, and the mixture was stirred at room temperature for 30 min, and filtered through celite. The filtrate was washed with brine, the organic layer was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate)
35 to give the title compound (27.7 g).

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¹H NMR (300 MHz, CDCl₃) δ 2.53-3.13 (4H, m), 3.57-4.08 (5H, m), 4.48 (1H, brs), 4.73 (1H, d, J = 1.9 Hz), 7.02-7.60 (8H, m).

[0662]

F) (6RS,7SR)-4-benzyl-6-{[tert-butyl(dimethyl)silyl]oxy}-7-(3,4-dichlorophenyl)-1,4-oxazepane

To a solution of (6RS,7SR)-4-benzyl-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-ol (27.7 g) in DMF (154 mL) were added tert-butylchlorodimethylsilane (17.8 g) and imidazole (10.7 g), and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with water - ethyl acetate for partitioning, and the organic layer was washed with distilled water and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (37.0 g).

¹H NMR (300 MHz, CDCl₃) δ -0.55 (3H, s), -0.34 (3H, s), 0.46-0.80 (9H, m), 2.64-3.12 (4H, m), 3.54-3.86 (4H, m), 3.88-4.08 (1H, m), 4.35 (1H, d, J = 8.3 Hz), 6.98-7.24 (3H, m), 7.27-7.50 (5H, m).

[0663]

G) tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepane-4-carboxylate

To a solution of (6RS,7SR)-4-benzyl-6-{[tert-butyl(dimethyl)silyl]oxy}-7-(3,4-dichlorophenyl)-1,4-oxazepane (37.0 g) in acetonitrile (200 mL) was added 1-chloroethyl chloroformate (13.0 mL), and the mixture was stirred at 80°C for 1 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with methanol (200 mL). The reaction mixture was stirred at 80°C for 1 hr, and ice-cooled, and THF (200 mL), triethylamine (16.6 mL) and di-tert-butyl dicarbonate (27.6 mL) were added. The reaction mixture was stirred at room temperature for 1 hr, and diluted with water - ethyl acetate for partitioning, and the organic layer was washed with distilled water and brine, dried over

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anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in THF (200 mL), 1 M tetrabutylammonium fluoride (159 mL) was added, and the mixture was stirred at room temperature overnight. The

5 reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (23.2 g).

¹H NMR (300 MHz, CDCl₃) δ 1.52 (9H, s), 3.08-3.26 (1H, m), 3.45 (1H, dd, J = 14.9, 4.3 Hz), 3.55-3.75 (1H, m), 3.77-4.26 (6H, 10 m), 7.27-7.47 (2H, m), 7.56 (1H, s).

[0664]

H) tert-butyl (6SR,7SR)-6-azido-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

Methanesulfonyl chloride (316 mg) was added to a solution 15 of tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepane-4-carboxylate (500 mg) and triethylamine (0.58 mL) in THF (5 mL), and the mixture was stirred at room temperature for 1 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was 20 washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. To a solution of the residue in DMF (5 mL) was added sodium azide (270 mg), and the mixture was stirred at 80°C overnight. Water was added to the reaction mixture, and the mixture was 25 extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (272 mg).

30 ¹H NMR (300 MHz, CDCl₃) δ 1.51 (9H, d, J = 8.7 Hz), 3.16-4.38 (8H, m), 4.60 (1H, d, J = 4.5 Hz), 7.18 (1H, d, J = 9.4 Hz), 7.35-7.65 (1H, m).

[0665]

I) tert-butyl (6SR,7SR)-6-amino-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate 35

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To a solution of cobalt bromide (15 mg) in ethanol (5 mL) was added 2,2'-bipyridyl (33 mg), sodium tetrahydroborate (53 mg) was added, and the mixture was stirred at 0-5°C for 5 min. To the reaction mixture was added a solution of tert-butyl (6SR,7SR)-6-azido-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (270 mg) in ethanol (5 mL), and the mixture was stirred at 0-5°C for 30 min. Acetic acid was added to the reaction mixture, and the mixture was stirred at room temperature for 5 min. The solvent was evaporated under reduced pressure. The residue was neutralized with saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (191 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.50 (9H, d, J = 5.3 Hz), 1.62 (2H, s), 2.90-4.23 (7H, m), 4.50 (1H, brs), 7.11 (1H, t, J = 8.9 Hz), 7.35-7.63 (2H, m).

MS (ESI+): [M+H]⁺ 361.1.

[0666]

J) tert-butyl (6S,7S)-6-(acetylamino)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

Acetyl chloride (23 mg) was added to a solution of tert-butyl (6SR,7SR)-6-amino-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (90 mg) and triethylamine (33 mg) in THF (5 mL), and the mixture was stirred at room temperature for 1 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (93 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.48 (9H, s), 1.83 (3H, s), 3.31-4.84 (8H, m), 5.73 (1H, d, J = 9.8 Hz), 7.10 (1H, d, J = 8.7 Hz),

7.38 (1H, d, J = 8.7 Hz), 7.46 (1H, brs).

MS (ESI+): [M+H]⁺ 401.0.

[0667]

K) N-[(6RS,7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]acetamide monohydrochloride

Using tert-butyl (6S,7S)-6-(acetylamino)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (93 mg), and in the same manner as in Example 39, step B, the title compound (75 mg) was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 1.72 (3H, s), 3.12-3.31 (1H, m), 3.44-3.62 (1H, m), 3.81-4.02 (1H, m), 4.08-4.23 (1H, m), 4.32 (2H, brs), 4.45-4.69 (1H, m), 5.02 (1H, d, J = 1.5 Hz), 7.30 (1H, dd, J = 8.7, 1.9 Hz), 7.49-7.68 (2H, m), 7.94 (1H, d, J = 9.1 Hz), 9.34 (1H, brs), 9.77 (1H, brs).

MS (ESI+): [M+H]⁺ 303.1.

[0668]

Example 63

N-[(6RS,7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methanesulfonamide monohydrochloride

[0669]

A) tert-butyl (6SR,7SR)-7-(3,4-dichlorophenyl)-6-[(methanesulfonyl)amino]-1,4-oxazepane-4-carboxylate

Methanesulfonyl chloride (34 mg) was added to a solution of tert-butyl (6SR,7SR)-6-amino-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (90 mg) and triethylamine (33 mg) in THF (5 mL), and the mixture was stirred at room temperature for 1 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (90 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.52 (9H, brs), 2.19 (2H, s), 2.53 (1H, brs), 3.21-4.29 (7H, m), 4.54-4.89 (2H, m), 7.16 (1H, dd, J = 8.3, 1.9 Hz), 7.45 (1H, d, J = 8.3 Hz), 7.50 (1H, d, J =

1.5 Hz).

MS (ESI+): [M+H]⁺ 437.0.

[0670]

B) N-[(6RS,7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methanesulfonamide monohydrochloride

Using tert-butyl (6SR,7SR)-7-(3,4-dichlorophenyl)-6-[(methylsulfonyl)amino]-1,4-oxazepane-4-carboxylate (90 mg), and in the same manner as in Example 39, step B, the title compound (57 mg) was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 2.53 (3H, s), 3.35-3.67 (4H, m), 3.92 (1H, ddd, J = 13.3, 6.9, 4.0 Hz), 4.10 (2H, qd), 5.07 (1H, d, J = 1.5 Hz), 7.31 (1H, d, J = 9.1 Hz), 7.38 (1H, dd, J = 8.3, 1.9 Hz), 7.63 (1H, d, J = 8.3 Hz), 7.66 (1H, d, J = 1.9 Hz), 9.63 (2H, brs).

MS (ESI+): [M+H]⁺ 339.1.

[0671]

Example 64

1-[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]-3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one monohydrochloride

[0672]

A) tert-butyl (6RS,7SR)-6-(3-cyano-2-oxopyridin-1(2H)-yl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

Methanesulfonyl chloride (949 mg) was added to a solution of tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepane-4-carboxylate (1.50 g) and triethylamine (1.73 mL) in THF (30 mL), and the mixture was stirred at room temperature for 1 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. To a solution of the residue (608 mg) in DMF (12 mL) were added 2-oxo-1,2-dihydropyridine-3-carbonitrile (199 mg) and potassium carbonate (286 mg), and the mixture was stirred at 80°C overnight. To the reaction mixture was added distilled

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water, and the mixture was extracted with ethyl acetate. The extract was washed with 0.1 N hydrochloric acid and brine, and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (108 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.43 (9H, s), 3.44-3.99 (4H, m), 4.00-4.22 (1H, m), 4.27-4.60 (1H, m), 4.98 (1H, d, J = 4.1 Hz), 5.82-6.16 (2H, m), 6.23 (1H, t, J = 7.0 Hz), 6.99 (1H, d, J = 8.3 Hz), 7.29-7.66 (2H, m), 7.72-8.11 (1H, m).

[0673]

B) tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-[2-oxo-3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl]-1,4-oxazepane-4-carboxylate

Sodium hydrogen carbonate (145 mg) and hydroxylamine monohydrochloride (120 mg) were added to a solution of tert-butyl (6RS,7SR)-6-(3-cyano-2-oxopyridin-1(2H)-yl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (100 mg) in DMSO (4 mL), and the mixture was stirred at 80°C overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in THF (10 mL), diazabicycloundecene (0.032 mL) and CDI (52 mg) were added, and the mixture was heated under reflux for 1 hr. To the reaction mixture was added 1 N aqueous hydrochloric acid solution, and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title compound (56 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.41 (9H, brs), 3.38-4.26 (4H, m), 4.27-4.60 (1H, m), 4.89-5.15 (1H, m), 5.87-6.32 (2H, m), 6.93-7.14 (1H, m), 7.27-7.63 (3H, m), 7.79-8.22 (2H, m), 10.28 (1H,

brs).

[0674]

C) 1-[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]-3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one
5 monohydrochloride

Using tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-[2-oxo-3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridin-1(2H)-yl]-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 2, step B, the title compound (26 mg) was obtained.

10 MS (ESI+): [M+H]⁺ 423.1.

[0675]

Example 65

[(6RS,7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]acetonitrile monohydrochloride

15 [0676]

A) tert-butyl (6RS,7RS)-6-(cyanomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-[(methanesulfonyl)methyl]-1,4-oxazepane-4-carboxylate (1.26 g) in DMF (10 mL) was added sodium cyanide (204 mg), and the mixture was stirred at 80°C for 18 hr. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried
25 over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (990 mg).

MS (ESI+): [M+H-Boc]⁺ 285.1.

30 [0677]

B) [(6RS,7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]acetonitrile monohydrochloride

To a solution of tert-butyl (6RS,7RS)-6-(cyanomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (88 mg) in
35 ethyl acetate (0.5 mL) was added 2 N hydrogen chloride-ethanol

solution (3 mL), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was crystallized from ethyl acetate and diisopropyl ether to give the title compound (63 mg).

5 MS (ESI+): $[M+H]^+$ 285.1.

[0678]

Example 66

[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]acetic acid monohydrochloride

10 [0679]

A) tert-butyl (6R,7R)-6-(cyanomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

Potassium cyanide (1.720 g) was added to a solution of tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-

15 {[(methylsulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate (3

g) in DMF (30 mL), and the mixture was stirred at 80°C

overnight. To the reaction mixture was added aqueous sodium hydrogen carbonate solution, and the mixture was extracted

with ethyl acetate. The extract was washed with brine, and

20 dried over anhydrous sodium sulfate. The solvent was

evaporated under reduced pressure. The residue was purified by

silica gel column chromatography to give the title compound

(2.00 g).

^1H NMR (300 MHz, CDCl_3) δ 1.47-1.56 (9H, m), 2.06-2.37 (3H, m),

25 3.33-4.24 (7H, m), 7.11-7.22 (1H, m), 7.40-7.49 (2H, m).

[0680]

B) tert-butyl (6R,7R)-6-(2-amino-2-oxoethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7R)-6-(cyanomethyl)-7-

30 (3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (1 g) in DMSO

(10 mL) were added potassium carbonate (0.502 g) and 30%

aqueous hydrogen peroxide (1.22 mL) at room temperature. The

reaction mixture was stirred at room temperature for 1.5 hr.

Diluted aqueous sodium thiosulfate solution was added, and the

35 mixture was extracted with ethyl acetate. The extract was

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washed with brine, and dried over anhydrous sodium sulfate.

The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (746 mg).

5 ^1H NMR (300 MHz, CDCl_3) δ 1.50 (9H, s), 1.90 (1H, d, $J = 12.5$ Hz), 2.29 (1H, t, $J = 12.1$ Hz), 2.38-2.54 (1H, m), 3.19-3.32 (1H, m), 3.42 (1H, dd, $J = 14.6, 4.7$ Hz), 3.60 (1H, td, $J = 12.3, 3.0$ Hz), 3.88-4.15 (4H, m), 5.41 (1H, brs), 7.16 (1H, dd, $J = 8.3, 2.3$ Hz), 7.30 (1H, brs), 7.39-7.45 (2H, m).

10 [0681]

C) [(6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]acetic acid

8 N Aqueous sodium hydroxide solution (0.620 mL) was added to a solution of tert-butyl (6R,7R)-6-(2-amino-2-oxoethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (500 mg) in n-butanol (5 mL), and the mixture was stirred at 120°C for 4.5 hr. The reaction mixture was neutralized with 1 N hydrochloric acid, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (434 mg).

15 ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 1.21-1.39 (1H, m), 1.43 (9H, s), 1.85 (1H, d, $J = 13.6$ Hz), 2.11-2.36 (2H, m), 3.34-3.74 (4H, m), 3.89-4.03 (1H, m), 4.14-4.29 (1H, m), 7.32 (1H, d, $J = 6.8$ Hz), 7.51-7.65 (2H, m), 12.14 (1H, brs).

[0682]

D) [(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]acetic acid monohydrochloride

30 Using [(6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]acetic acid (150 mg), and in the same manner as in Example 39, step B, the title compound (75 mg) was obtained.

MS (ESI+): $[M+H]^+$ 304.0.

35 [0683]

Example 67

3-[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]propanoic acid monohydrochloride

A) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-[(1E)-3-ethoxy-3-oxoprop-1-en-1-yl]-1,4-oxazepane-4-carboxylate

To a solution of lithium chloride (136 mg) and diazabicycloundecene (0.403 mL) in acetonitrile (26.7 mL) was added ethyl (diethoxyphosphoryl)acetate (0.642 mL), and the mixture was stirred at 20 min. tert-Butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-formyl-1,4-oxazepane-4-carboxylate (1.00 g) was added and the mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure, distilled water was added, and the mixture was extracted with ethyl acetate. The extract was washed with distilled water and brine, and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (902 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.26 (3H, t, J = 7.2 Hz), 1.51 (9H, s), 2.68-4.31 (10H, m), 5.47-5.68 (1H, m), 6.59-6.96 (1H, m), 7.03 (1H, d, J = 8.3 Hz), 7.32-7.42 (2H, m).

[0684]

B) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-(3-ethoxy-3-oxopropyl)-1,4-oxazepane-4-carboxylate

To a solution (1.1 mL) of tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-[(1E)-3-ethoxy-3-oxoprop-1-en-1-yl]-1,4-oxazepane-4-carboxylate (100 mg) in methanol was added, under a nitrogen atmosphere, 3% platinum/activated carbon (23 mg), and the mixture was stirred under a hydrogen atmosphere for 1 hr. The reaction mixture was filtered through celite, and concentrated under reduced pressure to give the title compound (113 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.18 (3H, t, J = 7.2 Hz), 1.32-1.46 (2H, m), 1.50 (9H, s), 1.86-2.60 (3H, m), 3.35-3.90 (5H, m), 3.93-4.15 (4H, m), 7.15 (1H, dd, J = 8.1, 2.1 Hz), 7.41 (1H,

d, J = 5.3 Hz), 7.43 (1H, s).

[0685]

C) 3-[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]propanoic acid monohydrochloride

Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-(3-ethoxy-3-oxopropyl)-1,4-oxazepane-4-carboxylate (103 mg), and in the same manner as in Example 44, step B, the title compound (45.8 g) was obtained.

MS (ESI+): [M+H]⁺ 318.2.

[0686]

Example 68

2-[(6RS,7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]acetamide monohydrochloride

[0687]

A) tert-butyl (6RS,7RS)-6-(2-amino-2-oxoethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6RS,7RS)-6-(cyanomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (900 mg) in methanol (7 mL) - water (2 mL) were added saturated aqueous sodium hydrogen carbonate (1 mL) and 35% aqueous hydrogen peroxide (3 mL), and the mixture was stirred for 3 days. To the reaction mixture was added saturated aqueous sodium thiosulfate solution, and the mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (492 mg).

MS (ESI+): [M+H-Boc]⁺ 302.9.

[0688]

B) 2-[(6RS,7RS)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]acetamide monohydrochloride

To a solution of tert-butyl (6RS,7RS)-6-(2-amino-2-oxoethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (100 mg) in ethyl acetate (0.5 mL) was added 2 N hydrogen

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chloride-ethanol solution (1 mL), and the mixture was stirred at room temperature for 3 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate, and the mixture was extracted twice with ethyl acetate. The combined
5 organic layers were washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. To the residue was added 1 N hydrochloric acid. The solvent was evaporated under reduced pressure to give the title compound (14 mg).

10 MS (ESI+): [M+H-Boc]⁺ 302.9.

[0689]

Example 69

N-{[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]acetyl}-
2-methylalanine monohydrochloride

15 [0690]

In the same manner as in Example 39, step A, and Example 44, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 389.0.

[0691]

20 Example 70

3-({[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]acetyl}amino)benzoic acid monohydrochloride

[0692]

In the same manner as in Example 39, step A and Example
25 44, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 423.1.

[0693]

Example 71

[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl
30 acetate monohydrochloride

[0694]

Using tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate obtained in Example 4, step G, and by O-acetylation under similar
35 conditions as in the acetylation in Example 6, step C, and in

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the same manner as in Example 6, step D, the title compound was obtained.

MS (ESI+): [M+H]⁺ 318.2

[0695]

5 Example 72

[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methanol
monohydrochloride

[0696]

Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-
10 (hydroxymethyl)-1,4-oxazepane-4-carboxylate, and in the same
manner as in Example 1, step I, the title compound was
obtained.

MS (ESI+): [M+H]⁺ 276.1.

[0697]

15 Example 73

[(6R,7S)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methanol
monohydrochloride

[0698]

Using tert-butyl (6R,7S)-7-(3,4-dichlorophenyl)-6-
20 (hydroxymethyl)-1,4-oxazepane-4-carboxylate, and in the same
manner as in Example 1, step I, the title compound was
obtained.

MS (ESI+): [M+H]⁺ 275.9.

[0699]

25 Example 74

7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepan-6-ol
monohydrochloride

[0700]

A) tert-butyl (7RS)-7-(3,4-dichlorophenyl)-6-oxo-1,4-
30 oxazepane-4-carboxylate

Dess-Martin reagent (1.4 g) was added to a solution of
tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-
oxazepane-4-carboxylate (800 mg) in acetonitrile (10 mL), and
the mixture was stirred at 0°C for 1 hr. To the reaction
35 mixture were added saturated aqueous sodium hydrogen carbonate

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and aqueous sodium sulfite solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (624 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.50 (9H, s), 2.95-3.49 (1H, m), 3.60-4.77 (5H, m), 4.85 (1H, brs), 7.10 (1H, dd, J = 8.3, 1.5 Hz), 7.33-7.50 (2H, m).

10 [0701]

B) tert-butyl (3RS,4SR)-4-(3,4-dichlorophenyl)-1,5-dioxa-8-azaspiro[2.6]nonane-8-carboxylate

A solution (3 M, 0.56 mL) of methyllithium in diethyl ether was added to a solution of tert-butyl (7RS)-7-(3,4-dichlorophenyl)-6-oxo-1,4-oxazepane-4-carboxylate (300 mg) and diiodomethane (335 mg) in THF (3 mL), and the mixture was stirred at 0°C for 30 min, and at room temperature for 1 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography and HPLC to give the title compound (59 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.50 (9H, s), 2.08-2.37 (1H, m), 2.69 (1H, brs), 3.08-3.37 (1H, m), 3.41-3.91 (2H, m), 3.91-4.32 (3H, m), 4.61 (1H, s), 7.11 (1H, dd, J = 8.3, 1.9 Hz), 7.32-7.47 (2H, m).

MS (ESI+): [M+H-Boc]⁺ 274.0.

[0702]

30 C) 7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepan-6-ol monohydrochloride

Bismuth(III) trifluoromethanesulfonate (228 mg) was added to a mixed solution of tert-butyl (3RS,4SR)-4-(3,4-dichlorophenyl)-1,5-dioxa-8-azaspiro[2.6]nonane-8-carboxylate (59 mg) in THF/water (v/v = 4/1, 5 mL), and the mixture was

stirred at 80°C overnight. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent
5 was evaporated under reduced pressure. To the residue was added a solution (4 M, 4 mL) of hydrogen chloride in ethyl acetate. The solvent was evaporated under reduced pressure. To a solution of the residue in THF (4 mL) were added triethylamine (0.033 mL) and di-tert-butyl dicarbonate (52
10 mg), and the mixture was stirred at room temperature for 1 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. To the residue was
15 added a solution (4 M, 3 mL) of hydrogen chloride in ethyl acetate, and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure, 8 M aqueous sodium hydroxide solution (3 mL) was added, and the mixture was stirred at 90°C overnight. Water was added to the
20 reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. To the residue was added a solution (4 M, 3 mL) of hydrogen chloride in ethyl acetate. The solvent was
25 evaporated under reduced pressure to give the title compound (7 mg).

MS (ESI+): [M+H]⁺ 292.1.

[0703]

Example 75

30 2-[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]propan-2-ol monohydrochloride

[0704]

A) 4-tert-butyl 6-methyl (6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4,6-dicarboxylate

35 To a mixed solution of (6R,7R)-4-(tert-butoxycarbonyl)-7-

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(3,4-dichlorophenyl)-1,4-oxazepane-6-carboxylic acid (0.82 g)

in toluene (10 mL) and methanol (2 mL) was added

trimethylsilyldiazomethane (1.576 mL, 2 mol/l hexane solution)

at 0°C and the mixture was stirred for 30 min. Acetic acid was

5 added until the solution became colorless. The solvent was

evaporated under reduced pressure, and the residue was

extracted with ethyl acetate and water. The organic layer was

washed with brine, and dried over anhydrous sodium sulfate.

The solvent was evaporated under reduced pressure to give the

10 title compound (0.51 g).

¹H NMR (300 MHz, CDCl₃) δ 1.48 (9H, s), 2.84-2.99 (1H, m),

3.32-3.56 (1H, m), 3.60 (3H, s), 3.63-4.04 (4H, m), 4.09-4.19

(1H, m), 4.70-4.83 (1H, m), 7.13 (1H, dd, J = 8.3, 2.3 Hz),

7.37 (1H, d, J = 8.3 Hz), 7.43 (1H, d, J = 1.9 Hz).

15 MS (ESI+): [M+H-Boc]⁺ 304.1.

[0705]

B) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-(1-hydroxy-1-methylethyl)-1,4-oxazepane-4-carboxylate

To a solution of 4-tert-butyl 6-methyl (6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4,6-dicarboxylate (0.51 g) in THF (10 mL) was added methyllithium (925 µL, 3 mol/L diethyl ether solution) at -78°C, and the mixture was stirred for 3 hr. A saturated ammonium chloride solution was added at -78°C to discontinue the reaction, and the mixture was warmed to room temperature, and partitioned with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give the title
30 compound (0.12 g).

¹H NMR (300 MHz, CDCl₃) δ 0.91-1.31 (6H, m), 1.50 (9H, s),

2.32-2.43 (1H, m), 3.04-4.35 (7H, m), 4.61-4.74 (1H, m), 7.21

(1H, dd, J = 8.3, 2.3 Hz), 7.42 (1H, d, J = 8.3 Hz), 7.47 (1H,

d, J = 1.9 Hz).

35 [0706]

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C) 2-[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]propan-2-ol monohydrochloride

To a solution of tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-(1-hydroxy-1-methylethyl)-1,4-oxazepane-4-carboxylate (0.12 g) in ethyl acetate (1 mL) was added 4 N hydrogen chloride/ethyl acetate solution (1 mL) at room temperature, and the mixture was stirred overnight. The solvent was evaporated under reduced pressure to give the title compound (0.10 g).

¹H NMR (300 MHz, DMSO-d₆) δ 1.01 (6H, d, J = 5.7 Hz), 2.71-2.81 (1H, m), 3.09 (2H, t, J = 4.5 Hz), 3.24-3.31 (1H, m), 3.48-3.68 (2H, m), 3.80-3.93 (1H, m), 4.82 (1H, d, J = 8.3 Hz), 7.50-7.56 (1H, m), 7.63-7.69 (1H, m), 7.82-7.85 (1H, m), 3H not detected.

[0707]

Example 76

2-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methoxy}benzonitrile monohydrochloride

[0708]

Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-{[(methylsulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 44, step A and Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 377.0.

[0709]

Example 77

2-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methoxy}benzoic acid monohydrochloride

[0710]

Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-{[(methylsulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 44, step A, Example 58, step B and Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 395.9.

[0711]

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Example 78

2-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methoxy}-
6-fluorobenzoic acid monohydrochloride

[0712]

5 Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-
{[(methanesulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate, and
in the same manner as in Example 44, step A, Example 58, step
B and Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 414.1.

10 [0713]

Example 79

methyl 2-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
yl]methoxy}benzoate monohydrochloride

[0714]

15 Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-
{[(methanesulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate, and
in the same manner as in Example 44, step A and Example 39,
step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 410.0.

20 [0715]

Example 80

2-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methoxy}-
N-(methanesulfonyl)benzamide monohydrochloride

[0716]

25 A) tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-
{[2-(methoxycarbonyl)phenoxy]methyl}-1,4-oxazepane-4-carboxylate

Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-
{[(methanesulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate (300
mg), and in the same manner as in Example 44, step A, the
30 title compound (260 mg) was obtained.

MS (ESI+): [M+H-Boc]⁺ 410.2.

[0717]

B) 2-{[(6S,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-
1,4-oxazepan-6-yl]methoxy}benzoic acid

35 Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-
{[2-

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(methoxycarbonyl)phenoxy)methyl}-1,4-oxazepane-4-carboxylate

(260 mg), and in the same manner as in Example 58, step B, the title compound (260 mg) was obtained.

MS (ESI+): [M+H-Boc]⁺ 396.1.

5 [0718]

C) tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-({2-[(methysulfonyl)carbamoyl]phenoxy)methyl}-1,4-oxazepane-4-carboxylate

To a solution of 2-{{[(6S,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methoxy}benzoic acid
10 (100 mg) in DMF (1 mL) were added methanesulfonamide (38.3 mg), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (62.5 mg) and N,N-dimethyl-4-aminopyridine (49.2 mg) at room temperature, and the mixture was stirred at room
15 temperature for 2 hr. The reaction mixture was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography
20 (hexane/ethyl acetate) to give the title compound (40 mg).

MS (ESI+): [M+H-Boc]⁺ 472.9.

[0719]

D) 2-{{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methoxy}-N-(methysulfonyl)benzamide monohydrochloride.

25 Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-({2-[(methysulfonyl)carbamoyl]phenoxy)methyl}-1,4-oxazepane-4-carboxylate (40 mg), and in the same manner as in Example 58, step C, the title compound (17 mg) was obtained.

MS (ESI+): [M+H]⁺ 473.2.

30 [0720]

Example 81

3-{{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methoxy}-N-(methysulfonyl)benzamide monohydrochloride

[0721]

35 In the same manner as in Example 80, the title compound

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was obtained.

MS (ESI+): [M+H]⁺ 473.0.

[0722]

Example 82

5 (6S,7R)-7-(3,4-dichlorophenyl)-6-([2-(methysulfonyl)phenoxy]methyl)-1,4-oxazepane
monohydrochloride

[0723]

In the same manner as in Example 44, step A and Example
10 38, step F, the title compound was obtained.

MS (ESI+): [M+H]⁺ 430.3.

[0724]

Example 83

3-(2-([(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
15 yl]methoxy}phenyl)-1,2,4-oxadiazol-5(4H)-one monohydrochloride

[0725]

Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-
{[(methysulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate, and
in the same manner as in Example 44, step A, Example 31, step
20 D and Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 436.0.

[0726]

Example 84

3-(3-([(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
25 yl]methoxy}phenyl)-1,2,4-oxadiazol-5(4H)-one monohydrochloride

[0727]

In the same manner as in Example 44, step A and Example
43, steps B and C, the title compound was obtained.

MS (ESI+): [M+H]⁺ 436.0.

30 [0728]

Example 85

3-(3-([(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
yl]methoxy}phenyl)-1,2,4-oxadiazole-5(4H)-thione
monohydrochloride

35 [0729]

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Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-
{[(methanesulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate, and
in the same manner as in Example 44, step A, Example 31, step
D and Example 39, step B, the title compound was obtained.

5 MS (ESI+): [M+H]⁺ 452.0.

[0730]

Example 86

3-(2-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
yl]methoxy}pyridin-3-yl)-1,2,4-oxadiazol-5(4H)-one

10 monohydrochloride

[0731]

In the same manner as in Example 44, step A and Example
43, steps B and C, the title compound was obtained.

MS (ESI+): [M+H]⁺ 436.9.

15 [0732]

Example 87

3-(6-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
yl]methoxy}pyridin-3-yl)-1,2,4-oxadiazol-5(4H)-one

monohydrochloride

20 [0733]

In the same manner as in Example 44, step A and Example
43, steps B and C, the title compound was obtained.

MS (ESI+): [M+H]⁺ 437.0.

[0734]

25 Example 88

3-[3-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
yl]methoxy}methyl)phenyl]-1,2,4-oxadiazol-5(4H)-one

monohydrochloride

[0735]

30 A) tert-butyl (6S,7R)-6-{[(3-cyanobenzyl)oxy]methyl}-7-(3,4-
dichlorophenyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6S,7R)-7-(3,4-
dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate

(144.5 mg) in DMF (3 mL) was added 60% sodium hydride (36.9

35 mg) at 0°C, and the mixture was stirred for 30 min. 3-

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(Bromomethyl)benzonitrile (90 mg) was added, and the mixture

was warmed to room temperature and stirred overnight. The

reaction mixture was poured into water, and the mixture was

extracted twice with ethyl acetate. The organic layers were

5 combined, and the mixture was washed with brine, and dried

over anhydrous magnesium sulfate. The solvent was evaporated

under reduced pressure. The residue was purified by silica gel

column chromatography (ethyl acetate/hexane) to give the title

compound (162 mg).

10 ^1H NMR (300 MHz, CDCl_3) δ 1.49 (9H, s), 2.13-2.27 (1H, m),
3.14-3.38 (2H, m), 3.45-3.96 (5H, m), 4.02-4.17 (1H, m), 4.21-
4.42 (3H, m), 7.12 (1H, dd, $J = 8.3, 1.9$ Hz), 7.35-7.69 (6H,
m).

[0736]

15 B) 3-[3-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
yl]methoxy)methyl}phenyl]-1,2,4-oxadiazol-5(4H)-one
monohydrochloride

tert-Butyl (6S,7R)-6-{[(3-cyanobenzyl)oxy]methyl}-7-(3,4-
dichlorophenyl)-1,4-oxazepane-4-carboxylate was reacted under
20 conditions similar to those in Example 31, steps D and E to
give the title compound.

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 2.58-2.74 (1H, m), 3.10-3.55 (6H,
m), 3.76-3.90 (1H, m), 3.97-4.12 (1H, m), 4.32-4.41 (1H, m),
4.44-4.55 (2H, m), 7.31 (1H, dd, $J = 8.3, 1.5$ Hz), 7.45-7.64
25 (4H, m), 7.70-7.78 (2H, m), 3H not detected.

MS (ESI+): $[\text{M}+\text{H}]^+$ 450.1.

[0737]

Example 89

3-(2-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
30 yl]methoxy}pyridin-4-yl)-1,2,4-oxadiazol-5(4H)-one
monohydrochloride

[0738]

In the same manner as in Example 44, step A and Example
43, steps B and C, the title compound was obtained.

35 MS (ESI+): $[\text{M}+\text{H}]^+$ 436.9.

[0739]

Example 90

(6R,7R)-7-(3,4-dichlorophenyl)-6-[(methylsulfonyl)methyl]-1,4-oxazepane monohydrochloride

5 [0740]

Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-[[methylsulfonyl]oxy]methyl}-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 5, step B, and Example 39, step B, the title compound was obtained.

10 MS (ESI+): $[M+H]^+$ 306.1.

[0741]

Example 91

(6R,7R)-7-(3,4-dichlorophenyl)-6-[(methylsulfinyl)methyl]-1,4-oxazepane monohydrochloride

15 [0742]

Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-[[methylsulfonyl]oxy]methyl}-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 5, steps B and C and Example 39, step B, the title compound was obtained.

20 MS (ESI+): $[M+H]^+$ 322.0.

[0743]

Example 92

(6R,7R)-7-(3,4-dichlorophenyl)-6-[(methylsulfonyl)methyl]-1,4-oxazepane monohydrochloride

25 [0744]

Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-[[methylsulfonyl]oxy]methyl}-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 5, steps B, C and D, the title compound was obtained.

30 MS (ESI+): $[M+H]^+$ 338.3.

[0745]

Example 93

(6S,7S)-7-(3,4-dichlorophenyl)-6-[(methylsulfonyl)methyl]-1,4-oxazepane monohydrochloride

35 [0746]

Using tert-butyl (6R,7S)-7-(3,4-dichlorophenyl)-6-(hydroxymethyl)-1,4-oxazepan-4-carboxylate, and in the same manner as in Example 5, the title compound was obtained.

MS (ESI+): [M+H]⁺ 338.2.

5 [0747]

Example 94

2-({[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}sulfanyl)benzoic acid monohydrochloride

[0748]

10

Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-({[(methanesulfonyl)oxy]methyl})-1,4-oxazepan-4-carboxylate, and in the same manner as in Example 44, step A, Example 58, step B and Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 412.0.

15 [0749]

Example 95

2-({[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}sulfonyl)benzoic acid monohydrochloride

[0750]

20

Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-({[(methanesulfonyl)oxy]methyl})-1,4-oxazepan-4-carboxylate, and in the same manner as in Example 44, step A, Example 5, step C, Example 58, step B and Example 39, step B, the title compound was obtained.

25 MS (ESI+): [M+H]⁺ 443.9.

[0751]

Example 96

3-[3-({[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}sulfonyl)phenyl]-1,2,4-oxadiazol-5(4H)-one

30 monohydrochloride

[0752]

Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-({[(methanesulfonyl)oxy]methyl})-1,4-oxazepan-4-carboxylate and, 3-sulfanylbenzonitrile, and in the same manner as in Example 44, step A, Example 5, step C and Example 31, steps D and E,

the title compound was obtained.

MS (ESI+): [M+H]⁺ 484.1.

[0753]

Example 97

5 1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}azetidine-3-carboxylic acid monohydrochloride

Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-
{[(methanesulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate, and
in the same manner as in Example 44, step A, Example 58, step
10 B and Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 359.1.

[0754]

Example 98

15 N-{[(6R,7S)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}acetamide monofumarate

[0755]

Using tert-butyl (6R,7S)-7-(3,4-dichlorophenyl)-6-
{[(methanesulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate, and
in the same manner as in Example 6, steps A, B and C and
20 Example 32, step D, the title compound was obtained.

MS (ESI+): [M+H]⁺ 317.0.

[0756]

Example 99

25 N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
N-methylacetamide monohydrochloride

[0757]

A) tert-butyl (6R,7R)-6-{[acetyl(methyl)amino]methyl}-7-(3,4-
dichlorophenyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7R)-6-
30 [(acetylamino)methyl]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-
carboxylate (180 mg) in THF (4 mL) was added sodium hydride
(32 mg, 60%) under ice-cooling, and the mixture was stirred
under ice-cooling for 30 min. To the reaction mixture was
added methyl iodide (0.107 mL) under ice-cooling, and the
35 mixture was stirred at room temperature overnight. The

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reaction mixture was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (100 mg).

MS (ESI+): $[M+H]^+$ 431.3.

[0758]

B) N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-N-methylacetamide monohydrochloride

To tert-butyl (6R,7R)-6-{[acetyl(methyl)amino]methyl}-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (100 mg) was added 4.0 M hydrogen chloride-ethyl acetate solution (4 mL), and the mixture was stirred at room temperature for 1 hr. The residue obtained by concentration under reduced pressure was separated by HPLC (C18, mobile phase: water/acetonitrile (containing 10 mM NH_4HCO_3)), and the obtained fraction was concentrated under reduced pressure to give the title compound (60 mg).

MS (ESI+): $[M+H]^+$ 331.3.

[0759]

Example 100

N-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepan-6-yl]methyl}acetamide monohydrochloride

[0760]

A) tert-butyl (6RS,7SR)-6-(azidomethyl)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (3RS,4SR)-4-(3,4-dichlorophenyl)-1,5-dioxo-8-azaspiro[2.6]nonane-8-carboxylate (460 mg) in DMF (5 mL) was added sodium azide (240 mg), and the mixture was stirred at 80°C overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel

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column chromatography to give the title compound (232 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.52 (9H, s), 2.96-3.10 (1H, m), 3.09-3.27 (1H, m), 3.29-4.22 (7H, m), 4.27 (1H, s), 7.19 (1H, brs), 7.42 (1H, d, J = 7.9 Hz), 7.45-7.59 (1H, m).

5 [0761]

B) tert-butyl (6SR,7SR)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepane-4-carboxylate

Using tert-butyl (6RS,7SR)-6-(azidomethyl)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepane-4-carboxylate (230 mg), and in the same manner as in Example 62, step I, the title compound was obtained.

MS (ESI⁺): [M+H]⁺ 391.2.

[0762]

C) N-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepan-6-yl]methyl}acetamide monohydrochloride

Using tert-butyl (6SR,7SR)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepane-4-carboxylate (1/2 weight), and in the same manner as in Example 62, step J, tert-butyl (6SR,7SR)-6-[(acetylamino)methyl]-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepane-4-carboxylate (45 mg) was obtained.

Using the obtained tert-butyl (6SR,7SR)-6-[(acetylamino)methyl]-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepane-4-carboxylate (45 mg), and in the same manner as in Example 39, step B, the title compound (20 mg) was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 1.87 (3H, s), 2.76-2.97 (2H, m), 2.96-3.26 (4H, m), 3.70-4.00 (1H, m), 4.08-4.30 (1H, m), 4.58 (1H, s), 5.64 (1H, s), 7.43 (1H, dd, J = 8.3, 1.9 Hz), 7.61 (1H, d, J = 8.3 Hz), 7.69 (1H, d, J = 1.9 Hz), 8.08 (1H, t, J = 5.9 Hz), 8.33 (1H, brs), 9.69 (1H, brs).

MS (ESI⁺): [M+H]⁺ 333.1.

[0763]

Example 101

N-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-6-methoxy-1,4-oxazepan-6-yl]methyl}acetamide monohydrochloride

[0764]

A) tert-butyl (6RS,7SR)-6-(azidomethyl)-7-(3,4-dichlorophenyl)-6-methoxy-1,4-oxazepane-4-carboxylate

Under ice-cooling, sodium hydride (60% oil, 8 mg) was added to a solution of tert-butyl (6RS,7SR)-6-(azidomethyl)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepane-4-carboxylate (120 mg) in DMF (5 mL). The mixture was stirred at room temperature for 20 min, methyl iodide (122 mg) was added, and the mixture was stirred at the same temperature for 30 min. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (115 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.50 (9H, s), 2.07-2.82 (1H, m), 2.92-4.78 (11H, m), 7.02-7.23 (1H, m), 7.32-7.60 (2H, m).

[0765]

B) tert-butyl (6SR,7SR)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-6-methoxy-1,4-oxazepane-4-carboxylate

Using tert-butyl (6RS,7SR)-6-(azidomethyl)-7-(3,4-dichlorophenyl)-6-methoxy-1,4-oxazepane-4-carboxylate (115 mg), and in the same manner as in Example 62, step I, the title compound was obtained.

MS (ESI⁺): [M+H]⁺ 405.2.

[0766]

C) tert-butyl (6SR,7SR)-6-[(acetylamino)methyl]-7-(3,4-dichlorophenyl)-6-methoxy-1,4-oxazepane-4-carboxylate

Using tert-butyl (6SR,7SR)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-6-methoxy-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 62, step J, the title compound (56 mg) was obtained.

MS (ESI⁺): [M+H]⁺ 447.3.

[0767]

D) N-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-6-methoxy-1,4-

oxazepan-6-yl)methyl}acetamide monohydrochloride

Using tert-butyl (6SR,7SR)-6-[(acetylamino)methyl]-7-(3,4-dichlorophenyl)-6-methoxy-1,4-oxazepane-4-carboxylate (56 mg), and in the same manner as in Example 39, step B, the
5 title compound (37 mg) was obtained.

MS (ESI+): [M+H]⁺ 347.1.

[0768]

Example 102

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
10 yl)methyl}propanamide monohydrochloride

[0769]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 32, step C and Example 39, step B, the
15 title compound was obtained.

MS (ESI+): [M+H]⁺ 331.3.

[0770]

Example 103

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
20 yl)methyl}butanamide monohydrochloride

[0771]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 32, step C and Example 39, step B, the
25 title compound was obtained.

MS (ESI+): [M+H]⁺ 345.4.

[0772]

Example 104

2-cyano-N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
30 yl)methyl}acetamide monohydrochloride

[0773]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 39, the title compound was obtained.
35 MS (ESI+): [M+H]⁺ 342.1.

[0774]

Example 105

2-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}amino)-2-oxoethyl acetate monofumarate

5 [0775]

A) tert-butyl (6R,7R)-6-({[(acetyloxy)acetyl]amino}methyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 6, step C, the title compound was obtained.

MS (ESI+): [M+H-Boc]⁺ 375.1.

[0776]

15 B) 2-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}amino)-2-oxoethyl acetate monofumarate

Using tert-butyl (6R,7R)-6-({[(acetyloxy)acetyl]amino}methyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 32, step D, the title compound was obtained.

20 MS (ESI+): [M+H]⁺ 375.1.

[0777]

Example 106

N-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-2-hydroxyacetamide 0.5 fumarate

25 [0778]

A) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-({[(hydroxyacetyl)amino]methyl}-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (171 mg) in dimethoxyethane (3 mL) was added 1 N aqueous sodium hydroxide solution (0.72 mL), and the mixture was stirred overnight. The solvent was evaporated under reduced pressure. Water was added to the residue, and the mixture was extracted twice with ethyl acetate. The combined organic layers were washed with brine, and dried over anhydrous magnesium sulfate. The solvent was

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evaporated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to give the title compound (157 mg).

MS (ESI+): [M+H-t-Bu]⁺ 376.9.

5 [0779]

B) N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-2-hydroxyacetamide 0.5 fumarate

Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-{[(hydroxyacetyl)amino]methyl}-1,4-oxazepane-4-carboxylate,

10 and in the same manner as in Example 32, step D, the title compound was obtained.

MS (ESI+): [M+H]⁺ 333.1.

[0780]

Example 107

15 N-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepan-6-yl]methyl}-2-methoxyacetamide monohydrochloride

[0781]

Using tert-butyl (6RS,7SR)-6-(azidomethyl)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepane-4-carboxylate (1/2

20 weight) obtained in Example 100, step A, and in the same manner as in Example 38, step E, tert-butyl (6SR,7SR)-7-(3,4-dichlorophenyl)-6-hydroxy-6-{[(methoxyacetyl)amino]methyl}-1,4-oxazepane-4-carboxylate (55 mg) was obtained.

MS (ESI+): [M-H]⁺ 461.0.

25 Using obtained tert-butyl (6SR,7SR)-7-(3,4-dichlorophenyl)-6-hydroxy-6-{[(methoxyacetyl)amino]methyl}-1,4-oxazepane-4-carboxylate (55 mg), and in the same manner as in Example 39, step B, the title compound (35 mg) was obtained.

30 MS (ESI+): [M+H]⁺ 363.1.

[0782]

Example 108

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-2-phenoxyacetamide monohydrochloride

35 [0783]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate and 2-phenoxyacetic acid, and in the same manner as in Example 39, the title compound was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 2.81-2.95 (1H, m), 3.00-3.25 (2H, m), 3.70-3.85 (1H, m), 3.91-4.08 (2H, m), 4.38 (1H, d, J = 10.2 Hz), 4.44 (3H, s), 6.88-7.02 (4H, m), 7.25-7.37 (3H, m), 7.40-7.50 (1H, m), 7.66 (1H, d, J = 8.3 Hz), 7.76 (1H, d, J = 1.9 Hz), 8.26-8.38 (1H, m), 8.78-9.42 (2H, m).

MS (ESI⁺): [M+H]⁺ 409.1.

[0784]

Example 109

2-[2-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}amino)-2-oxoethoxy]benzoic acid monohydrochloride

[0785]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate and 2-(2-methoxycarbonyl)phenoxy)acetic acid, and in the same manner as in Example 39, step A and Example 44, step B, the title compound was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 2.87-4.09 (10H, m), 4.37-4.62 (3H, m), 7.00-7.14 (2H, m), 7.37-7.59 (2H, m), 7.60-7.67 (1H, m), 7.68-7.84 (2H, m), 8.39-8.90 (2H, m), 1H not detected.

MS (ESI⁺): [M+H]⁺ 453.1.

[0786]

Example 110

N-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-2-[2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)phenoxy]acetamide monohydrochloride

[0787]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate and 2-cyanophenoxyacetic acid, and in the same manner as in Example 39, step A and Example 31, steps D and E, the title compound was obtained.

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¹H NMR (300 MHz, DMSO-d₆) δ 2.55-2.76 (1H, m), 2.92-3.43 (6H, m), 3.81 (1H, td, J = 9.1, 4.5 Hz), 3.94-4.05 (1H, m), 4.41 (1H, d, J = 10.2 Hz), 4.65 (2H, s), 7.09-7.21 (2H, m), 7.44 (1H, dd, J = 8.3, 1.9 Hz), 7.56-7.67 (2H, m), 7.71-7.77 (2H, m), 8.51 (1H, brs), 8.83-9.58 (2H, m), 12.41-12.86 (1H, m).
MS (ESI+): [M+H]⁺ 493.0.

[0788]

Example 111

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
N-(2-hydroxyethyl)-2-pyrrolidin-1-ylacetamide dihydrochloride
[0789]

A) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-{[(2-hydroxyethyl)amino]methyl}-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-{[(methanesulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate (1.9 g) in ethanol (41.8 mL) was added ethanolamine (7.57 mL), and the mixture was stirred at 80°C overnight. The reaction mixture was concentrated under reduced pressure, distilled water was added, and the mixture was extracted with ethyl acetate. The extract was washed with distilled water and brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to give the title compound (1.65 g).

¹H NMR (300 MHz, CDCl₃) δ 1.49 (9H, s), 2.11-2.24 (1H, m), 2.29-2.42 (1H, m), 2.45-2.64 (2H, m), 2.71-2.84 (1H, m), 3.18-3.78 (6H, m), 3.79-4.04 (2H, m), 4.04-4.20 (2H, m), 7.16 (1H, d, J = 8.0 Hz), 7.38-7.50 (2H, m), 1H not detected.

[0790]

B) tert-butyl (6R,7R)-6-{[(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)amino]methyl}-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

To a solution (13.2 mL) of tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-{[(2-hydroxyethyl)amino]methyl}-1,4-oxazepane-4-carboxylate (1.65 g) and triethylamine (0.605 mL) in THF was added, under ice-cooling, tert-

butylchlorodimethylsilane (654 mg), and the mixture was stirred at room temperature overnight. Then, tert-butylchlorodimethylsilane (654 mg) and triethylamine (0.605 mL) were added, and the mixture was stirred at 50°C for 1 hr.

5 Distilled water was added, and the mixture was extracted with ethyl acetate. The extract was washed with distilled water and brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (1.96 g).

¹H NMR (300 MHz, CDCl₃) δ -0.08 (6H, s), 0.77 (9H, s), 1.40 (9H, d, J = 4.5 Hz), 1.96-2.11 (1H, m), 2.19-2.55 (4H, m), 3.24-3.40 (1H, m), 3.44-3.78 (6H, m), 3.92-4.12 (2H, m), 7.06 (1H, d, J = 7.9 Hz), 7.26-7.36 (2H, m), 1H not detected.

15 [0791]

C) tert-butyl (6R,7R)-6-{[(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)(pyrrolidin-1-ylacetyl)amino]methyl}-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

20 Using tert-butyl (6R,7R)-6-{[(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)amino]methyl}-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (180 mg), and in the same manner as in Example 39, step A, the title compound (118 mg) was obtained.

25 ¹H NMR (300 MHz, CDCl₃) δ -0.10--0.04 (6H, m), 0.81 (9H, s), 1.49 (9H, s), 1.70-1.84 (4H, m), 2.25-2.65 (5H, m), 2.83-3.81 (13H, m), 3.98-4.21 (2H, m), 7.08-7.46 (3H, m).

[0792]

30 D) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-{[(2-hydroxyethyl)(pyrrolidin-1-ylacetyl)amino]methyl}-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7R)-6-{[(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)(pyrrolidin-1-ylacetyl)amino]methyl}-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (118 g) in THF (0.6 mL) was added, under ice-

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cooling, a solution (1.0 M, 0.219 mL) of tetrabutylammonium fluoride in THF, and the mixture was stirred at room temperature overnight. To the reaction mixture was added distilled water, and the mixture was extracted with ethyl acetate. The extract was washed with distilled water and brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (NH, hexane/ethyl acetate/methanol) to give the title compound (81.3 mg).

10 MS (ESI+): $[M+H]^+$ 530.1.

[0793]

E) N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-N-(2-hydroxyethyl)-2-pyrrolidin-1-ylacetamide dihydrochloride

15 Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-{[(2-hydroxyethyl)(pyrrolidin-1-ylacetyl)amino]methyl}-1,4-oxazepane-4-carboxylate (81.3 mg), and in the same manner as in Example 38, step F, the title compound (56.9 mg) was obtained.

20 MS (ESI+): $[M+H]^+$ 430.4.

[0794]

Example 112

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-2-(methylsulfanyl)acetamide monofumarate

25 [0795]

A) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-({[(methylsulfanyl)acetyl]amino}methyl)-1,4-oxazepane-4-carboxylate

30 Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 6, step C and Example 5, step B, the title compound was obtained.

MS (ESI+): $[M+H]^+$ 463.1.

[0796]

35 B) N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-

yl)methyl}-2-(methysulfanyl)acetamide monofumarate

Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-
({[(methysulfanyl)acetyl]amino)methyl)-1,4-oxazepane-4-
carboxylate, and in the same manner as in Example 32, step D,
5 the title compound was obtained.

MS (ESI+): [M+H]⁺ 362.9.

[0797]

Example 113

N-{{[(6R,7S)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl)methyl]-
10 2-(methysulfanyl)acetamide monohydrochloride

[0798]

Using tert-butyl (6S,7S)-6-(aminomethyl)-7-(3,4-
dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same
manner as in Example 112, the title compound was obtained.

15 MS (ESI+): [M+H]⁺ 362.9.

[0799]

Example 114

N-{{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl)methyl]-
2-(methysulfonyl)acetamide monohydrochloride

20 [0800]

A) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-
({[(methysulfonyl)acetyl]amino)methyl)-1,4-oxazepane-4-
carboxylate

Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-
25 ({[(methysulfanyl)acetyl]amino)methyl)-1,4-oxazepane-4-
carboxylate, and in the same manner as in Example 5, step C,
the title compound was obtained.

MS (ESI+): [M+H-Boc]⁺ 395.0.

[0801]

30 B) N-{{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
yl)methyl]-2-(methysulfonyl)acetamide monohydrochloride

Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-
({[(methysulfonyl)acetyl]amino)methyl)-1,4-oxazepane-4-
carboxylate, and in the same manner as in Example 5, step D,
35 the title compound was obtained.

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MS (ESI+): [M+H]⁺ 395.0.

[0802]

Example 115

N-{[(6R,7S)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-

5 2-(methanesulfonyl)acetamide monohydrochloride

[0803]

Using tert-butyl (6S,7S)-7-(3,4-dichlorophenyl)-6-
({[(methanesulfonyl)acetyl]amino}methyl)-1,4-oxazepane-4-
carboxylate, and in the same manner as in Example 114, the
10 title compound was obtained.

MS (ESI+): [M+H]⁺ 395.0.

[0804]

Example 116

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-

15 2-phenylacetamide monohydrochloride

[0805]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-
dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same
manner as in Example 32, step C and Example 39, step B, the
20 title compound was obtained.

MS (ESI+): [M+H]⁺ 393.1.

[0806]

Example 117

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-

25 2-[3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)phenyl]acetamide
monofumarate

[0807]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-
dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same
30 manner as in Example 39, step A, Example 31, step D and
Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 477.1.

[0808]

Example 118

35 N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-

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4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)benzamide

monohydrochloride

[0809]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate and 4-cyanobenzoic acid, and by a method similar to that in Example 39, step A and Example 31, steps D and E, the title compound was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 2.65-2.81 (1H, m), 2.98-3.49 (6H, m), 3.76-3.89 (1H, m), 3.93-4.05 (1H, m), 4.47 (1H, d, J = 10.2 Hz), 7.49 (1H, dd, J = 8.3, 2.3 Hz), 7.67 (1H, d, J = 8.3 Hz), 7.79 (1H, d, J = 1.9 Hz), 7.84-8.00 (5H, m), 8.71-9.55 (3H, m).

MS (ESI⁺): [M+H]⁺ 463.0.

[0810]

Example 119

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-2-(1H-1,2,4-triazol-1-yl)acetamide monohydrochloride

[0811]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-((3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate and 2-(1H-1,2,4-triazol-1-yl)acetic acid, and by a method similar to that in Example 39, steps A and B, the title compound was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 2.54-2.67 (1H, m), 2.93 (2H, t, J = 5.9 Hz), 3.05-3.44 (4H, m), 3.75-3.89 (1H, m), 4.02 (1H, dt, J = 13.6, 4.3 Hz), 4.17-5.10 (3H, m), 7.45 (1H, dd, J = 8.3, 1.9 Hz), 7.62-7.70 (1H, m), 7.75 (1H, d, J = 1.9 Hz), 7.99-8.10 (1H, m), 8.55-8.71 (2H, m), 9.12-9.34 (1H, m), 9.61-9.86 (1H, m).

MS (ESI⁺): [M+H]⁺ 384.1.

[0812]

Example 120

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-2-(1H-tetrazol-1-yl)acetamide monohydrochloride

[0813]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate and 2-(1H-tetrazol-1-yl)acetic acid, and by a method similar to that in Example 39, steps A and B, the title compound was obtained.

5 ¹H NMR (300 MHz, DMSO-d₆) δ 2.55-2.70 (1H, m), 2.90-3.00 (2H, m), 3.07-3.31 (3H, m), 3.07-3.39 (5H, m), 3.96-4.09 (1H, m), 4.43 (1H, d, J = 10.5 Hz), 5.26 (2H, s), 7.45 (1H, dd, J = 8.3, 1.9 Hz), 7.67 (1H, d, J = 8.3 Hz), 7.75 (1H, d, J = 1.9 Hz), 8.74-8.86 (1H, m), 9.10-9.29 (1H, m), 9.37 (1H, s), 9.57-10 9.76 (1H, m).

MS (ESI⁺): [M+H]⁺ 385.0.

[0814]

Example 121

1-[2-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}amino)-2-oxoethyl]-3-methyl-1H-pyrazole-5-carboxylic acid monohydrochloride

[0815]

A) ethyl 1-(2-tert-butoxy-2-oxoethyl)-3-methyl-1H-pyrazole-5-carboxylate

20 In the same manner as in Example 44, step A, the title compound was obtained.

¹H NMR (300 MHz, CDCl₃) δ 1.35 (3H, t, J = 7.2 Hz), 1.46 (9H, s), 2.29 (3H, s), 4.30 (2H, q, J = 7.2 Hz), 5.12 (2H, s), 6.67 (1H, s).

25 MS (ESI⁺): [M+H]⁺ 269.2.

[0816]

B) [5-(ethoxycarbonyl)-3-methyl-1H-pyrazol-1-yl]acetic acid

6 N Hydrochloric acid (4 mL, 24.00 mmol) was added to a solution of ethyl 1-(2-tert-butoxy-2-oxoethyl)-3-methyl-1H-pyrazole-5-carboxylate (324 mg, 1.21 mmol) in THF (4 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. 35 The residue was purified by silica gel column chromatography

to give the title compound (206 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.35 (3H, t, J = 7.2 Hz), 2.29 (3H, s), 4.32 (2H, q, J = 7.2 Hz), 5.33 (2H, s), 6.68 (1H, s), 8.27 (1H, brs).

5 MS (ESI⁺): [M+H]⁺ 211.3.

[0817]

C) 1-[2-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}amino)-2-oxoethyl]-3-methyl-1H-pyrazole-5-carboxylic acid monohydrochloride

10 Using [5-(ethoxycarbonyl)-3-methyl-1H-pyrazol-1-yl]acetic acid, and in the same manner as in Example 39, step A and Example 44, step B, the title compound was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 2.21 (3H, s), 2.53-2.67 (1H, m), 2.94 (2H, t, J = 5.3 Hz), 3.05-3.21 (1H, m), 3.21-3.44 (3H, m), 3.75-3.90 (1H, m), 3.94-4.08 (1H, m), 4.42 (1H, d, J = 10.2 Hz), 4.82 (2H, s), 6.47 (1H, s), 7.45 (1H, dd, J = 8.3, 1.9 Hz), 7.66 (1H, d, J = 8.3 Hz), 7.75 (1H, d, J = 1.9 Hz), 8.59 (1H, t, J = 5.7 Hz), 9.25 (1H, brs), 9.72 (1H, brs), 1H not detected.

20 MS (ESI⁺): [M+H]⁺ 440.9.

[0818]

Example 122

N-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-2-(2-oxopyrrolidin-1-yl)acetamide monohydrochloride

25 Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate and (2-oxopyrrolidin-1-yl)acetic acid, and by a method similar to that in Example 39, the title compound was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 1.85-2.02 (2H, m), 2.17-2.29 (2H, m), 2.79-3.02 (2H, m), 3.06-3.36 (7H, m), 3.66-3.88 (3H, m), 3.93-4.06 (1H, m), 4.38 (1H, d, J = 10.2 Hz), 7.44 (1H, dd, J = 8.3, 1.9 Hz), 7.64-7.70 (1H, m), 7.74 (1H, d, J = 1.9 Hz), 8.09-8.21 (1H, m), 8.96-9.16 (1H, m), 9.37-9.54 (1H, m).

MS (ESI⁺): [M+H]⁺ 400.0.

35 [0819]

Example 123

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)acetamide
monohydrochloride

5 Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 39, step A, Example 31, step D and Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 401.0.

10 [0820]

Example 124

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
2-(2,4-dioxoimidazolidin-1-yl)acetamide monohydrochloride

[0821]

15 In the same manner as in Example 41, the title compound was obtained.

MS (ESI+): [M+H]⁺ 415.0.

[0822]

Example 125

20 1-[2-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}amino)-2-oxoethyl]-5-methyl-1H-pyrazole-3-carboxylic acid monohydrochloride

[0823]

In the same manner as in Example 121, the title compound
25 was obtained.

MS (ESI+): [M+H]⁺ 441.4.

[0824]

Example 126

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
30 yl]methyl}benzamide monohydrochloride

[0825]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 32, step C and Example 39, step B, the
35 title compound was obtained.

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MS (ESI+): [M+H]⁺ 379.0.

[0826]

Example 127

3,5-di-tert-butyl-N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-
5 oxazepan-6-yl]methyl}benzamide monohydrochloride

[0827]

In the same manner as in Example 39, the title compound
was obtained.

MS (ESI+): [M+H]⁺ 491.0.

10 [0828]

Example 128

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
yl]methyl}biphenyl-2-carboxamide monohydrochloride

[0829]

15 In the same manner as in Example 39, the title compound
was obtained.

MS (ESI+): [M+H]⁺ 455.0.

[0830]

Example 129

20 N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
yl]methyl}biphenyl-3-carboxamide monohydrochloride

[0831]

In the same manner as in Example 39, the title compound
was obtained.

25 MS (ESI+): [M+H]⁺ 455.0.

[0832]

Example 130

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
2-hydroxybiphenyl-3-carboxamide monohydrochloride

30 [0833]

In the same manner as in Example 39, the title compound
was obtained.

MS (ESI+): [M+H]⁺ 471.2.

[0834]

35 Example 131

2-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}carbamoyl)benzoic acid monohydrochloride
[0835]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 39, step A, Example 58, step B and Example 39, step B, the title compound was obtained.
MS (ESI+): [M+H]⁺ 423.1.

[0836]

10 Example 132

N-({[(6R*,7S*)-7-(4-chloro-3-methylphenyl)-1,4-oxazepan-6-yl]methyl}methanesulfonamide monohydrochloride
[0837]

Using tert-butyl (6R*,7S*)-7-(4-chloro-3-methylphenyl)-6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 38, steps B to D and Example 34, step A, the title compound was obtained.

MS (ESI+): [M+H]⁺ 333.2.

[0838]

20 Example 133

2-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}carbamoyl)-4,5-difluorobenzoic acid monohydrochloride
[0839]

25 A) 2-({[(6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}carbamoyl)-4,5-difluorobenzoic acid

To a solution of tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (100 mg) in DMF (2 mL) was added 5,6-difluoro-2-benzofuran-1,3-dione (73.6 mg) at room temperature, and the mixture was stirred at 80°C overnight. The reaction mixture was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue

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was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (102 mg).

MS (ESI+): [M+H-t-Bu]⁺ 502.9.

[0840]

- 5 B) 2-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}carbamoyl)-4,5-difluorobenzoic acid monohydrochloride

To 2-({[(6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}carbamoyl)-4,5-difluorobenzoic acid (102 mg) was added 4.0 M hydrogen chloride-ethyl acetate solution (4 mL), and the mixture was stirred at room temperature for 1 hr. The residue obtained by concentration under reduced pressure was separated by HPLC (C18, mobile phase: water/acetonitrile (containing 5 mM AcONH₄)), and the obtained fraction was concentrated under reduced pressure to give the title compound (17 mg).

MS (ESI+): [M+H]⁺ 459.1.

[0841]

Example 134

- 20 N-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl})-2-[(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)methyl]benzamide monohydrochloride

[0842]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 39, step A, Example 31, step D and Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 477.1.

[0843]

30 Example 135

3-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}carbamoyl)benzoic acid monohydrochloride

[0844]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same

manner as in Example 39, step A, Example 58, step B and Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 423.1.

[0845]

5 Example 136

4-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}carbamoyl)benzoic acid monohydrochloride

[0846]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 39, step A, Example 58, step B and Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 423.1.

[0847]

15 Example 137

3-cyano-N-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}benzamide monohydrochloride

[0848]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 39, the title compound was obtained.

MS (ESI+): [M+H]⁺ 404.0.

[0849]

Example 138

25 3-cyano-N-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-N-methylbenzamide monohydrochloride

[0850]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 39, step A, Example 99, step A and Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 418.3.

[0851]

Example 139

35 N-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-

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2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)benzamide
monohydrochloride

[0852]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 39, step A, Example 31, step D and Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 463.3.

[0853]

10 Example 140

3-(2-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methoxy}-6-fluorophenyl)-1,2,4-oxadiazol-5(4H)-one
monohydrochloride

[0854]

15 In the same manner as in Example 44, step A and Example 43, steps B and C, the title compound was obtained.

MS (ESI+): [M+H]⁺ 454.0.

[0855]

Example 141

20 3-(2-chloro-6-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methoxy}phenyl)-1,2,4-oxadiazol-5(4H)-one monohydrochloride

[0856]

In the same manner as in Example 44, step A and Example 43, steps B and C, the title compound was obtained.

25 MS (ESI+): [M+H]⁺ 469.9.

[0857]

Example 142

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)benzamide
30 monohydrochloride

[0858]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 39, step A, Example 31, step D and
35 Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 463.0.

[0859]

Example 143

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
5 N-methyl-3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)benzamide
monohydrochloride

[0860]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same
10 manner as in Example 39, step A, Example 99, step A, Example 31, step D and Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 477.4.

[0861]

15 Example 144

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
3-(1H-tetrazol-5-yl)benzamide monohydrochloride

[0862]

A) tert-butyl (6R,7R)-6-({[(3-cyanophenyl)carbonyl]amino)methyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate
20

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (300 mg), and in the same manner as in Example 39, step A, the title compound
25 (324 mg) was obtained.

MS (ESI+): [M+H-t-Bu]⁺ 448.0.

[0863]

B) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-({[3-(1H-tetrazol-5-yl)phenyl]carbonyl}amino)methyl)-1,4-oxazepane-4-carboxylate
30

To a solution of tert-butyl (6R,7R)-6-({[(3-cyanophenyl)carbonyl]amino)methyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (100 mg) in DMF (4 mL) were added sodium azide (38.7 mg) and ammonium chloride (37.1 mg) at room
35 temperature, and the mixture was stirred at 100°C overnight.

The reaction mixture was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (32 mg).

[M+H-Boc]⁺ 447.2.

[0864]

C) N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-3-(1H-tetrazol-5-yl)benzamide monohydrochloride

Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-[(3-(1H-tetrazol-5-yl)phenyl)carbonyl]amino)methyl]-1,4-oxazepane-4-carboxylate (32 mg), and in the same manner as in Example 58, step C, the title compound (17 mg) was obtained.

MS (ESI⁺): [M+H]⁺ 447.2.

[0865]

Example 145

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}pyridine-2-carboxamide dihydrochloride

[0866]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 32, step C and Example 39, step B, the title compound was obtained.

MS (ESI⁺): [M+H]⁺ 380.0.

[0867]

Example 146

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridine-2-carboxamide monohydrochloride

[0868]

In the same manner as in Example 41, step A and Example 31, steps D and E, the title compound was obtained.

MS (ESI⁺): [M+H]⁺ 464.1.

[0869]

Example 147

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridine-2-
carboxamide monohydrochloride

5 [0870]

In the same manner as in Example 146, the title compound
was obtained.

MS (ESI+): [M+H]⁺ 464.0.

[0871]

10 Example 148

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
4-methyl-1,3-thiazole-5-carboxamide monohydrochloride

[0872]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-
15 dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same
manner as in Example 39, the title compound was obtained.

MS (ESI+): [M+H]⁺ 400.0.

[0873]

Example 149

20 N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
2-oxobutanamide monohydrochloride

[0874]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-
dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same
25 manner as in Example 39, the title compound was obtained.

MS (ESI+): [M+H]⁺ 359.0.

[0875]

Example 150

30 methyl {[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
yl]methyl}carbamate monohydrochloride

[0876]

In the same manner as in Example 38, steps E and F, the
title compound was obtained.

MS (ESI+): [M+H]⁺ 333.4.

35 [0877]

Example 151

1-methylethyl {[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}carbamate monohydrochloride

[0878]

5 In the same manner as in Example 150, the title compound was obtained.

MS (ESI+): [M+H]⁺ 361.1.

[0879]

Example 152

10 1- {[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}urea monofumarate

[0880]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same
15 manner as in Example 3, the title compound was obtained.

MS (ESI+): [M+H]⁺ 318.1.

[0881]

Example 153

1- {[(6R,7S)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}urea monofumarate

20

[0882]

Using tert-butyl (6S,7S)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same
manner as in Example 3, the title compound was obtained.

25 MS (ESI+): [M+H]⁺ 318.1.

[0883]

Example 154

1- {[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-3-ethylurea monohydrochloride

30 [0884]

Using tert-butyl (6RS,7RS)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate and ethyl isocyanate, and in the same manner as in Example 3, the title compound was obtained.

35 MS (ESI+): [M+H]⁺ 346.1.

[0885]

Example 155

1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
3-ethylurea monofumarate

5 [0886]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 154, the title compound was obtained.

MS (ESI+): [M+H]⁺ 346.3.

10 [0887]

Example 156

1-{[(6R,7S)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
3-ethylurea monohydrochloride

[0888]

15 Using tert-butyl (6S,7S)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 154, the title compound was obtained.

MS (ESI+): [M+H]⁺ 346.1.

[0889]

20 Example 157

1-tert-butyl-3-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}urea monohydrochloride

[0890]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepane-4-carboxylate and tert-butyl isocyanate, and by a method similar to that in Example 158, steps A and C, the title compound was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 1.19 (9H, s), 2.69-2.92 (2H, m), 3.06-3.52 (5H, m), 3.72-3.87 (1H, m), 3.94-4.08 (1H, m), 4.36
30 (1H, d, J = 9.8 Hz), 5.67-5.86 (1H, m), 6.02-6.16 (1H, m), 7.43 (1H, dd, J = 8.3, 1.5 Hz), 7.66 (1H, d, J = 8.3 Hz), 7.72 (1H, d, J = 1.5 Hz), 9.05-9.26 (1H, m), 9.48-9.67 (1H, m).

MS (ESI+): [M+H]⁺ 374.2.

[0891]

35 Example 158

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}pyrrolidine-1-carboxamide monohydrochloride
[0892]

A) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-{[(4-nitrophenoxy)carbonylamino]methyl}-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (250.2 mg) and triethylamine (186 μ L) in THF (5 mL) was added 4-nitrophenyl chloroformate (161 mg) at 0°C, and the mixture was stirred overnight. The reaction mixture was poured into water, and the mixture was extracted twice with ethyl acetate. The organic layers were combined, and the mixture was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (295 mg).

^1H NMR (300 MHz, CDCl_3) δ 1.53 (9H, s), 2.26-2.41 (1H, m), 3.00-3.66 (5H, m), 4.02-4.22 (4H, m), 6.97-7.07 (1H, m), 7.21 (1H, dd, $J = 8.3, 1.9$ Hz), 7.30 (2H, d, $J = 9.0$ Hz), 7.41 (1H, d, $J = 8.3$ Hz), 7.48-7.53 (1H, m), 8.19-8.27 (2H, m).
[0893]

B) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-[(pyrrolidine-1-carboxamide)methyl]-1,4-oxazepane-4-carboxylate

A solution of tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-{[(4-nitrophenoxy)carbonylamino]methyl}-1,4-oxazepane-4-carboxylate (187.8 mg), pyrrolidine (35 μ L) and potassium carbonate (96 mg) in DMF (3 mL) was stirred at 80°C overnight. The reaction mixture was poured into water, and the mixture was extracted twice with ethyl acetate. The organic layers were combined, and the mixture was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give the title compound (151 mg).

^1H NMR (300 MHz, CDCl_3) δ 1.49 (9H, s), 1.80-1.93 (3H, m), 2.30

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(1H, d, $J = 6.8$ Hz), 2.78-2.92 (1H, m), 3.09-3.25 (2H, m), 3.26-3.40 (4H, m), 3.47-3.63 (2H, m), 3.90-4.19 (4H, m), 5.79 (1H, d, $J = 1.9$ Hz), 7.21-7.30 (1H, m), 7.37-7.44 (1H, m), 7.51 (1H, s), 8.02 (1H, s).

5 [0894]

C) N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}pyrrolidine-1-carboxamide monohydrochloride

Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-[(pyrrolidine-1-carboxamide)methyl]-1,4-oxazepane-4-carboxylate, and by a method similar to that in Example 39, step B, the title compound was obtained.

^1H NMR (300 MHz, DMSO- d_6) δ 1.66-1.83 (4H, m), 2.58-2.71 (1H, m), 2.77-3.02 (3H, m), 3.04-3.28 (6H, m), 3.29-3.42 (1H, m), 3.77 (1H, ddd, $J = 13.8, 7.8, 3.6$ Hz), 3.88-4.01 (1H, m), 4.39 (1H, d, $J = 10.2$ Hz), 6.19-6.31 (1H, m), 7.45 (1H, dd, $J = 8.7, 2.1$ Hz), 7.66 (1H, d, $J = 8.3$ Hz), 7.74 (1H, d, $J = 1.9$ Hz), 8.92-9.12 (1H, m), 9.35-9.52 (1H, m).

MS (ESI+): $[M+H]^+$ 372.1.

[0895]

20 Example 159

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}morpholine-4-carboxamide monohydrochloride

[0896]

Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-{[(4-nitrophenoxy)carbonylamino]methyl}-1,4-oxazepane-4-carboxylate and morpholine, and by a method similar to that in Example 158, steps B and C, the title compound was obtained.

^1H NMR (300 MHz, DMSO- d_6) δ 2.57-2.71 (1H, m), 2.79-3.01 (2H, m), 3.11-3.26 (6H, m), 3.34 (2H, s), 3.45-3.54 (4H, m), 3.72-3.84 (1H, m), 3.90-4.01 (1H, m), 4.39 (1H, d, $J = 9.8$ Hz), 6.68-6.78 (1H, m), 7.45 (1H, dd, $J = 8.5, 2.1$ Hz), 7.66 (1H, d, $J = 8.3$ Hz), 7.75 (1H, d, $J = 1.9$ Hz), 8.95-9.19 (1H, m), 9.41-9.66 (1H, m).

MS (ESI+): $[M+H]^+$ 388.0.

35 [0897]

Example 160

1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
1-(2-hydroxyethyl)-3-methylurea monohydrochloride
[0898]

5 Using tert-butyl (6R,7R)-6-{[(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)amino]methyl}-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 38, step E and Example 111, steps D and E, the title compound was obtained.

10 MS (ESI+): [M+H]⁺ 376.1.
[0899]

Example 161

N-{[(6R,7S)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}methanesulfonamide monohydrochloride

15 [0900]

Using tert-butyl (6S,7S)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 8, the title compound was obtained.

MS (ESI+): [M+H]⁺ 353.0.

20 [0901]

Example 162

N-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepan-6-yl]methyl}methanesulfonamide monohydrochloride

[0902]

25 A) tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-hydroxy-6-
{[(methanesulfonyl)amino]methyl}-1,4-oxazepane-4-carboxylate

Triphenylphosphine (330 mg) was added to a solution of tert-butyl (6RS,7SR)-6-(azidomethyl)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepane-4-carboxylate (120 mg) in acetonitrile
30 (5 mL), and the mixture was stirred at 80°C overnight. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced
35 pressure. To a solution of the residue in THF (5 mL) were

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successively added dropwise triethylamine (0.11 mL) and methanesulfonyl chloride (86 mg), and the mixture was stirred at 0°C for 1 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography and HPLC to give the title compound (133 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.51 (9H, s), 2.16 (1H, s), 2.79-2.93 (1H, m), 2.95 (3H, s), 2.99-3.13 (1H, m), 3.15-3.41 (2H, m), 3.46-3.79 (1H, m), 3.90-4.25 (3H, m), 4.41 (1H, s), 6.31 (1H, brs), 7.24 (1H, brs), 7.43 (1H, d, J = 8.3 Hz), 7.54 (1H, s). MS (ESI⁺): [M+H]⁺ 467.0.

[0903]

B) N-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepan-6-yl]methyl}methanesulfonamide monohydrochloride

Using tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-hydroxy-6-[(methylsulfonyl)amino]methyl}-1,4-oxazepane-4-carboxylate (133 mg), and in the same manner as in Example 39, step B, the title compound (99 mg) was obtained.

MS (ESI⁺): [M+H]⁺ 369.1.

[0904]

Example 163

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-2-methoxyethanesulfonamide monohydrochloride

[0905]

A) tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-[(ethenylsulfonyl)amino]methyl}-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (633 mg) in THF (10 mL) were added triethylamine (0.705 mL) and 2-chloroethanesulfonyl chloride (0.213 mL) at 0°C, and the mixture was gradually warmed from 0°C to room temperature, and stirred overnight. The reaction mixture was diluted with ethyl acetate. The diluted solution was washed with distilled water

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and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (0.965 g).

5 MS (ESI+): [M+H-Boc]⁺ 365.2.

[0906]

B) tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-({[(2-methoxyethyl)sulfonyl]amino}methyl)-1,4-oxazepane-4-carboxylate

10 To a solution of tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-({[(ethenylsulfonyl)amino]methyl}-1,4-oxazepane-4-carboxylate (200 mg) in methanol (1 mL) was added 28% sodium methoxide-methanol (4 mL) solution at room temperature, and the mixture was stirred at 60°C for 4 hr. The
15 reaction mixture was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title
20 compound (132 mg).

MS (ESI+): [M+H-Boc]⁺ 397.0.

[0907]

C) N-{{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-2-methoxyethanesulfonamide monohydrochloride

25 Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-({[(2-methoxyethyl)sulfonyl]amino}methyl)-1,4-oxazepane-4-carboxylate (132 mg), and in the same manner as in Example 58, step C, the title compound (81 mg) was obtained.

MS (ESI+): [M+H]⁺ 397.0.

30 [0908]

Example 164

N-{{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-2-(morpholin-4-yl)ethanesulfonamide dihydrochloride

[0909]

35 Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-

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dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 163, the title compound was obtained.

MS (ESI+): [M+H]⁺ 452.3.

[0910]

5 Example 165

N-([[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl]-1,1,1-trifluoromethanesulfonamide monohydrochloride

[0911]

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 32, step C and Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 406.9.

[0912]

15 Example 166

3-([[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl]sulfamoyl)benzoic acid monohydrochloride

[0913]

In the same manner as in Example 38, step E and Example 20 44, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 458.9.

[0914]

Example 167

3-[2-([[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl]sulfonyl)phenyl]-1,2,4-oxadiazol-5(2H)-one monohydrochloride

[0915]

A) tert-butyl (6R,7R)-6-([[(2-bromophenyl)sulfanyl]methyl]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

30 Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-([[(methylsulfonyl)oxy]methyl]-1,4-oxazepane-4-carboxylate (400 mg), and in the same manner as in Example 44, step A, the title compound (424 mg) was obtained.

¹H NMR (300 MHz, CDCl₃) δ 1.50 (9H, s), 2.08-2.29 (1H, m), 2.62-2.87 (2H, m), 3.26-3.80 (3H, m), 3.86-4.26 (4H, m), 6.50-

35

6.89 (1H, m), 6.94-7.16 (3H, m), 7.34-7.52 (3H, m).

[0916]

B) tert-butyl (6R,7R)-6-{[(2-cyanophenyl)sulfanyl]methyl}-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

5 To a solution (7.8 mL) of tert-butyl (6R,7R)-6-{[(2-bromophenyl)sulfanyl]methyl}-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (424 mg) in DMF was added copper cyanide (139 mg), and the mixture was stirred under an argon atmosphere at 150°C overnight. The reaction mixture was
10 filtered through celite, distilled water was added, and the mixture was extracted with ethyl acetate. The extract was washed with distilled water and brine, and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel
15 chromatography (hexane/ethyl acetate) to give the title compound (146 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.51 (9H, s), 2.06-2.27 (1H, m), 2.68-2.98 (2H, m), 3.23-3.82 (3H, m), 3.86-4.26 (4H, m), 6.67-7.15 (2H, m), 7.17-7.47 (4H, m), 7.51-7.59 (1H, m).

20 [0917]

C) tert-butyl (6R,7R)-6-{[(2-cyanophenyl)sulfonyl]methyl}-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

Using tert-butyl (6R,7R)-6-{[(2-cyanophenyl)sulfanyl]methyl}-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (146 mg), and in the same manner as in
25 Example 5, step C, the title compound (133 mg) was obtained.

¹H NMR (300 MHz, CDCl₃) δ 1.45-1.67 (9H, m), 2.08-2.37 (1H, m), 3.04-3.28 (2H, m), 3.46-3.67 (2H, m), 3.80-4.49 (5H, m), 6.88-7.11 (2H, m), 7.27-7.35 (1H, m), 7.53-7.66 (1H, m), 7.67-7.78
30 (2H, m), 7.89-8.08 (1H, m).

[0918]

D) 3-[2-({[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl)sulfonyl}phenyl)-1,2,4-oxadiazol-5(2H)-one monohydrochloride

35 Using tert-butyl (6R,7R)-6-{[(2-

cyanophenyl)sulfonyl)methyl}-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (133 mg), and in the same manner as in Example 31, steps D and E, the title compound (85.7 mg) was obtained.

5 MS (ESI+): $[M+H]^+$ 484.1.

[0919]

Example 168

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl)methyl}-3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)benzenesulfonamide
10 monohydrochloride

[0920]

In the same manner as in Example 38, step E and Example 31, steps D and E, the title compound was obtained.

MS (ESI+): $[M+H]^+$ 499.3.

15 [0921]

Example 169

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl)methyl}pyridine-3-sulfonamide monohydrochloride

[0922]

20 Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 32, step C and Example 39, step B, the title compound was obtained.

MS (ESI+): $[M+H]^+$ 416.0.

25 [0923]

Example 170

6-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl)methyl}sulfamoyl)pyridine-2-carboxylic acid
monohydrochloride

30 [0924]

In the same manner as in Example 166, the title compound was obtained.

MS (ESI+): $[M+H]^+$ 460.0.

[0925]

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5-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}sulfamoyl)pyridine-3-carboxylic acid monohydrochloride

[0926]

5 In the same manner as in Example 166, the title compound was obtained.

MS (ESI+): [M+H]⁺ 460.3.

[0927]

Example 172

10 5-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}sulfamoyl)pyridine-2-carboxylic acid monohydrochloride

[0928]

15 In the same manner as in Example 166, the title compound was obtained.

MS (ESI+): [M+H]⁺ 460.0.

[0929]

Example 173

20 N-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-5-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridine-3-sulfonamide monohydrochloride

[0930]

In the same manner as in Example 168, the title compound was obtained.

25 MS (ESI+): [M+H]⁺ 500.2.

[0931]

Example 174

N-({[(6R,7S)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}sulfamide monohydrochloride

30 [0932]

Using tert-butyl (6S,7S)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 9, the title compound was obtained.

MS (ESI+): [M+H]⁺ 354.2.

35 [0933]

Example 175

N-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
N'-methoxysulfamide monohydrochloride

[0934]

- 5 Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate and o-methylhydroxylamine, and in the same manner as in Example 9, the title compound was obtained.

MS (ESI+): [M+H]⁺ 383.9.

10 [0935]

Example 176

2-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}amino)pyridine-3-carboxylic acid monohydrochloride
[0936]

- 15 A) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-({[3-(methoxycarbonyl)pyridin-2-yl]amino}methyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (200 mg) in
20 DMF (4 mL) were added potassium carbonate (110 mg) and methyl 2-chloronicotinate (137 mg) at room temperature, and the mixture was stirred at 100°C for 48 hr. The reaction mixture was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried over
25 anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (120 mg).

MS (ESI+): [M+H]⁺ 510.4.

30 [0937]

B) 2-({[(6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}amino)pyridine-3-carboxylic acid

Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-({[3-(methoxycarbonyl)pyridin-2-yl]amino}methyl)-1,4-oxazepane-4-

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carboxylate (120 mg), and in the same manner as in Example 58, step B, the title compound (60 mg) was obtained.

MS (ESI+): [M+H]⁺ 496.3.

[0938]

5 C) 2-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}amino)pyridine-3-carboxylic acid monohydrochloride

Using 2-({[(6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}amino)pyridine-3-carboxylic acid (60 mg), and in the same manner as in Example
10 58, step C, the title compound (40 mg) was obtained.

MS (ESI+): [M+H]⁺ 396.1.

[0939]

Example 177

N-{2-[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]ethyl}acetamide monohydrochloride
15

[0940]

Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-{{[(methanesulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 66, step A, Example 1, step
20 G, Example 32, step C and Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 331.1.

[0941]

Example 178

25 (6S,7R)-7-(3,4-dichlorophenyl)-6-[(4-methyl-1H-pyrazol-1-yl)methyl]-1,4-oxazepane monohydrochloride

[0942]

In the same manner as in Example 44, step A and Example 43, step C, the title compound was obtained.

30 MS (ESI+): [M+H]⁺ 340.0.

[0943]

Example 179

1-({[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-1H-pyrazole-3-carboxylic acid monohydrochloride

35 [0944]

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In the same manner as in Example 44, the title compound was obtained.

MS (ESI+): [M+H]⁺ 370.3.

[0945]

5 Example 180

1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
1H-pyrazole-4-carboxylic acid monohydrochloride

[0946]

10 In the same manner as in Example 44, the title compound was obtained.

MS (ESI+): [M+H]⁺ 370.0.

[0947]

Example 181

1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
15 1H-pyrazole-5-carboxylic acid monohydrochloride

[0948]

In the same manner as in Example 44, the title compound was obtained.

MS (ESI+): [M+H]⁺ 370.3.

20 [0949]

Example 182

1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
3-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid
monohydrochloride

25 [0950]

In the same manner as in Example 44, the title compound was obtained.

MS (ESI+): [M+H]⁺ 437.9.

[0951]

30 Example 183

[1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
3-(trifluoromethyl)-1H-pyrazol-4-yl]methanol

[0952]

35 In the same manner as in Example 44, step A and Example 1, steps G and I, the title compound was obtained.

MS (ESI+): $[M+H]^+$ 424.0.

[0953]

Example 184

1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
5 3-methyl-1H-pyrazole-5-carboxylic acid monohydrochloride

[0954]

In the same manner as in Example 44, the title compound was obtained.

MS (ESI+): $[M+H]^+$ 384.2.

10 [0955]

Example 185

5-cyclopropyl-1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-
6-yl]methyl}-1H-pyrazole-3-carboxylic acid monohydrochloride

[0956]

15 Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-
{[(methanesulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate and,
ethyl 3-cyclopropyl-1H-pyrazole-5-carboxylate, and in the same
manner as in Example 44, the title compound was obtained.

MS (ESI+): $[M+H]^+$ 410.3.

20 [0957]

Example 186

1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
5-(2-methoxyethoxy)-1H-pyrazole-3-carboxylic acid
monohydrochloride

25 [0958]

In the same manner as in Example 185, the title compound was obtained.

MS (ESI+): $[M+H]^+$ 444.2.

[0959]

30 Example 187

1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
5-methyl-1H-pyrazole-3-carboxylic acid monohydrochloride

[0960]

In the same manner as in Example 44, the title compound
35 was obtained.

MS (ESI+): [M+H]⁺ 384.2.

[0961]

Example 188

3-tert-butyl-1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-
5 6-yl]methyl}-1H-pyrazole-5-carboxylic acid monohydrochloride

[0962]

In the same manner as in Example 185, the title compound was obtained.

MS (ESI+): [M+H]⁺ 426.2.

10 [0963]

Example 189

3-cyclopropyl-1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-
6-yl]methyl}-1H-pyrazole-5-carboxylic acid monohydrochloride

[0964]

15 In the same manner as in Example 185, the title compound was obtained.

MS (ESI+): [M+H]⁺ 410.3.

[0965]

Example 190

20 1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
3-(2-methoxyethoxy)-1H-pyrazole-5-carboxylic acid
monohydrochloride

[0966]

25 In the same manner as in Example 185, the title compound was obtained.

MS (ESI+): [M+H]⁺ 444.2.

[0967]

Example 191

3-{[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
30 1-methyl-1H-pyrazole-4-carboxylic acid monohydrochloride

[0968]

A) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-(4-ethoxy-2,4-
dioxobutyl)-1,4-oxazepane-4-carboxylate

CDI (0.991 g, 6.11 mmol) was added to a solution of
35 [(6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-

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oxazepan-6-yl]acetic acid (1.9 g, 4.70 mmol) in THF (20 mL), and the mixture was stirred at room temperature for 1 hr. To the reaction mixture were added potassium 3-ethoxy-3-oxopropanoate (0.880 g, 5.17 mmol) and magnesium chloride (0.492 g, 5.17 mmol). The reaction mixture was stirred at 60°C for 5 hr. To the reaction mixture was added 1 N hydrochloric acid, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (1.959 g).

¹H NMR (300 MHz, CDCl₃) δ 1.17-1.25 (3H, m), 1.49 (9H, s), 2.23-2.34 (1H, m), 2.48-2.80 (2H, m), 3.25-3.87 (7H, m), 4.01-4.18 (4H, m), 7.13 (1H, dd, J = 8.3, 1.9 Hz), 7.37-7.45 (2H, m).

[0969]

B) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-([4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-3-yl]methyl)-1,4-oxazepane-4-carboxylate

N,N-Dimethylformamide dimethyl acetal (0.210 mL, 1.58 mmol) was added to a solution of tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-(4-ethoxy-2,4-dioxobutyl)-1,4-oxazepane-4-carboxylate (500 mg, 1.05 mmol) in toluene (5 mL), and the mixture was stirred at 80°C for 2 hr, and concentrated under reduced pressure. The residue was dissolved in ethanol (5 mL), and methylhydrazine (0.062 mL, 1.16 mmol) was added. The reaction mixture was stirred at 80°C for 1.5 hr, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (175 mg).

MS (ESI⁺): [M+H-Boc]⁺ 412.3.

[0970]

C) 3-([[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl]-1-methyl-1H-pyrazole-4-carboxylic acid

monohydrochloride

Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-[[4-(ethoxycarbonyl)-1-methyl-1H-pyrazol-3-yl]methyl]-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 44, step B, the title compound was obtained.

5 MS (ESI+): [M+H]⁺ 384.2.

[0971]

Example 192

(6R,7R)-7-(3,4-dichlorophenyl)-6-[(5-methyl-1,2,4-oxadiazol-3-yl)methyl]-1,4-oxazepane monohydrochloride

10 [0972]

A) tert-butyl (6R,7R)-6-[2-amino-2-(hydroxyimino)ethyl]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

Sodium hydrogen carbonate (872 mg, 10.38 mmol) was added to a suspension of hydroxylamine monohydrochloride (721 mg, 10.38 mmol) in DMSO (3 mL), and the mixture was stirred at 80°C for 15 min. The precipitate was filtered off, and a solution of tert-butyl (6R,7R)-6-(cyanomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (500 mg, 1.30 mmol) in DMSO (4 mL) was added to the filtrate. The reaction mixture was stirred at 80°C overnight. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give the title compound (588 mg). This compound was used for the next reaction without purification.

25 MS (ESI+): [M+H]⁺ 418.2.

[0973]

B) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-[(5-methyl-1,2,4-oxadiazol-3-yl)methyl]-1,4-oxazepane-4-carboxylate

30 To a solution of tert-butyl (6R,7R)-6-[2-amino-2-(hydroxyimino)ethyl]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (388 mg, 0.93 mmol) in toluene (4 mL) were added potassium tert-butoxide (208 mg, 1.86 mmol) and ethyl acetate (1 mL, 0.93 mmol). The reaction mixture was stirred at 100°C overnight. To the reaction mixture was added water, and the

mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the
5 title compound (183.4 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.38-1.55 (9H, m), 2.48 (3H, s), 2.49-2.79 (3H, m), 3.43-3.57 (1H, m), 3.59-3.83 (4H, m), 4.00-4.27 (2H, m), 7.15 (1H, dd, J = 8.3, 1.9 Hz), 7.35-7.44 (2H, m).

10 [0974]

C) (6R,7R)-7-(3,4-dichlorophenyl)-6-[(5-methyl-1,2,4-oxadiazol-3-yl)methyl]-1,4-oxazepane monohydrochloride

Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-[(5-methyl-1,2,4-oxadiazol-3-yl)methyl]-1,4-oxazepane-4-
15 carboxylate, and in the same manner as in Example 39, step B, the title compound was obtained.

MS (ESI⁺): [M+H]⁺ 342.1.

[0975]

Example 193

20 3-{[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-1,2,4-oxadiazol-5(4H)-one monohydrochloride

In the same manner as in Example 31, steps D and E, the title compound was obtained.

MS (ESI⁺): [M+H]⁺ 344.0.

25 [0976]

Example 194

2-{[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-1,3-thiazole-4-carboxylic acid monohydrochloride

[0977]

30 A) tert-butyl (6R,7R)-6-(2-amino-2-thioxoethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7R)-6-(2-amino-2-oxoethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (528 mg, 1.31 mmol) in THF (6 mL) was added Lawesson's reagent
35 (794 mg, 1.96 mmol), and the mixture was stirred at 70°C for

2.5 hr. To the reaction mixture was added aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (289 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.50 (9H, s), 2.45 (1H, d, J = 11.3 Hz), 2.59-2.81 (2H, m), 3.15 (1H, ddd, J = 14.0, 12.3, 4.0 Hz), 3.31 (1H, dd, J = 14.9, 4.7 Hz), 3.59 (1H, td, J = 12.3, 3.0 Hz), 3.93 (1H, d, J = 9.4 Hz), 3.99-4.09 (2H, m), 4.11-4.19 (1H, m), 7.23-7.30 (1H, m), 7.42-7.47 (1H, m), 7.49 (1H, d, J = 2.3 Hz), 7.55 (1H, brs), 9.48 (1H, brs).

[0978]

15 B) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-([4-(ethoxycarbonyl)-1,3-thiazol-2-yl]methyl)-1,4-oxazepane-4-carboxylate

Ethyl bromopyruvate (0.070 mL, 0.50 mmol) was added to a solution of tert-butyl (6R,7R)-6-(2-amino-2-thioxoethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (140 mg, 0.33 mmol) in EtOH (5 mL). The reaction mixture was stirred at 80°C for 2 hr, triethylamine (0.140 mL, 1.00 mmol) and di-tert-butyl dicarbonate (0.115 mL, 0.50 mmol) were added at room temperature, and the mixture was stirred at room temperature for 5 hr. To the reaction mixture was added aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (173 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.35-1.56 (12H, m), 2.63 (1H, brs), 2.80-3.15 (2H, m), 3.38-3.82 (5H, m), 4.02-4.29 (2H, m), 4.40 (2H, q, J = 7.2 Hz), 7.13 (1H, dd, J = 8.3, 1.9 Hz), 7.32-7.41 (2H, m), 7.99 (1H, s).

MS (ESI+): [M+H]⁺ 515.0.

[0979]

C) 2-{[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-1,3-thiazole-4-carboxylic acid monohydrochloride

Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-{[4-(ethoxycarbonyl)-1,3-thiazol-2-yl]methyl}-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 44, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 386.9.

[0980]

Example 195

2-{[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-1,3-thiazole-5-carboxylic acid monohydrochloride

In the same manner as in Example 194, the title compound was obtained.

MS (ESI+): [M+H]⁺ 386.9.

[0981]

Example 196

4-{[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-2-methyl-1,3-thiazole-5-carboxylic acid monohydrochloride

[0982]

A) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-{[5-(ethoxycarbonyl)-2-methyl-1,3-thiazol-4-yl]methyl}-1,4-oxazepane-4-carboxylate

Sulfuryl chloride (0.094 mL, 1.16 mmol) was added to a solution of tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-(4-ethoxy-2,4-dioxobutyl)-1,4-oxazepane-4-carboxylate (500 mg, 1.05 mmol) in toluene (5 mL). The reaction mixture was stirred at room temperature for 45 min, and concentrated under reduced pressure. To the residue were added ethanol (5 mL) and thioacetamide (87 mg, 1.16 mmol), and the mixture was stirred at 80°C for 1.5 hr. To the reaction mixture were added triethylamine (0.294 mL, 2.11 mmol) and di-tert-butyl dicarbonate (0.291 mL, 1.26 mmol) at room temperature, and the mixture was stirred at room temperature for 30 min, and

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concentrated under reduced pressure. To the residue was added aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent
5 was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (358 mg).

^1H NMR (300 MHz, CDCl_3) δ 1.34 (3H, t, $J = 7.2$ Hz), 1.38-1.52 (9H, m), 2.58 (3H, s), 2.69-2.90 (1H, m), 2.96-3.15 (2H, m),
10 3.51-3.80 (5H, m), 3.99-4.32 (4H, m), 7.02-7.09 (1H, m), 7.23-7.32 (2H, m).

MS (ESI+): $[\text{M}+\text{H}]^+$ 529.0.

[0983]

B) 4-{[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-2-methyl-1,3-thiazole-5-carboxylic acid
15 monohydrochloride

Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-{[5-(ethoxycarbonyl)-2-methyl-1,3-thiazol-4-yl]methyl}-1,4-oxazepane-4-carboxylate, and in the same manner as in Example
20 44, step B, the title compound was obtained.

MS (ESI+): $[\text{M}+\text{H}]^+$ 401.2.

[0984]

Example 197

2-{[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
25 4-methyl-1,3-thiazole-5-carboxylic acid monohydrochloride

[0985]

In the same manner as in Example 194, the title compound was obtained.

MS (ESI+): $[\text{M}+\text{H}]^+$ 401.0.

30 [0986]

Example 198

(2-{[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-1,3-thiazol-4-yl)acetic acid monohydrochloride

[0987]

35 In the same manner as in Example 194, the title compound

was obtained.

MS (ESI+): [M+H]⁺ 401.0.

[0988]

Example 199

5 3-(2-{[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-1,3-thiazol-4-yl)-1,2,4-oxadiazol-5(4H)-one monohydrochloride

[0989]

A) tert-butyl (6R,7R)-6-[(4-carbamoyl-1,3-thiazol-2-yl)methyl]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

Using 2-{[(6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-1,3-thiazole-4-carboxylic acid, and in the same manner as in Example 39, step A, the title compound was obtained.

15 ¹H NMR (300 MHz, CDCl₃) δ 1.33-1.56 (9H, m), 2.55-2.81 (2H, m), 2.86-3.09 (1H, m), 3.45-3.85 (4H, m), 4.04-4.20 (3H, m), 5.71 (1H, d, J = 19.3 Hz), 7.14 (1H, dd, J = 8.1, 2.1 Hz), 7.38-7.46 (2H, m), 7.55 (1H, brs), 7.97 (1H, brs).

MS (ESI+): [M+H]⁺ 485.9.

20 [0990]

B) tert-butyl (6R,7R)-6-[(4-cyano-1,3-thiazol-2-yl)methyl]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

Trifluoroacetic anhydride (0.080 mL, 0.57 mmol) was added to a solution of tert-butyl (6R,7R)-6-[(4-carbamoyl-1,3-thiazol-2-yl)methyl]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (126 mg, 0.26 mmol) and pyridine (0.084 mL, 1.04 mmol) in THF (4 mL) under ice-cooling. The reaction mixture was stirred at room temperature overnight, triethylamine (0.144 mL, 1.04 mmol) and trifluoroacetic anhydride (0.080 mL, 0.57 mmol) were added, and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was

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purified by silica gel column chromatography to give the title compound (100 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.36-1.54 (9H, m), 2.56-2.85 (2H, m), 2.96-3.16 (1H, m), 3.35-3.51 (1H, m), 3.51-3.84 (4H, m), 4.04-4.27 (2H, m), 7.17 (1H, d, J = 7.6 Hz), 7.37-7.45 (2H, m), 7.84 (1H, s).

MS (ESI⁺): [M+H]⁺ 468.1.

[0991]

C) 3-(2-([(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl)-1,3-thiazol-4-yl)-1,2,4-oxadiazol-5(4H)-one monohydrochloride

Using tert-butyl (6R,7R)-6-[(4-cyano-1,3-thiazol-2-yl)methyl]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 31, steps D and E, the title compound was obtained.

MS (ESI⁺): [M+H]⁺ 427.0.

[0992]

Example 200

(6R,7R)-7-(3,4-dichlorophenyl)-6-[(5-methyl-4H-1,2,4-triazol-3-yl)methyl]-1,4-oxazepane monohydrochloride

[0993]

A) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-[(5-methyl-4H-1,2,4-triazol-3-yl)methyl]-1,4-oxazepane-4-carboxylate

Methyl iodide (0.214 mL, 3.43 mmol) was added to a suspension of tert-butyl (6R,7R)-6-(2-amino-2-thioxoethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (288 mg, 0.69 mmol) and potassium carbonate (142 mg, 1.03 mmol) in acetone (5 mL) at room temperature. The reaction mixture was stirred at room temperature for 4 hr, and concentrated under reduced pressure. To the residue was added aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was dissolved in toluene (5 mL), acetohydrazide (61.1 mg, 0.82 mmol) was added, and the mixture

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was stirred at 120°C overnight while using a Dean-Stark trap. To the reaction mixture was added aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over
5 anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (241 mg, 0.545 mmol, 79%).

¹H NMR (300 MHz, CDCl₃) δ 1.52 (9H, s), 2.33 (4H, s), 2.55-2.74
10 (2H, m), 3.22-3.42 (2H, m), 3.64 (1H, td, J = 12.3, 3.0 Hz), 3.75-3.83 (1H, m), 3.94 (1H, d, J = 14.0 Hz), 4.01 (1H, d, J = 9.4 Hz), 4.12-4.19 (1H, m), 7.16 (1H, dd, J = 8.3, 1.9 Hz), 7.39-7.45 (2H, m), 1H not detected.

MS (ESI⁺): [M+H]⁺ 441.4.

15 [0994]

B) (6R,7R)-7-(3,4-dichlorophenyl)-6-[(5-methyl-4H-1,2,4-triazol-3-yl)methyl]-1,4-oxazepane monohydrochloride

Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-[(5-methyl-4H-1,2,4-triazol-3-yl)methyl]-1,4-oxazepane-4-
20 carboxylate, and in the same manner as in Example 31, step E, the title compound was obtained.

MS (ESI⁺): [M+H]⁺ 341.3.

[0995]

Example 201

25 1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-5-methyl-1H-1,2,3-triazole-4-carboxylic acid monohydrochloride

[0996]

A) tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-{[4-(methoxycarbonyl)-5-methyl-1H-1,2,3-triazol-1-yl]methyl}-1,4-
30 oxazepane-4-carboxylate

To a solution of tert-butyl (6S,7R)-6-(azidomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (200 mg) in DMSO (2 mL) were added potassium carbonate (276 mg) and methyl acetoacetate (0.08 mL) at room temperature, and the mixture
35 was stirred at 80°C overnight. The reaction mixture was

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diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (149 mg).

MS (ESI+): [M+H]⁺ 499.0.

[0997]

B) 1-{[(6S,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-5-methyl-1H-1,2,3-triazole-4-carboxylic acid

Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-{[4-(methoxycarbonyl)-5-methyl-1H-1,2,3-triazol-1-yl]methyl}-1,4-oxazepane-4-carboxylate (149 mg), and in the same manner as in Example 58, step B, the title compound (149 mg) was obtained.

MS (ESI+): [M+H-t-Bu]⁺ 429.1.

[0998]

C) 1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-5-methyl-1H-1,2,3-triazole-4-carboxylic acid monohydrochloride

Using 1-{[(6S,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (149 mg), and in the same manner as in Example 58, step C, the title compound (85 mg) was obtained.

MS (ESI+): [M+H]⁺ 385.3.

[0999]

Example 202

1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-1H-indazole-3-carboxylic acid monohydrochloride

[1000]

Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-{[(methanesulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 44, step A, Example 58, step B and Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 420.1.

[1001]

Example 203

1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}imidazolidine-2,4-dione monohydrochloride

[1002]

A) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-{[(2-ethoxy-2-oxoethyl)amino]methyl}-1,4-oxazepane-4-carboxylate

Using tert-butyl (6R,7R)-6-(aminomethyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 44, step A, the title compound was obtained.

MS (ESI+): [M+H]⁺ 461.2.

[1003]

B) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-[(2,4-dioxoimidazolidin-1-yl)methyl]-1,4-oxazepane-4-carboxylate

To a solution (1.9 mL) of tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-{[(2-ethoxy-2-oxoethyl)amino]methyl}-1,4-oxazepane-4-carboxylate (180 mg) in THF were added isocyanatotrimethylsilane (0.078 mL) and triethylamine (0.082 mL), and the mixture was stirred at room temperature for 2 hr. Then, isocyanatotrimethylsilane (0.156 mL) and triethylamine (0.164 mL) were added, and the mixture was stirred at 50°C for 2 hr, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate). The obtained residue was diluted with methanol (1.4 mL), triethylamine (0.080 mL) was added, and the mixture was stirred at 50°C for 2 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (115 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.49 (9H, s), 2.24-2.50 (1H, m), 2.99-4.12 (11H, m), 7.16 (1H, d, J = 8.3 Hz), 7.38-7.47 (2H, m), 7.59-7.90 (1H, m).

[1004]

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C) 1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}imidazolidine-2,4-dione monohydrochloride

Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-[(2,4-dioxoimidazolidin-1-yl)methyl]-1,4-oxazepane-4-carboxylate,
5 and in the same manner as in Example 38, step F, the title compound was obtained.

MS (ESI+): [M+H]⁺ 358.0.

[1005]

Example 204

10 1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
2-oxo-1,2-dihydropyridine-3-carbonitrile monohydrochloride
[1006]

In the same manner as in Example 44, step A and Example 31, step E, the title compound was obtained.

15 MS (ESI+): [M+H]⁺ 378.1.

[1007]

Example 205

1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
2-oxo-1,2-dihydropyridine-3-carboxylic acid monohydrochloride
20 [1008]

In the same manner as in Example 44, the title compound was obtained.

MS (ESI+): [M+H]⁺ 397.1.

[1009]

25 Example 206

1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
5-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one
monohydrochloride
[1010]

30 In the same manner as in Example 44, step A and Example 31, steps D and E, the title compound was obtained.

MS (ESI+): [M+H]⁺ 437.0.

[1011]

Example 207

35 1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-

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4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridin-2(1H)-one
monohydrochloride

[1012]

In the same manner as in Example 44, step A and Example
5 31, steps D and E, the title compound was obtained.

MS (ESI+): [M+H]⁺ 436.9.

[1013]

Example 208

1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-
10 3-(1H-tetrazol-5-yl)pyridin-2(1H)-one monohydrochloride

[1014]

A) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-{[2-oxo-3-(1H-
tetrazol-5-yl)pyridin-1(2H)-yl]methyl}-1,4-oxazepane-4-
carboxylate

15 Tributyltin azide (0.340 mL, 1.24 mmol) was added to a
solution of tert-butyl (6R,7R)-6-[(3-cyano-2-oxopyridin-1(2H)-
yl)methyl]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate
(198 mg, 0.41 mmol) in toluene (5 mL). The reaction mixture
was stirred at 100°C overnight. The reaction mixture was
20 concentrated under reduced pressure. The residue was purified
by silica gel column chromatography to give the title compound
(148 mg, 0.284 mmol, 68.6%).

¹H NMR (300 MHz, CDCl₃) δ 1.55 (9H, s), 2.98 (1H, brs), 3.08-
3.35 (2H, m), 3.65 (1H, t, J = 11.1 Hz), 3.89-4.15 (5H, m),
25 4.29-4.42 (1H, m), 6.59 (1H, t, J = 6.6 Hz), 7.06 (1H, d, J =
7.9 Hz), 7.16 (1H, dd, J = 7.9, 1.9 Hz), 7.57 (1H, brs), 8.57
(1H, d, J = 5.3 Hz), 8.66 (1H, d, J = 6.8 Hz), 14.40 (1H,
brs).

MS (ESI+): [M+H]⁺ 521.3.

30 [1015]

B) 1-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-
yl]methyl}-3-(1H-tetrazol-5-yl)pyridin-2(1H)-one
monohydrochloride

Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-{[2-
35 oxo-3-(1H-tetrazol-5-yl)pyridin-1(2H)-yl]methyl}-1,4-

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oxazepane-4-carboxylate, and in the same manner as in Example 31, step E, the title compound was obtained.

MS (ESI+): [M+H]⁺ 421.0.

[1016]

5 Example 209

2-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridazin-3(2H)-one monohydrochloride

Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-
10 {[(methanesulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate and 3-hydroxypyridazine-4-carbonitrile, and in the same manner as in Example 44, step A and Example 31, steps D and E, the title compound was obtained.

MS (ESI+): [M+H]⁺ 438.1.

15 [1017]

Example 210

2-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-5,6-dimethyl-3-oxo-2,3-dihydropyridazine-4-carbonitrile monohydrochloride

20 Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-{[(methanesulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 44, step A and Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 407.3.

25 [1018]

Example 211

2-{[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]methyl}-5,6-dimethyl-4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridazin-3(2H)-one monohydrochloride

30 Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-{[(methanesulfonyl)oxy]methyl}-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 44, step A, Example 31, step D and Example 39, step B, the title compound was obtained.

MS (ESI-): [M-H]⁺ 464.2.

35 [1019]

Example 212

3-[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]propan-1-ol monohydrochloride

Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-(3-ethoxy-3-oxopropyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 4, step B and Example 38, step F, the title compound was obtained.

MS (ESI+): [M+H]⁺ 304.3

[1020]

10 Example 213

1-{3-[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]propyl}-3-methyl-1H-pyrazole-5-carboxylic acid monohydrochloride

Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-(3-ethoxy-3-oxopropyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 4, step B, Example 3, step A and Example 44, the title compound was obtained.

MS (ESI+): [M+H]⁺ 412.3.

[1021]

20 Example 214

1-{3-[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]propyl}-5-methyl-1H-pyrazole-3-carboxylic acid monohydrochloride

[1022]

25 In the same manner as in Example 213, the title compound was obtained.

MS (ESI+): [M+H]⁺ 412.3.

[1023]

Example 215

30 1-[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]-2,2,2-trifluoroethanol monohydrochloride (diastereomer ratio about 3:1 mixture)

[1024]

A) tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-(2,2,2-trifluoro-1-hydroxyethyl)-1,4-oxazepane-4-carboxylate

(diastereomer mixture)

To a solution (2.6 mL) of tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-formyl-1,4-oxazepane-4-carboxylate (100 mg) in THF were added a solution (1.0 M, 0.534 mL) of
5 trimethyl(trifluoromethyl)silane (190 mg) and tetrabutylammonium fluoride in THF under ice-cooling, and the mixture was stirred at room temperature overnight. To the reaction mixture was added 1 M hydrochloric acid (0.5 mL), and the mixture was further stirred for 3 hr. Distilled water was
10 added, and the mixture was extracted with ethyl acetate. The extract was washed with distilled water and brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the
15 title compound (91.7 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.50 (9H, s), 2.60-2.72 (1H, m), 3.01-4.41 (8H, m), 4.68 (1H, d, J = 8.7 Hz), 7.17 (1H, dd, J = 8.3, 1.9 Hz), 7.41 (1H, d, J = 8.3 Hz), 7.45 (1H, d, J = 1.9 Hz).

20 [1025]

B) 1-[(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]-2,2,2-trifluoroethanol monohydrochloride (diastereomer ratio about 3:1 mixture)

Using tert-butyl (6S,7R)-7-(3,4-dichlorophenyl)-6-(2,2,2-trifluoro-1-hydroxyethyl)-1,4-oxazepane-4-carboxylate, and in
25 the same manner as in Example 38, step F, the title compound was obtained.

MS (ESI⁺): [M+H]⁺ 344.0.

[1026]

30 Example 216

1-[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]ethanone monohydrochloride

[1027]

Using (6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-6-carboxylic acid, and in the
35

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same manner as in Example 75, the title compound was obtained.

¹H NMR (300 MHz, DMSO-d₆) δ 2.45-2.54 (3H, m), 2.98 (2H, t, J = 5.3 Hz), 3.62 (2H, q, J = 5.0 Hz), 3.89 (2H, s), 5.23 (1H, t, J = 4.9 Hz), 7.61 (1H, dd, J = 8.3, 1.9 Hz), 7.73-7.80 (1H, m), 7.90 (1H, d, J = 1.9 Hz), 8.07 (1H, s), 8.58-8.82 (2H, m).
MS (ESI+): [M+H]⁺ 288.2.

[1028]

Example 217

(6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepane-6-carbonitrile
monohydrochloride

[1029]

A) tert-butyl (6R,7R)-6-carbamoyl-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

To a solution of (6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-6-carboxylic acid (450 mg) and 1H-benzotriazol-1-ol ammonium salt (211 mg) in DMF (5.8 mL) was added N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (265 mg), and the mixture was stirred overnight. To the reaction mixture was added distilled water, and the mixture was extracted with ethyl acetate. The extract was washed with distilled water and brine, and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (437 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.50 (9H, s), 2.49-2.86 (1H, m), 3.46-4.05 (6H, m), 4.75 (1H, d, J = 9.1 Hz), 5.05-6.38 (2H, m), 7.17 (1H, dd, J = 8.3, 1.9 Hz), 7.38 (1H, d, J = 8.0 Hz), 7.46 (1H, d, J = 1.9 Hz).

[1030]

B) tert-butyl (6S,7R)-6-cyano-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7R)-6-carbamoyl-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (437 mg) and triethylamine (0.344 mL) in THF (5.6 mL) was added

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trifluoroacetic anhydride (0.171 mL), and the mixture was stirred at 0°C for 2 hr. Then, the mixture was stirred at room temperature for 1 hr, distilled water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with distilled water and brine, and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (205 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.56 (9H, s), 2.90-3.10 (1H, m), 3.18-3.34 (1H, m), 3.52-3.87 (3H, m), 4.03-4.31 (2H, m), 4.50 (1H, d, J = 9.8 Hz), 7.20-7.26 (1H, m), 7.46 (1H, d, J = 8.3 Hz), 7.53 (1H, s).

[1031]

C) (6S,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepane-6-carbonitrile monohydrochloride

Using tert-butyl (6S,7R)-6-cyano-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 38, step F, the title compound was obtained.

MS (ESI⁺): [M+H]⁺ 271.0.

[1032]

Example 218

(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepane-6-carboxylic acid monohydrochloride

[1033]

Using (6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-6-carboxylic acid, and in the same manner as in Example 39, step B, the title compound was obtained.

MS (ESI⁺): [M+H]⁺ 290.0.

[1034]

Example 219

(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepane-6-carboxamide monohydrochloride

[1035]

Using tert-butyl (6R,7R)-6-carbamoyl-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 38, step F, the title compound was obtained.

5 MS (ESI+): $[M+H]^+$ 289.0.

[1036]

Example 220

(6R,7R)-7-(3,4-dichlorophenyl)-N-methyl-1,4-oxazepane-6-carboxamide monohydrochloride

10 [1037]

Using (6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-6-carboxylic acid, and in the same manner as in Example 41, the title compound was obtained.

MS (ESI+): $[M+H]^+$ 303.0.

15 [1038]

Example 221

(6R,7R)-7-(3,4-dichlorophenyl)-N,N-dimethyl-1,4-oxazepane-6-carboxamide monohydrochloride

[1039]

20 Using (6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-6-carboxylic acid, and in the same manner as in Example 39, the title compound was obtained.

MS (ESI+): $[M+H]^+$ 317.3.

[1040]

25 Example 222

(6R,7R)-7-(3,4-dichlorophenyl)-N-(2-hydroxy-2-methylpropyl)-1,4-oxazepane-6-carboxamide monohydrochloride

[1041]

30 Using (6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-6-carboxylic acid, and in the same manner as in Example 41, the title compound was obtained.

MS (ESI+): $[M+H]^+$ 361.0.

[1042]

Example 223

35 (6R,7R)-7-(3,4-dichlorophenyl)-N-[2-(methylsulfonyl)ethyl]-

1,4-oxazepane-6-carboxamide monohydrochloride

[1043]

Using (6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-6-carboxylic acid, and in the same manner as in Example 41, the title compound was obtained.

MS (ESI+): [M+H]⁺ 395.0.

[1044]

Example 224

3-({[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]carbonyl}amino)benzoic acid monohydrochloride

[1045]

Using (6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-6-carboxylic acid, and in the same manner as in Example 41, step A and Example 44, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 409.0.

[1046]

Example 225

(6R,7R)-7-(3,4-dichlorophenyl)-N-(methylsulfonyl)-1,4-oxazepane-6-carboxamide monohydrochloride

[1047]

Using (6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-6-carboxylic acid, and in the same manner as in Example 226, step A and Example 39, step B, the title compound was obtained.

MS (ESI+): [M+H]⁺ 367.0.

[1048]

Example 226

(6R,7R)-7-(3,4-dichlorophenyl)-N-methyl-N-(methylsulfonyl)-1,4-oxazepane-6-carboxamide monohydrochloride

[1049]

A) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-[(methylsulfonyl)carbamoyl]-1,4-oxazepane-4-carboxylate

To a solution of (6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-6-carboxylic acid (590 mg) in

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acetonitrile (15.1 mL) were added N,N-dimethyl-4-aminopyridine (203 mg), methanesulfonamide (158 mg) and 2-methyl-6-nitrobenzoic anhydride (625 mg) at room temperature, and the mixture was stirred at room temperature for 2 hr. To the reaction mixture was added aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The extract was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (323 mg).

MS (ESI+): $[M+H-t-Bu]^+$ 411.2.

[1050]

B) tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-

[methyl(methylsulfonyl)carbamoyl]-1,4-oxazepane-4-carboxylate

To a solution of tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-[(methylsulfonyl)carbamoyl]-1,4-oxazepane-4-carboxylate (246 mg) in DMF (3 mL) were added potassium carbonate (109 mg) and methyl iodide (0.049 mL) at room temperature, and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate. The diluted solution was washed with distilled water and brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel chromatography (hexane/ethyl acetate) to give the title compound (174 mg).

MS (ESI-): $[M-H]^+$ 479.0.

[1051]

C) (6R,7R)-7-(3,4-dichlorophenyl)-N-methyl-N-(methylsulfonyl)-

1,4-oxazepane-6-carboxamide monohydrochloride

Using tert-butyl (6R,7R)-7-(3,4-dichlorophenyl)-6-[methyl(methylsulfonyl)carbamoyl]-1,4-oxazepane-4-carboxylate (174 mg), and in the same manner as in Example 58, step C, the title compound (133 mg) was obtained.

MS (ESI+): $[M+H]^+$ 381.1.

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[1052]

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Example 227

(6R,7R)-7-(3,4-dichlorophenyl)-N-{[4-(difluoromethoxy)phenyl]sulfonyl}-1,4-oxazepane-6-carboxamide
5 monohydrochloride

[1053]

Using (6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-6-carboxylic acid, and in the same manner as in Example 226, step A and Example 38, step F,
10 the title compound was obtained.

MS (ESI+): [M+H]⁺ 495.2.

[1054]

Example 228

(6R,7R)-7-(3,4-dichlorophenyl)-N-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4-oxazepane-6-carboxamide
15 monohydrochloride

[1055]

Using (6R,7R)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepane-6-carboxylic acid, and in the same manner as in Example 226, step A and Example 38, step F,
20 the title compound was obtained.

MS (ESI+): [M+H]⁺ 496.9.

[1056]

Example 229

25 2-[(6R,7R)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]-1,3-thiazole-4-carboxylic acid monohydrochloride

[1057]

Using tert-butyl (6R,7R)-6-carbamoyl-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate, and in the same manner as in Example 194, the title compound was obtained.
30

MS (ESI+): [M+H]⁺ 373.0.

[1058]

Example 230

(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-ol
35 monohydrochloride

Using tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepane-4-carboxylate (150 mg), and in the same manner as in Example 39, step B, the title compound (93 mg) was obtained.

MS (ESI+): [M+H]⁺ 262.1.

[1060]

Example 231

6-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]oxy}pyridine-2-carboxylic acid monohydrochloride
[1061]

A) tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-{[6-(methoxycarbonyl)pyridin-2-yl]oxy}-1,4-oxazepane-4-carboxylate

Under ice-cooling, sodium hydride (60% in oil, 53 mg) was added to a solution of tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepane-4-carboxylate (400 mg) in DMF (5 mL). After stirring at room temperature for 20 min, methyl 6-chloropicolinate (280 mg) and sodium iodide (330 mg) were added, and the mixture was stirred at the same temperature for 1 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (207 mg).

¹H NMR (300 MHz, CDCl₃) δ 1.16-1.54 (9H, m), 2.92-4.98 (11H, m), 7.28-7.89 (6H, m).

MS (ESI+): [M+H]⁺ 497.3.

[1062]

B) 6-{[(6RS,7SR)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]oxy}pyridine-2-carboxylic acid

2M Aqueous sodium hydroxide solution (1.7 mL) was added to a solution of tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-{[6-(methoxycarbonyl)pyridin-2-yl]oxy}-1,4-oxazepane-4-

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carboxylate (210 mg) in ethanol (5 mL), and the mixture was stirred at room temperature overnight and at 70°C for 2 hr. Water was added to the reaction mixture, and the mixture was washed with diethyl ether. The obtained aqueous layer was
5 neutralized with 1 M hydrochloric acid, and the mixture was extracted with ethyl acetate. The obtained extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to give the title compound (69 mg).

10 ¹H NMR (300 MHz, CDCl₃) δ 1.54 (9H, s), 3.07-3.44 (2H, m), 3.73-3.94 (1H, m), 3.97-4.09 (1H, m), 4.25 (1H, ddd, J = 13.1, 5.6, 1.7 Hz), 4.46 (1H, d, J = 9.0 Hz), 4.62-4.89 (2H, m), 6.82 (1H, d, J = 8.3 Hz), 7.22 (1H, dd, J = 8.3, 2.3 Hz), 7.36 (1H, d, J = 8.3 Hz), 7.51 (1H, d, J = 1.9 Hz), 7.66-7.78 (1H,
15 m), 7.83 (1H, d, J = 7.2 Hz), 1H not detected.

MS (ESI⁺): [M+H]⁺ 481.0.

[1063]

C) 6-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]oxy}pyridine-2-carboxylic acid monohydrochloride

20 Using 6-{[(6RS,7SR)-4-(tert-butoxycarbonyl)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]oxy}pyridine-2-carboxylic acid (69 mg), and in the same manner as in Example 39, step B, the title compound (50 mg) was obtained.

MS (ESI⁺): [M+H]⁺ 383.1.

25 [1064]

Example 232

6-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]oxy}pyridine-2-carbonitrile monohydrochloride

[1065]

30 A) tert-butyl (6RS,7SR)-6-[(6-cyanopyridin-2-yl)oxy]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

Using tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepane-4-carboxylate (400 mg), and in the same manner as in Example 231, step A, the title compound (237 mg)
35 was obtained.

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¹H NMR (300 MHz, CDCl₃) δ 1.54 (9H, s), 2.86-5.38 (m), 6.78-7.85 (6H, m).

MS (ESI⁺): [M+H-Boc]⁺ 364.1.

[1066]

5 B) 6-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]oxy}pyridine-2-carbonitrile monohydrochloride

Using tert-butyl (6RS,7SR)-6-[(6-cyanopyridin-2-yl)oxy]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (60 mg), and in the same manner as in Example 39, step B, the title
10 compound (32 mg) was obtained.

MS (ESI⁺): [M+H]⁺ 364.1.

[1067]

Example 233

2-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]oxy}pyridine-3-carbonitrile monohydrochloride
15

[1068]

A) tert-butyl (6RS,7SR)-6-[(3-cyanopyridin-2-yl)oxy]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

Using tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-hydroxy-1,4-oxazepane-4-carboxylate (400 mg), and by a method similar to that of Example 231, step A, the title compound
20 (430 mg) was obtained.

¹H NMR (300 MHz, CDCl₃) δ 1.26-1.50 (9H, m), 2.98-3.47 (1H, m), 3.58 (1H, dd, J = 15.6, 4.0 Hz), 3.74-4.09 (1H, m), 4.09-4.53
25 (3H, m), 4.53-4.85 (1H, m), 4.93-5.62 (1H, m), 6.84-7.11 (1H, m), 7.28-7.65 (3H, m), 7.75-8.10 (1H, m), 8.17-8.76 (1H, m).

MS (ESI⁺): [M+H-t-Bu]⁺ 407.2.

[1069]

B) 2-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]oxy}pyridine-3-carbonitrile monohydrochloride
30

Using tert-butyl (6RS,7SR)-6-[(3-cyanopyridin-2-yl)oxy]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (60 mg), and in the same manner as in Example 39, step B, the title compound (77 mg) was obtained.

35 MS (ESI⁺): [M+H]⁺ 364.1.

[1070]

Example 234

2-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]oxy}pyridine-3-carboxamide monohydrochloride

5 [1071]

A) tert-butyl (6RS,7SR)-6-[(3-carbamoylpyridin-2-yl)oxy]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate

33% Aqueous hydrogen peroxide (1 mL) was added to a solution of tert-butyl (6RS,7SR)-6-[(3-cyanopyridin-2-yl)oxy]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (100 mg) and potassium carbonate (45 mg) in DMSO (3 mL), and the mixture was stirred at room temperature for 2 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography and HPLC to give the title compound (57 mg).

MS (ESI+): [M+H]⁺ 482.2.

20 [1072]

B) 2-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]oxy}pyridine-3-carboxamide monohydrochloride

Using tert-butyl (6RS,7SR)-6-[(3-carbamoylpyridin-2-yl)oxy]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (57 mg), and in the same manner as in Example 39, step B, the title compound (39 mg) was obtained.

MS (ESI+): [M+H]⁺ 382.2.

[1073]

Example 235

3-(6-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]oxy}pyridin-2-yl)-1,2,4-oxadiazol-5(4H)-one monohydrochloride

[1074]

A) tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-{[6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridin-2-yl]oxy}-1,4-

oxazepane-4-carboxylate

Using tert-butyl (6RS,7SR)-6-[(6-cyanopyridin-2-yl)oxy]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (170 mg), and in the same manner as in Example 31, step D, the title compound (165 mg) was obtained.

¹H NMR (300 MHz, CDCl₃) δ 1.60 (9H, s), 3.11 (1H, dd, J = 14.0, 10.2 Hz), 3.18-3.33 (1H, m), 3.84 (1H, td, J = 12.5, 4.2 Hz), 4.02-4.20 (1H, m), 4.20-4.37 (1H, m), 4.44 (1H, d, J = 9.4 Hz), 4.72 (1H, td, J = 9.8, 3.4 Hz), 4.87 (1H, dd, J = 14.4, 3.0 Hz), 6.72 (1H, d, J = 7.9 Hz), 7.23 (1H, dd, J = 8.3, 1.9 Hz), 7.37 (1H, d, J = 8.3 Hz), 7.51 (1H, d, J = 2.3 Hz), 7.59-7.72 (2H, m), 11.68 (1H, brs).

MS (ESI⁺): [M-H]⁺ 521.1.

[1075]

15 B) 3-(6-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]oxy}pyridin-2-yl)-1,2,4-oxadiazol-5(4H)-one monohydrochloride

Using tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-{[6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridin-2-yl]oxy}-1,4-oxazepane-4-carboxylate (165 mg), and in the same manner as in Example 39, step B, the title compound (111 mg) was obtained.

MS (ESI⁺): [M+H]⁺ 423.1.

[1076]

Example 236

25 3-(2-{[(6RS,7SR)-7-(3,4-dichlorophenyl)-1,4-oxazepan-6-yl]oxy}pyridin-3-yl)-1,2,4-oxadiazol-5(4H)-one monohydrochloride

[1077]

A) tert-butyl (6RS,7SR)-7-(3,4-dichlorophenyl)-6-{[3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridin-2-yl]oxy}-1,4-oxazepane-4-carboxylate

Using tert-butyl (6RS,7SR)-6-[(3-cyanopyridin-2-yl)oxy]-7-(3,4-dichlorophenyl)-1,4-oxazepane-4-carboxylate (330 mg), and in the same manner as in Example 31, step D, the title compound (290 mg) was obtained.

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 369

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 369

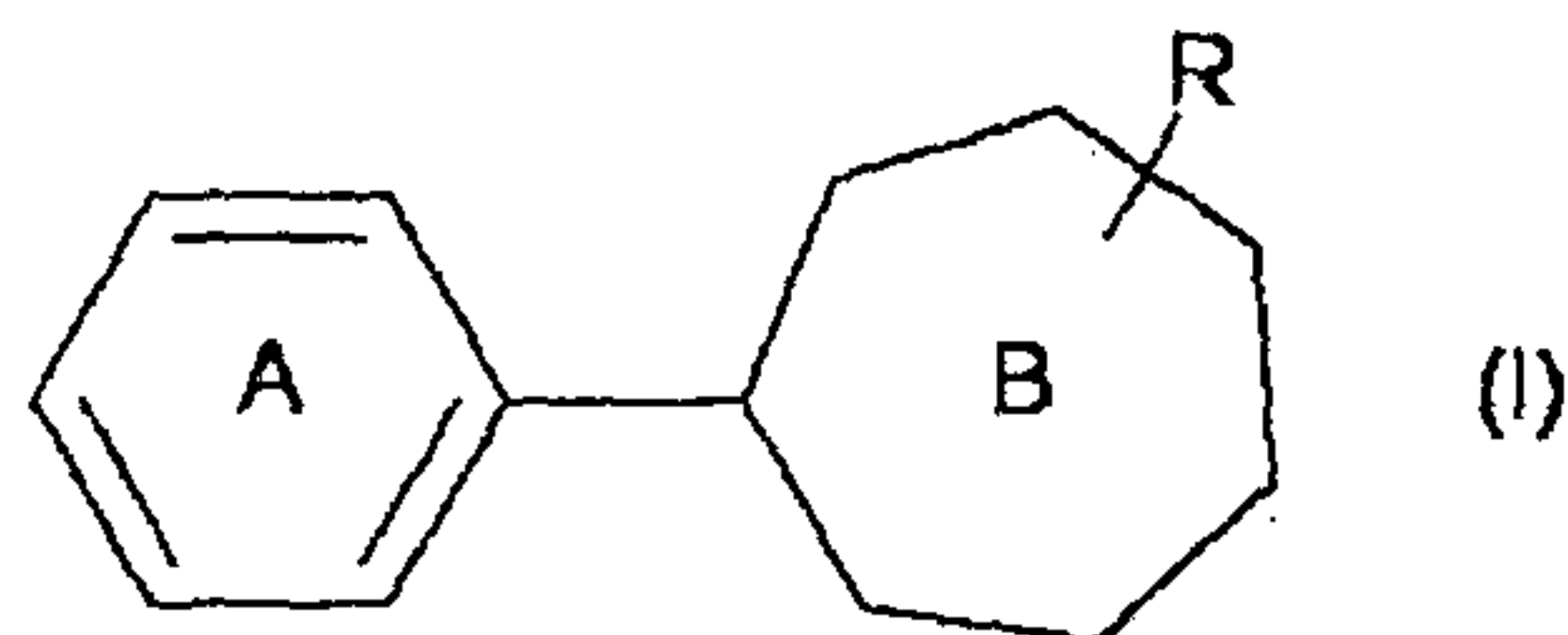
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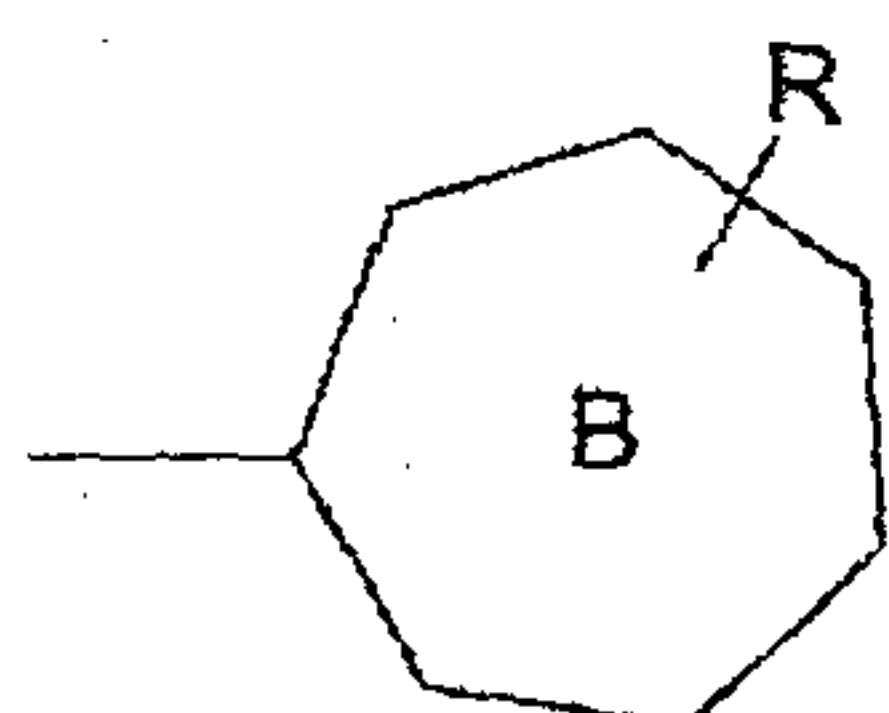
CLAIMS

1. A compound represented by the formula (I)

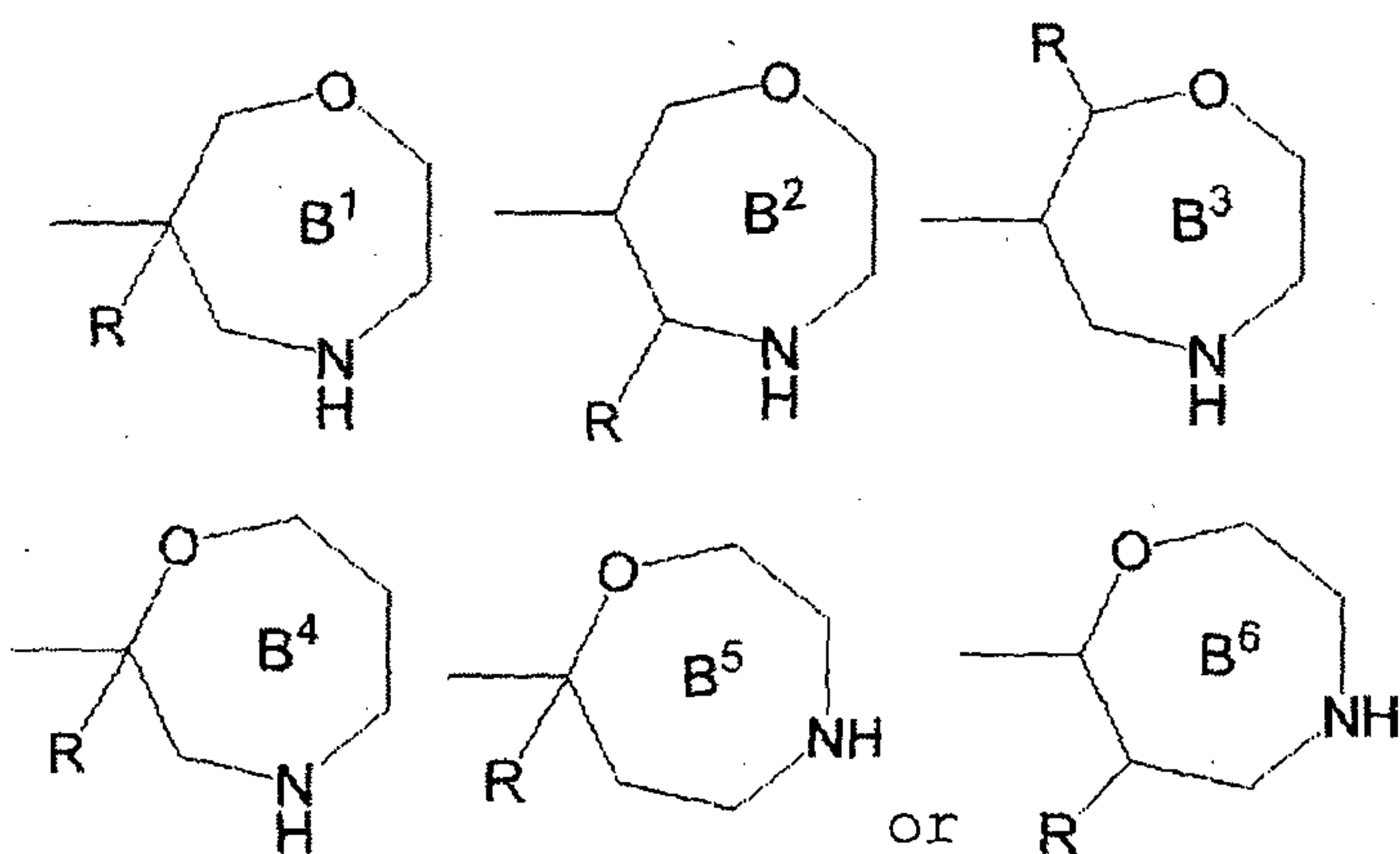


5 wherein

ring A is an optionally substituted 6-membered aromatic ring,
and a group represented by



is

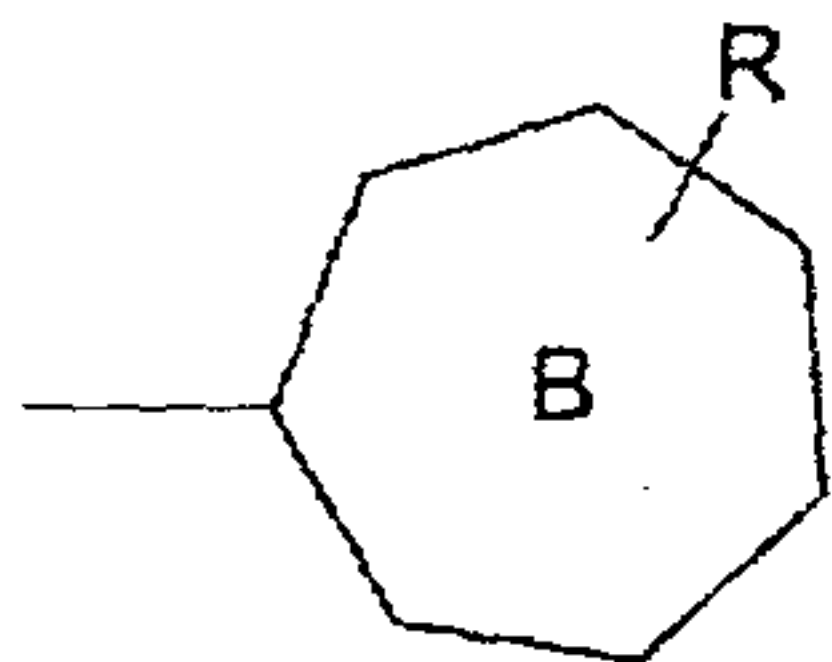


10 wherein ring B¹ - B⁶ are optionally further substituted,
provided a hydrogen atom bonded to a nitrogen atom
constituting rings B¹ - B⁶ is not substituted, and R is a
hydroxy group, a cyano group, an optionally substituted
15 carboxy group, an optionally substituted amino group, an
optionally substituted C₁₋₆ alkyl group, an optionally
substituted C₁₋₆ alkoxy group, an optionally substituted C₁₋₆
alkyl-carbonyl group, an optionally substituted carbamoyl
group, an optionally substituted C₆₋₁₂ aryloxy group, an
20 optionally substituted aromatic heterocycl-yl-oxy group, an
optionally substituted aromatic heterocyclic group, or an
optionally substituted nonaromatic heterocyclic group,
wherein substituents on ring A are optionally bonded to form,

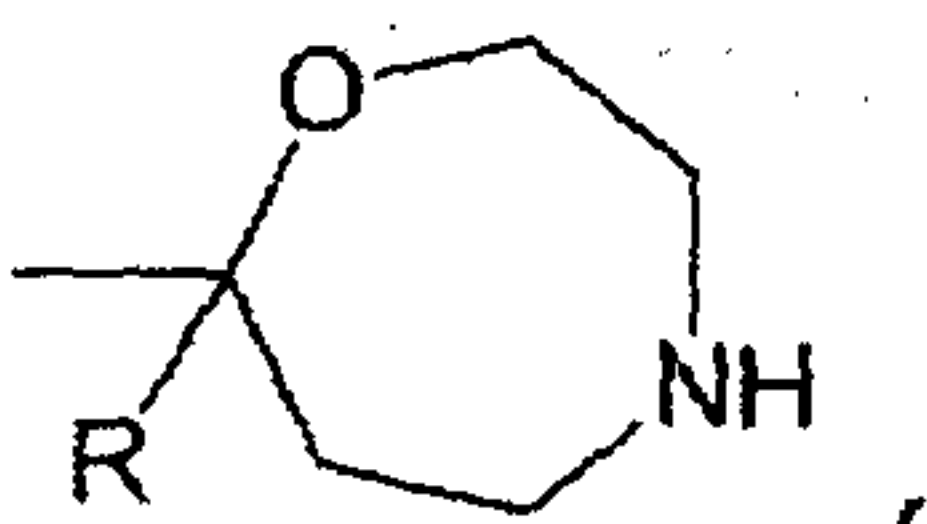
together with ring A, optionally substituted 9- or 10-membered aromatic fused ring,
provided that

(1) a compound, wherein a partial structure of the formula

5 (I):



is



10 ring A is a benzene ring, and

R is R^x-CH_2- (R^x is a phenoxy group optionally substituted by substituent(s) selected from a halogen atom and a methoxy group),

(2) 2-methyl-2-phenyl-1,4-oxazepane,

15 (3) 6-methyl-6-phenyl-1,4-oxazepane,

(4) (2R)-2-phenyl-2-(trifluoromethyl)-1,4-oxazepane,

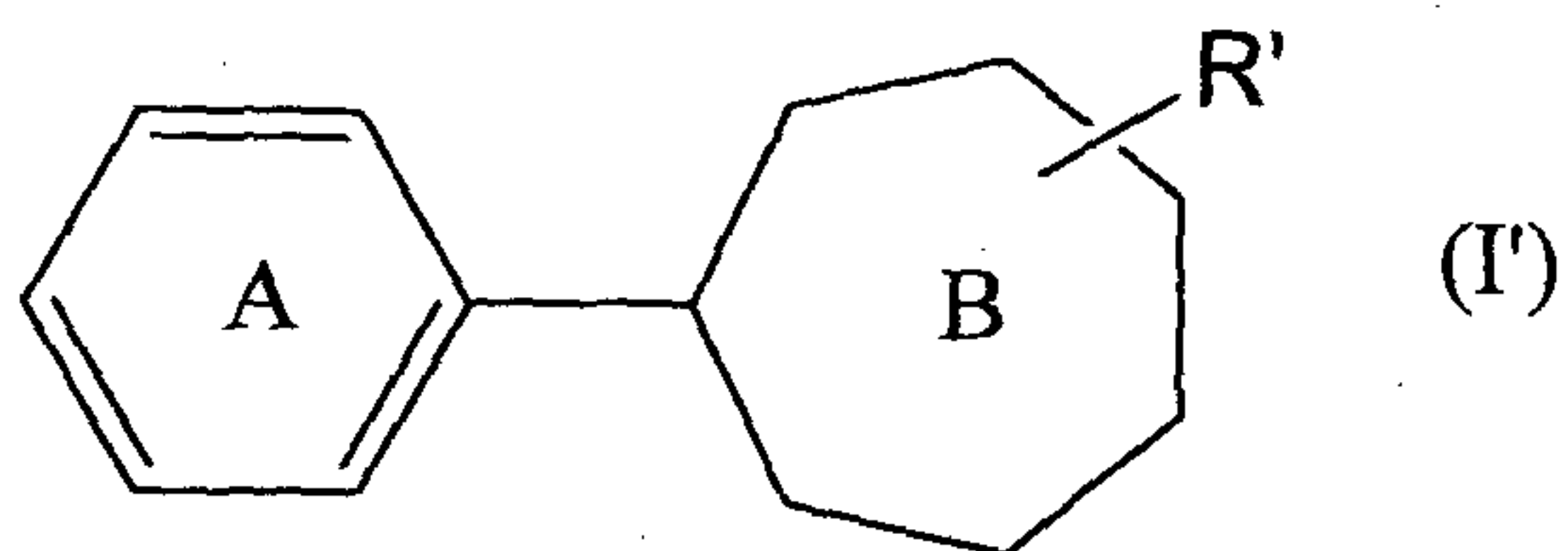
(5) 7-methyl-7-phenyl-1,4-oxazepane,

(6) (6R,7R)-6-hydroxy-7-phenyl-1,4-oxazepan-5-one, and

(7) 7-hydroxy-7-(4-methoxyphenyl)-1,4-oxazepan-2-one are

20 excluded, or a salt thereof.

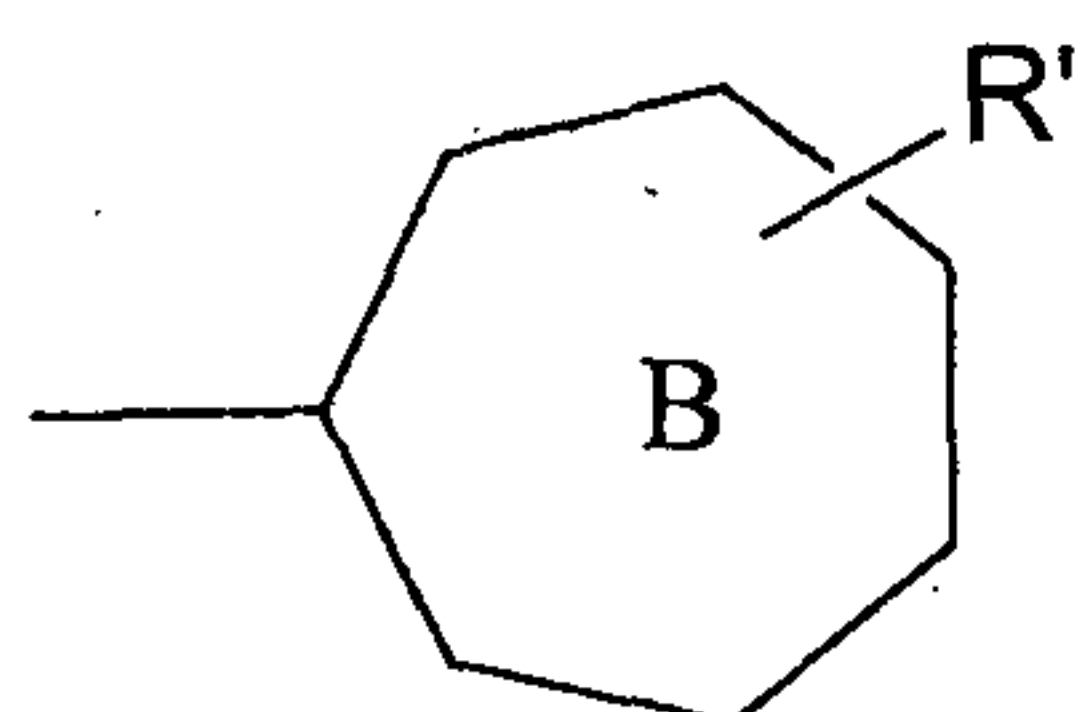
2. A compound represented by the formula (I')



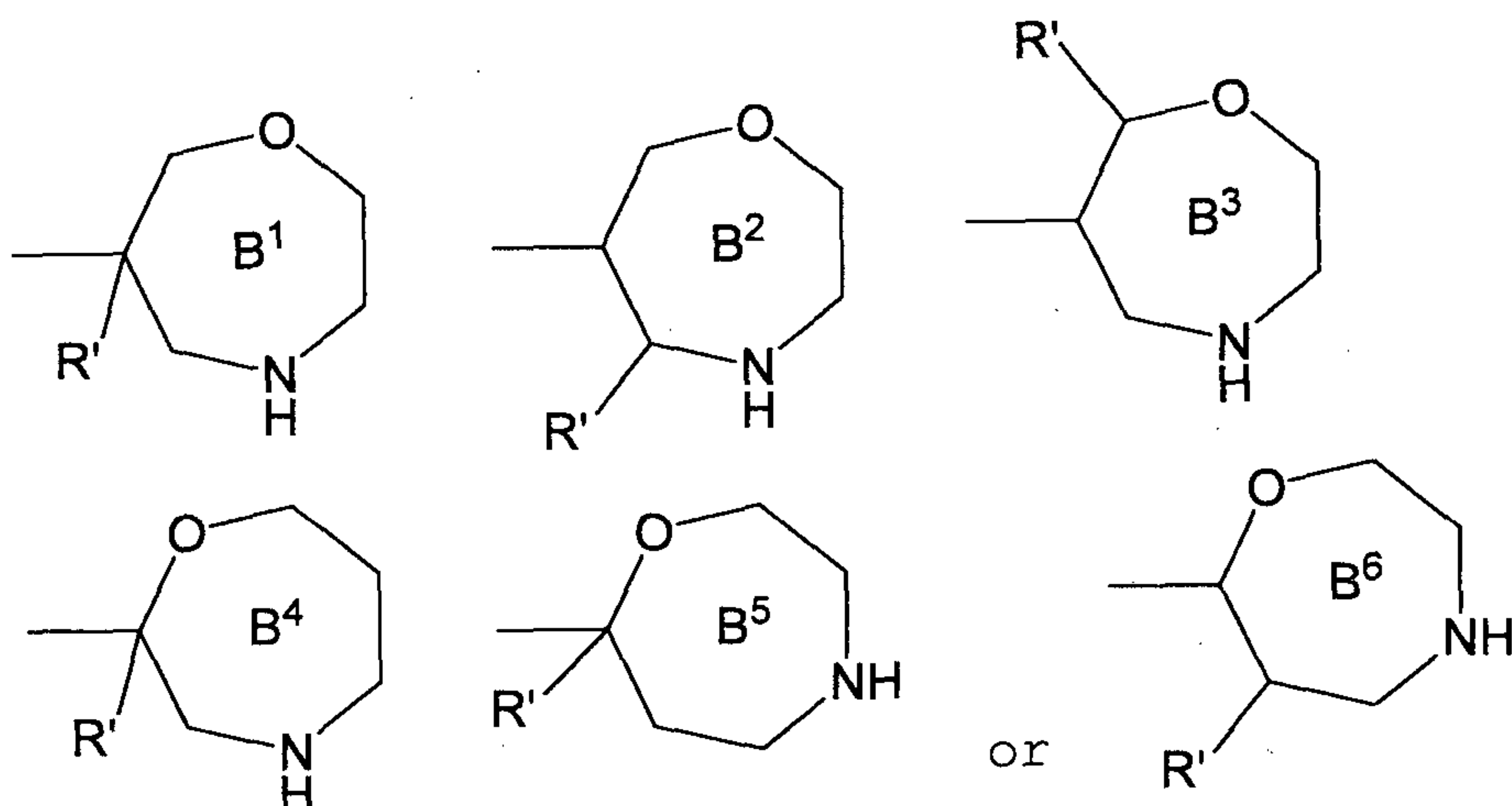
wherein

25 ring A is an optionally substituted 6-membered aromatic ring,
and

a group represented by



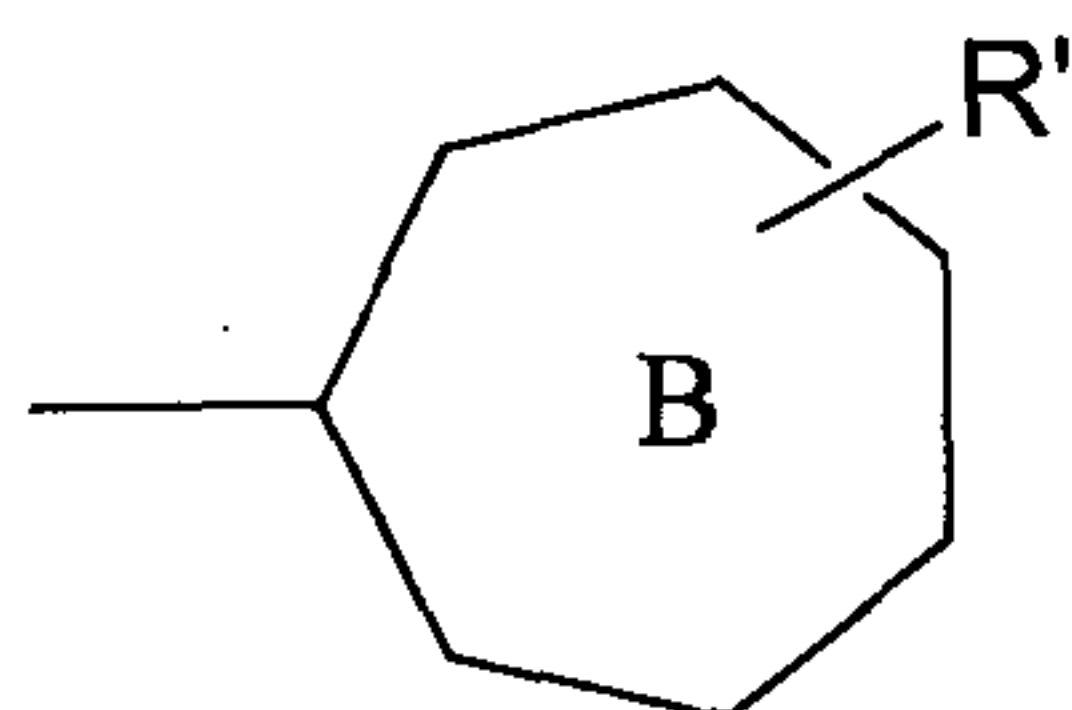
is



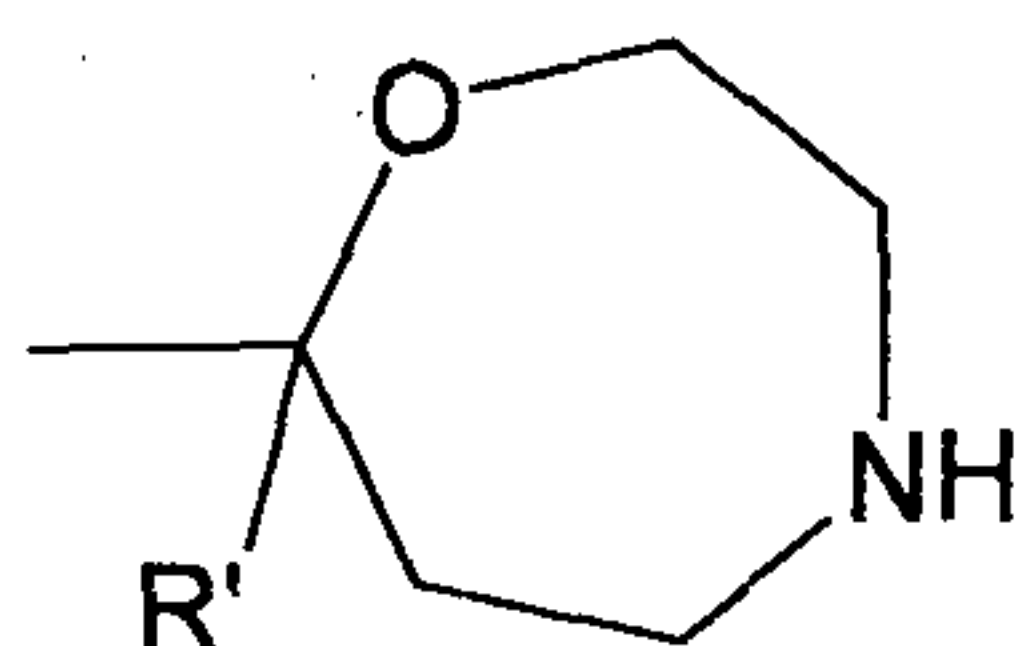
wherein ring B¹ - B⁶ are optionally further substituted,
 5 provided a hydrogen atom bonded to a nitrogen atom
 constituting rings B¹ - B⁶ is not substituted, and R' is a
 hydroxy group, a cyano group, an optionally substituted
 carboxy group, an optionally substituted amino group, an
 optionally substituted C₁₋₆ alkyl group, an optionally
 10 substituted C₁₋₆ alkoxy group, or an optionally substituted
 carbamoyl group,
 wherein substituents on ring A are optionally bonded to form,
 together with ring A, optionally substituted 9- or 10-membered
 aromatic fused ring,

15 provided that

(1) a compound, wherein a partial structure of the formula
 (I):



is



ring A is a benzene ring, and

R' is R^x-CH₂- (R^x is a phenoxy group optionally substituted by substituent(s) selected from a halogen atom and a methoxy group),

- (2) 2-methyl-2-phenyl-1,4-oxazepane,
- (3) 6-methyl-6-phenyl-1,4-oxazepane,
- (4) (2R)-2-phenyl-2-(trifluoromethyl)-1,4-oxazepane,
- (5) 7-methyl-7-phenyl-1,4-oxazepane,
- 10 (6) (6R,7R)-6-hydroxy-7-phenyl-1,4-oxazepan-5-one, and
- (7) 7-hydroxy-7-(4-methoxyphenyl)-1,4-oxazepan-2-one are excluded, or a salt thereof.

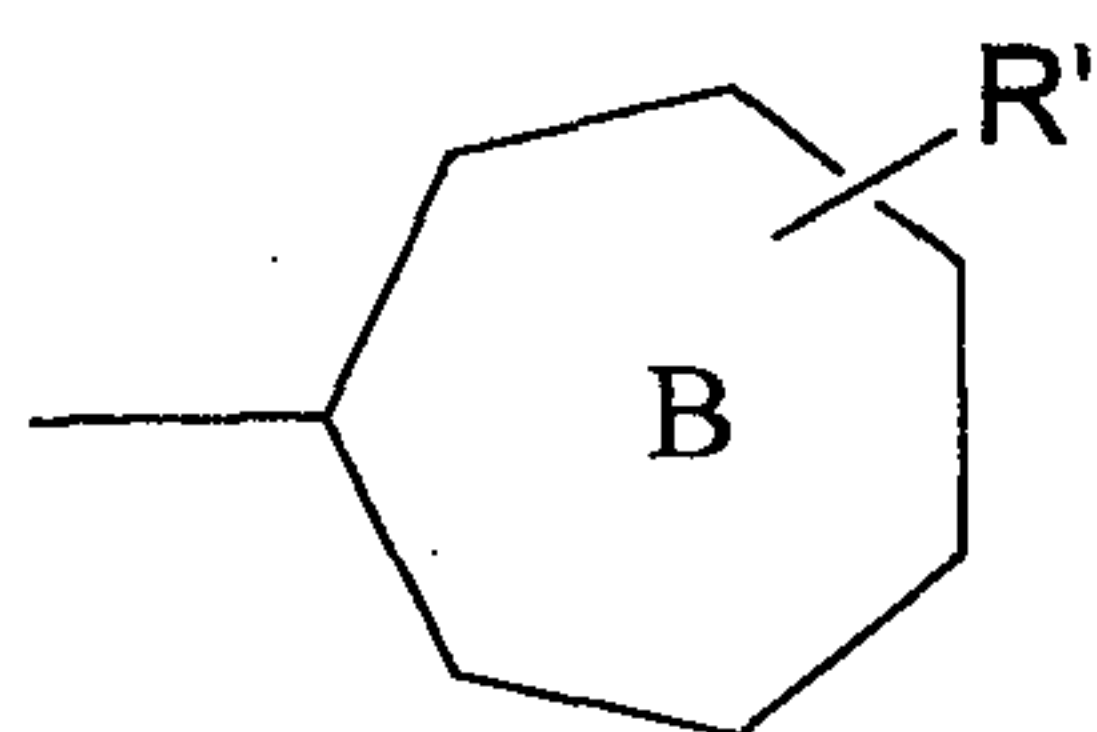
3. The compound according to claim 2, wherein ring A is an optionally substituted benzene ring, or a salt thereof.

4. The compound according to claim 2 or 3, wherein R' is

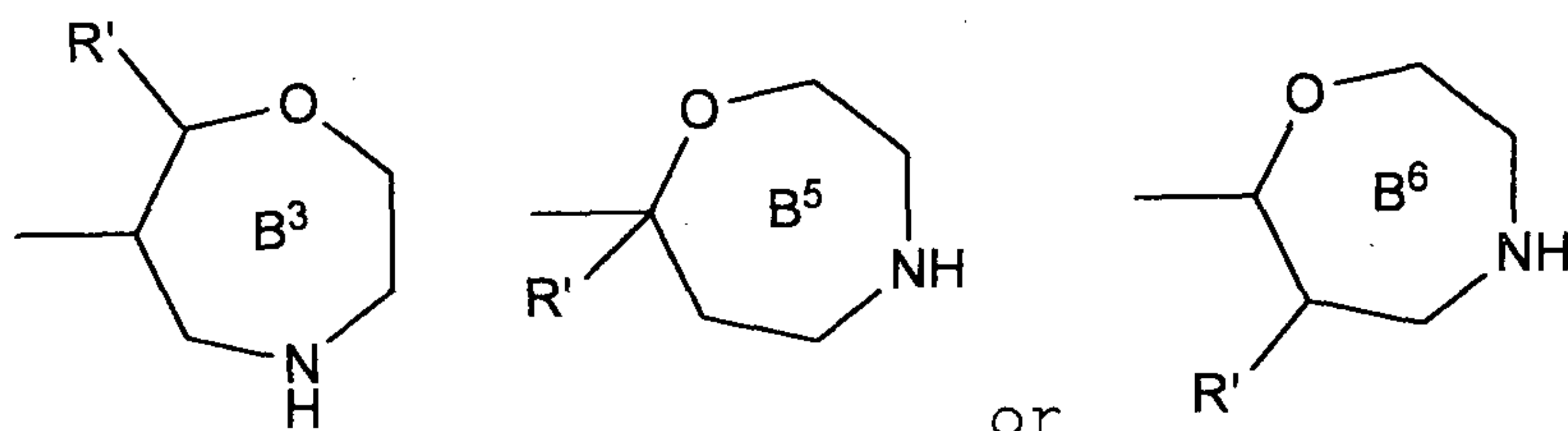
- (1) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group,
- (2) a sulfamoylamino group, or
- 20 (3) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituents selected from
 - (a) a hydroxy group,
 - (b) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group,
 - (c) a sulfamoylamino group,
 - 25 (d) a C₁₋₆ alkoxy-C₁₋₆ alkyl-carbonylamino group,
 - (e) a C₁₋₆ alkylsulfonfylamino group, and
 - (f) 2-oxopyridin-1(2H)-yl optionally substituted by 1 to 3 substituents selected from a carboxy group and 5-oxo-4,5-dihydro-1,2,4-oxadiazolyl,
 - 30 or a salt thereof.

5. The compound according to any one of claims 2 to 4, wherein

the group represented by

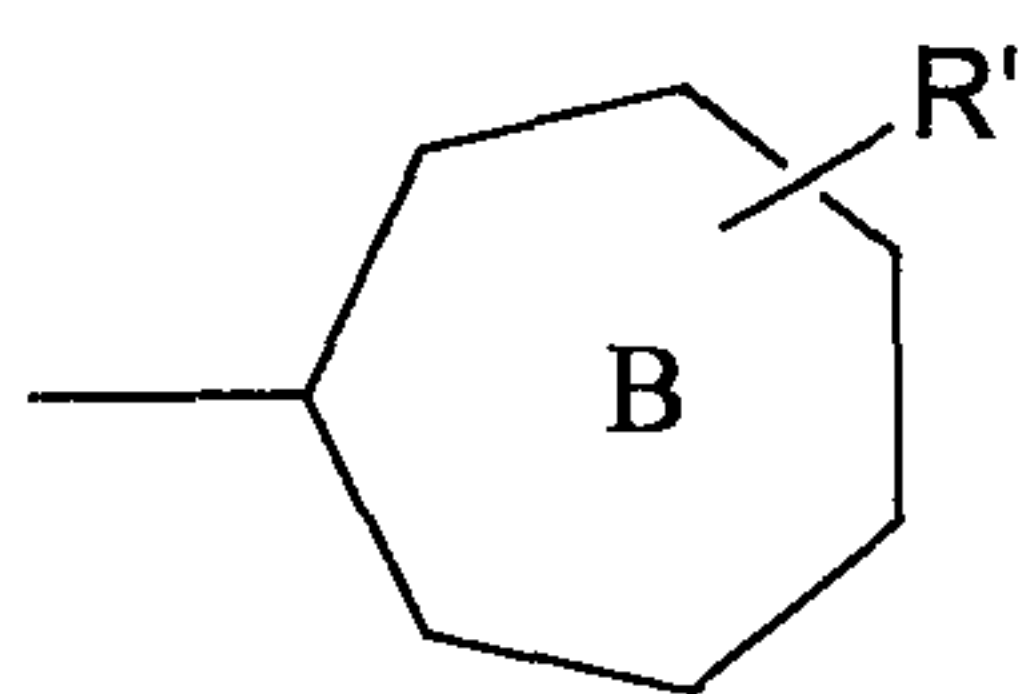


is

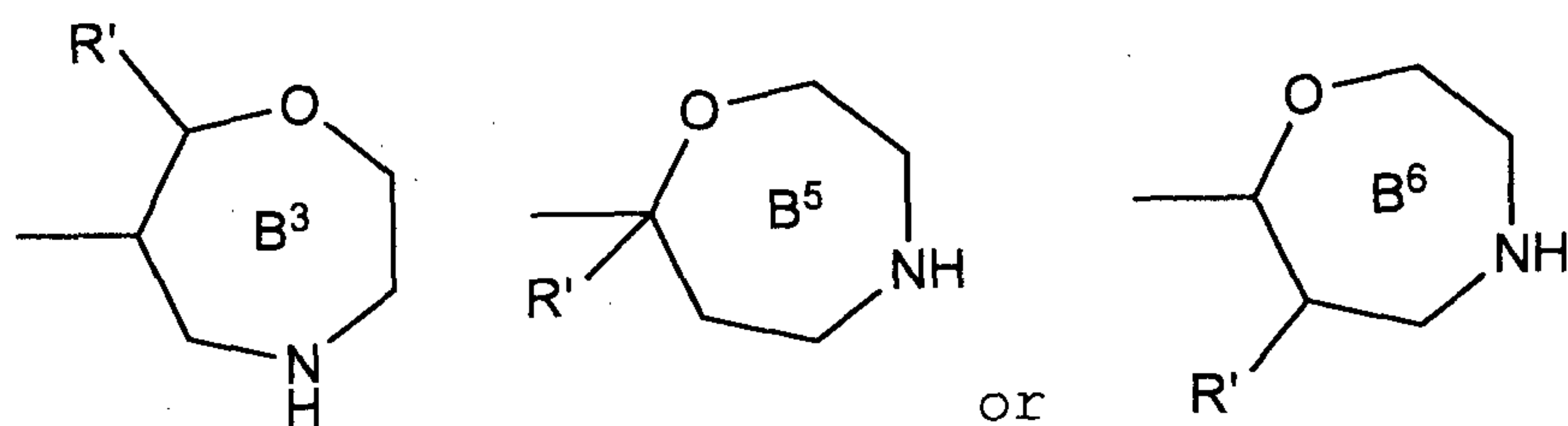


5 wherein each symbol is as defined in claim 2,
or a salt thereof.

6. The compound according to claim 2, wherein the ring A is a
benzene ring substituted by 2 substituents selected from a
10 fluorine atom and a chlorine atom, the group represented by



is



wherein

15 R' is

- (1) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group,
- (2) a sulfamoylamino group, or
- (3) a C₁₋₆ alkyl group optionally substituted by 1 to 3
substituents selected from

- 20 (a) a hydroxy group,
- (b) a mono- or di-(C₁₋₆ alkyl-carbonyl)amino group,

(c) a sulfamoylamino group,
(d) a C₁₋₆ alkoxy-C₁₋₆ alkyl-carbonylamino group,
(e) a C₁₋₆ alkylsulfonylamino group, and
(f) 2-oxopyridin-1(2H)-yl optionally substituted by 1
5 to 3 substituents selected from a carboxy group and 5-oxo-4,5-
dihydro-1,2,4-oxadiazolyl,
and other symbols are as defined in claim 2, or a salt
thereof.

10 7. N-{[(6S,7R)-7-(3,4-Dichlorophenyl)-1,4-oxazepan-6-
yl]methyl}-2-methoxyacetamide, or a salt thereof.

8. N-[(6R,7S)-7-(3,4-Dichlorophenyl)-1,4-oxazepan-6-
yl]acetamide, or a salt thereof.

15

9. N-{[(6S,7R)-7-(4-Chloro-3-fluorophenyl)-1,4-oxazepan-6-
yl]methyl}-2-[(²H₃)methyloxy]acetamide, or a salt thereof.

10. 1-{[(6S,7R)-7-(4-Chloro-3-fluorophenyl)-1,4-oxazepan-6-
20 yl]methyl}-2-oxo-1,2-dihydropyridine-3-carboxylic acid, or a
salt thereof.

11. (1S)-1-[(6R,7R)-6-(3,4-Dichlorophenyl)-1,4-oxazepan-7-
yl]ethane-1,2-diol, or a salt thereof.

25

12. [(7S)-7-(3,4-Dichlorophenyl)-1,4-oxazepan-7-yl]methanol,
or a salt thereof.

13. A medicament comprising the compound according to claim 1
30 or 2, or a salt thereof.

14. The medicament according to claim 13, which is a monoamine
reuptake inhibitor.

35 15. The medicament according to claim 13, which is a

prophylactic or therapeutic drug for depression, anxiety, attention deficit hyperactivity disorder, climacteric disorder, pain, stress urinary incontinence or mixed urinary incontinence.

5

16. A method for the prophylaxis or treatment of depression, anxiety, attention deficit hyperactivity disorder, climacteric disorder, pain, stress urinary incontinence or mixed urinary incontinence in a mammal, comprising administering an
10 effective amount of the compound according to claim 1 or 2, or a salt thereof to said mammal.

17. Use of the compound according to claim 1 or 2, or a salt thereof, for the production of a prophylactic or therapeutic
15 drug for depression, anxiety, attention deficit hyperactivity disorder, climacteric disorder, pain, stress urinary incontinence or mixed urinary incontinence.

18. The compound according to claim 1 or 2, or a salt thereof,
20 for the prophylaxis or treatment of depression, anxiety, attention deficit hyperactivity disorder, climacteric disorder, pain, stress urinary incontinence or mixed urinary incontinence.

